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Ionic Liquid Solvent Design Framework for Extraction of Phytochemicals using Microwave-Assisted Method

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Computer aided molecular design (CAMD) has been used widely for solvent design. It is a reverse approach in the selection of solvents for real application. CAMD is suitable for ionic liquid solvent design due the vast possibilities of ionic liquid molecular structures to be identified. Ionic liquid has broad ranges of applications especially in separation especially in carbon capture and azeotropic separation. This is due to the unique structures of ionic liquid that can be tailored for specific product separation. This study focuses on ionic liquid design framework for phytochemical extraction, incorporating the prediction of the extraction yield using the microwave-assisted method. The framework was developed in several stages. Stage 1 identifies the user needs, problems and constraints as well as target properties. Stage 2 comprise of comprehensive database development for ionic liquid and phytochemical properties; while property models' library was developed in Stage 3. Stage 4 involved the development of solvent design algorithm for ionic liquid selection for the targeted process. In Stage 5, depending on the type of extraction method considered, either using normal Soxhlet or a microwave-assisted extraction, the extraction yield can be predicted using the process performance model. The performance model for the liquid extraction is the thermodynamic solid-liquid equilibria model while for the advanced extraction method, the model was obtained through optimization of the experimental extraction process. This systematic framework is illustrated through a case study involving flavonoid and phenolic acid extraction from *Ortosiphon aureus*. Based on the yield prediction, 1-ethyl-3-propylimidazoilum bromide can extract 29.92 mg/g and was selected as a solvent for Flavonoid extraction using Microwave-assisted extraction. The design framework is able to find the optimal ionic liquid candidate for the extraction process.

1. Introduction

Ionic liquid has garnered attention of many researchers and industries. It has been integrated into many processes and used in many type of applications such as electrolytes (Vishwakarma, 2014), catalysis (Ratti, 2014) and separation process. Ionic liquid consist of an anion, a cation, a set of alkyl chain and other substituents that form different and unique properties (Ngo et al., 2000). This combination may develop various form of ionic liquid with different properties and abilities while maintaining liquid form under 100 °C. Ionic liquid can be sub-grouped into aprotic and protic ionic liquid. Aprotic ionic liquid mainly consists of bulky cations such as imidazolium and synthesised using metathesis halide. Protic ionic liquid is much simpler with combination of anion and cation using neutralisation of acid and base (Chen et al., 2014).

Currently, ionic liquid have been a favourable solvent for separation process such as azeotropic separation (Zhu et al., 2017) and extraction of pharmaceutical intermediate (Harini et al., 2014). This is due to the unique ionic liquid properties that is non-volatile and the capability to combine different type of ions thus capable to be design as per needed (Welton, 2011). The various possible forms of ionic liquid make the solvent screening challenging for researcher and engineer.

Systematic approach and predictive thermodynamic models are crucial in ionic liquid design to select optimal solvent for the process as well as simplifying experimental cost consumptions. The design usually considers the ionic liquid structure and also the physicochemical properties. Due to the unlimited structures of ionic liquid, many properties data of new ionic liquid molecules were unavailable. These data can be predicted by

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predictive models such as UNIFAC group contributions (Lei et al., 2012) and COSMO-RS model (Zhao et al., 2018).
UNIFAC group contributions model are broadly used as predictive thermodynamic models in predicting phase equilibria and had been expanded for ionic liquid system although the published UNIFAC matrices is limited. Currently, COSMO-RS is the novel method in predicting thermodynamic and physicochemical property of ionic liquid. This model used σ-profile to compare the polarity distribution of molecular surface as well as integrating electrostatic, hydrogen-bonding and hydrophobicity of the structure used in molecular force field analysis, thus correlate interaction parameters of ionic liquid structure. Currently, systematic approach of ionic liquid have been employed in azeotropic extraction of benzene and cyclohexane (Kulajanpeng and Suriyapraphadilok, 2016) and carbon capture (Venkatraman and Alsberg, 2017). Nur Rahilah et al. (2017) had designed an ionic liquid framework for phytochemical extraction by using systematic approach. Most of the framework designed applies thermodynamic models to predict yield of the solvent designed. The thermodynamic model used mainly predict extraction yield of conventional extraction method; but does not capture predicted yield of modern extraction methods such as microwave and ultrasonic-assisted extraction.
The aim of this study focus on the application of yield prediction model based on microwave-assisted extraction method towards the ionic liquid design framework for phytochemical extraction. This prediction model applied into the performance stage of solvent design framework; that usually based on thermodynamic solid-liquid equilibria model. The newly incorporated yield prediction model further improved the ionic liquid design framework for phytochemical extraction. Potential users can utilize this framework to select ionic liquid and compare the predicted yield of different types of extraction methods. The improved framework explained by a real case study of flavonoid and phenolic acid extraction from *Ortosiphon aureus* known as Misai Kucing.

2. Methodology

The methods of designing an ionic liquid framework consists of multiple stages (Nur Rahilah et al., 2017). Each stage contains multitasks which have been summarized in this section. The method for framework development includes computer-aided molecular design (CAMD) and predictive thermodynamic models to predict ionic liquid properties as well as target phytochemicals.

2.1 Stage 1: Problem definition

This stage will primarily define the needs of the solvent that translated into target properties. The constraints were identified to justify the need of a new solvent. All of the requirements and constraints were listed and translated into solvent performance characteristic that will be validated using model-based approach. In this study, solvent designed must dissolve target compound and does not react with the compound as well as reusable to reduce cost

2.2 Stage 2: Database collection development

Properties of ionic liquid as well as phytochemicals were listed and collected into a database. These data were collected based on extensive search of published literatures and available online database such as NIST ILThermo. All data obtained were reviewed then stored in two designed databases; database of phytochemicals properties and database of ionic liquid properties. These databases will later became an important input for ionic liquid design framework.

2.3 Stage 3: Property models library development

Property models were also collected based on published literatures and collected into an Excel file. This library consists of ionic liquid property prediction models. The collected equation models went through verification process to determine the accuracy of the equation. Only fit and suitable models compiled in the property library.

2.4 Stage 4: Development of solvent design framework

Systematic approach was employed in this stage. Related inputs from Stage 2 are the main ingredients for this stage. Based on the related properties, suitable property models of UNIFAC or COSMO were selected from Stage 3 to predict unknown or unavailable data in Stage 2. Solvent candidates were screened based on the target properties of ionic liquid design. Usually, the framework designed will be verified using a base case study. The objective of the case study is to confirm that the designed framework works correctly.

2.5 Stage 5: Experimental or performance validation

This stage usually employed as a performance validation of the solvent designed based on experimental runs. Usually, in this stage, experimental runs were done for the listed potential solvents based on a conventional

extraction method using selected parameters with constant value. In this study, this stage was enhanced by introducing different extraction methods into the validation steps. Factors of extraction and range of parameters were determined to carry the extraction process of phytochemicals. Experiment for different extraction methods were designed using Design of Experiment (DOE) software before running the phytochemical extraction. DOE used to optimize and analyze the results (yield of phytochemical) obtained during the experiment and interaction of different selected parameters. Based on the analysis, different process performance models were developed and incorporated into the design.

3. Results and discussions

3.1 Ionic liquid design framework

Based on the methodology described in Section 2, a new design framework was developed for ionic liquid solvent design for phytochemical extraction. This design framework allows a user to easily design or select an ionic liquid for separation process. Therefore, reducing the cost and time of experimental work to find suitable solvent for specific process. An improvement was made in the solvent design framework showed in Figure 1.

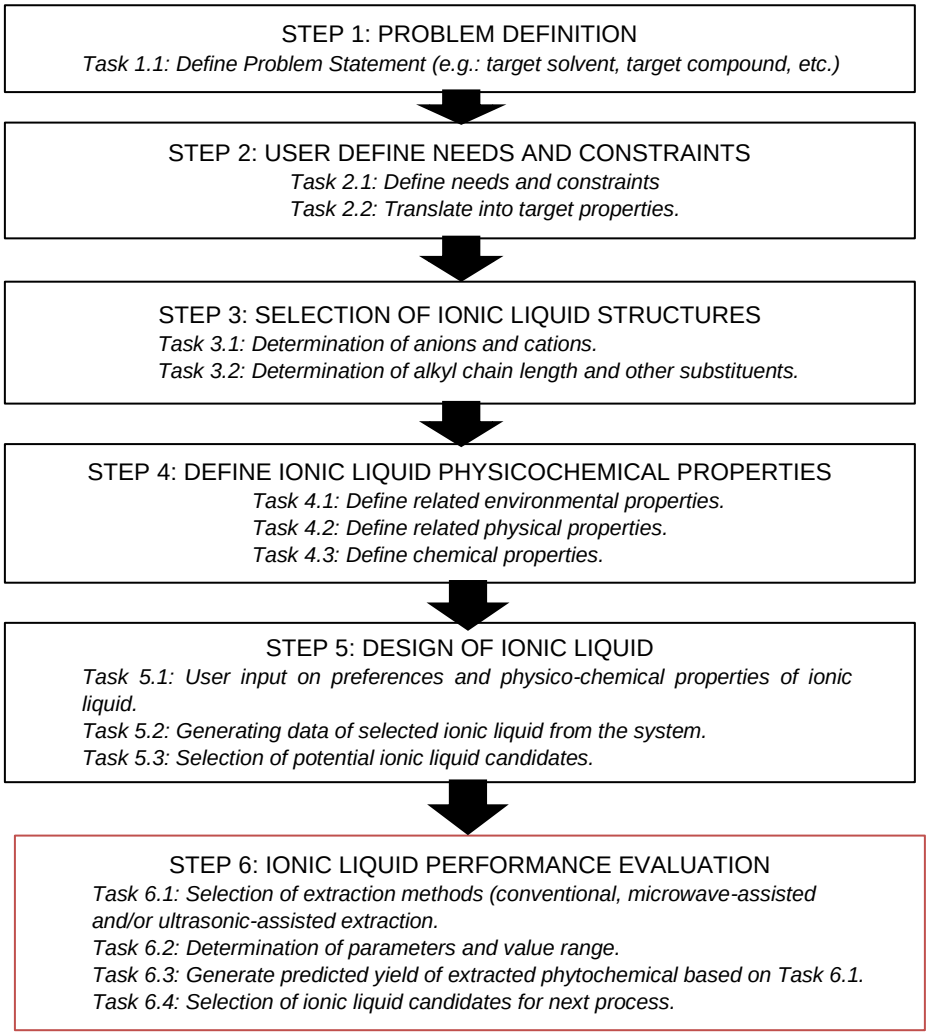

Figure 1: Improvement on ionic liquid design framework for phytochemical extraction.

Step 6 of this framework illustrate the further enhancement of phytochemical yield prediction based on different extraction methods. This will help user to interpret and select solvent along with the efficient process for phytochemical separation. In this step, user is allowed to select the desired methods after generating a list of potential ionic liquids. User will determine their own parameters and set the range of value for each of selected parameters.

Prediction models will be used to predict yield for each type of the extraction method. In this case, conventional extraction method used a thermodynamic solid-liquid equilibria model. For the advanced extraction methods, this stage provides user predictive models of extraction yield based on the optimized experimental runs in Stage 5. Two predictive models were developed based on previous study (Nur Rahilah et al., 2019) to predict flavonoid yield, y_F (Eq(1)) and phenolic acid yield, y_P (Eq(2)) of phytochemicals extraction using microwave-assisted extraction.

$$y_F = [3.549 + 0.177\,(\mathrm{A}) + 0.026\,(\mathrm{B}) + 0.063\,(\mathrm{C}) + 0.133\,(\mathrm{D}) - 0.014\,(\mathrm{AC}) - 0.017\,(\mathrm{AD}) - 0.016\,(\mathrm{CD}) + 2.954\,(\mathrm{A}^2)]^2 \quad (1)$$

$$y_P = [7.329 + 0.119\,(\mathrm{A}) + 0.058\,(\mathrm{B}) + 0.094\,(\mathrm{C}) + 0.192\,(\mathrm{D}) - 0.035\,(\mathrm{AB}) - 0.045\,(\mathrm{AC}) - 0.069\,(\mathrm{AD}) + 0.006\,(\mathrm{BC}) - 0.017\,(\mathrm{BD}) + 0.012\,(\mathrm{CD}) - 6.851\,(A^2) - 0.075\,(B^2) + 0.036\,(C^2) - 0.036\,(D^2)]^2 \quad (2)$$

where the coefficients A, B, C and D stands for dielectric point, extraction temperature, extraction time and irradiation power.

3.2 Case study: Phytochemical extraction from Malaysian herb

This part explained a case study based on the improved ionic liquid design framework. The case study involved the extraction of flavonoid from *Ortosiphon aureus. O. aureus* or Misai Kucing is a well-known herbal plant in Malaysia that have been commercialized into a health product. This health product associated with general well-being is commercialized as a health drink due to the high antioxidant activity of the plant. Flavonoid and phenolic acid, are found to be the main compounds in this plant associated with the high antioxidant activity. The selection of ionic liquid as the solvents for the extraction process follows the framework steps as describe below.

3.2.1 Step 1: Problem definitions

In Task 1.1, the target problem has been defined as to find a suitable solvent for the extraction of flavonoid from Misai Kucing plant. The target compound is flavonoid and the target solvent is imidazolium based ionic liquid.

3.2.2 Step 2: Define needs and constraints

In Task 2.1, the needs and constraints of the solvent is defined based on the problem statement stated above. The characteristics of the solvents identified based on meticulous reading and knowledge. Table 1 listed the needs and characteristics for the designed solvent. Basically, a solvent must dissolve the target compound and do not react with any of the element during the process to prevent and reduce production of any other substituents.

In Task 2.2, the needs and characteristics listed in the table above were translated into solvent properties. Based on the Table 1, the properties of ionic liquid related to the need of the solvent are (1) heat capacity, (2) solubility, (3) viscosity, (4) toxicity, (5) price and (6) density. These properties were selected and will be an input during ionic liquid design in Step 3 and 4.

Table 1: Solvent needs and characteristics for phytochemical extraction

#	Needs and characteristics
1	Solvent able to tolerate heat of the extraction process.
2	The solvent must be compatible with the extracted products and must extract the target products effectively.
3	Solvent must not be too sticky to be recover and recycle.
4	Solvent must be safe for human use as well as environmental.
5	The price of the solvent must be affordable.
6	The density of the solvent need to be low as the solvent usually sells based on weight.

3.2.3 Step 3: Selection of ionic liquid structures

Ionic liquid mainly consists of different structures of anion, cation, alkyl chain and a possible substituent. This step allowed the selection of ionic liquid structures. In this case study, cation selected for the ionic liquid is imidazolium ion; whilst anion selected are chlorine (Cl^-), bromide (Br^-), bis(trifluoromethylsulfonyl)imide (Tf_2N^-), tetrafluoroborate (BF_4^-) and Acetate (COO^-). The alkyl chain length of imidazolium allowed are between carbon C3 to C5. These types of ionic liquid were selected based on its structures that able to extract flavonoid efficiently. Anions selected have high probability in multiple interaction bonding with flavonoid such

as electrostatic and hydrogen bonding (Dróżdż and Pyrzynska, 2018). Imidazolium cation have the ring structures that could improve the surface area of flavonoid interaction (Zhou et al., 2015).

3.2.4 Step 4: Define ionic liquid physicochemical properties

In Task 4.1, the related environmental property is the toxicity. The toxicity property refers to Lethal Concentration at 50 % of fish population died (LC50). The range selected for this property is LC50 ≤ 5 mg/L in order to satisfy a safe environmental effect, based on the common range of products in market that meet safety standard (Tolls et al., 2009).
In Task 4.2, physical properties of ionic liquid are important to determine the weight, the constructed forms of ionic liquid and other related chemical properties. These properties affect the price and cost of the ionic liquid development later. The physical properties selected are molecular weight ($400 \geq M_r \geq 200$) and melting point ($T_m \leq 350$ K).
In Task 4.3, chemical properties selected for the ionic liquid design are heat capacity, density and viscosity. These properties affect the performance of the solvent itself. The range of value for the chemical properties are as follows: heat capacity ($Cp \geq 200$ J/K), density ($\delta \leq 1{,}200$ kg/m^3) and viscosity ($\rho \leq 0.2$ Pa.s). Solvent properties range of values selected based on the common flavonoid extraction solvent (Dhawan and Gupta, 2016).

3.2.5 Step 5: Ionic liquid design

In Task 5.1, data from Step 3 and Step 4 are crucial in determining the ionic liquid design. Here, data from the mentioned steps were inserted into Step 5 to initiate the development and screening of the ionic liquid solvent. The screening will run the data input simultaneously to generate a list of potential ionic liquid.
In Task 5.2, the list of potential candidates of ionic liquid was generated in this task were based from data input of previous steps. In this task, 23 potential imidazolium based ionic liquid were screened for further evaluation based on selected structures and physicochemical properties.
In Task 5.3, the ionic liquid candidates can be further selected based on user preferences. In this case study, 9 potential ionic liquid candidates were selected out of 23 potential solvents generated. The preferences can be up to the user based on the data selected. Table 2 showed the list of potential ionic liquid candidates selected for further process.

3.2.6 Step 6: Ionic liquid performance evaluation

In Task 6.1 and Task 6.2, the extraction methods selected for flavonoid extraction were conventional based and microwave-assisted extraction methods. Parameters selected are power (100 W), temperature (40 °C) and extraction time (5 min). These data input into the prediction models in the algorithm to predict the yield of the flavonoid extract.
In Task 6.3, the data input from Task 6.1 generated predicted yield of flavonoid for each of type of ionic liquid selected in Task 5.3. Table 2 listed the potential ionic liquid solvents selected from Task 5.3 along with physicochemical properties and predicted yield of flavonoid based on two type of extraction methods; conventional (Y_F_C) and microwave-assisted extraction (Y_F_MA). Based on this table, further selection can be made for the ionic liquid solvent.
In Task 6.4, 1-ethyl-3-propylimidazoilum bromide was selected as the optimal ionic liquid solvent based on the yield prediction in Table 2. The ionic liquid is further use as a solvent in the extraction process using microwave-assisted extraction method to extract flavonoid from Misai Kucing.

Table 2: Potential ionic liquid solvents for flavonoid extraction from Malaysian herbs with physicochemical properties data and predicted yield of flavonoid extraction.

#	Ionic liquid	M_r	T_m	LC50	C_p	δ	ρ	Y_F_C (mg/g)	Y_F_MA (mg/g)
1	[C4eim][BF_4]	240.05	282	3.13	411.11	1,165.61	0.064	14.21	28.54
2	[C3pim][BF_4]	240.05	251	3.68	411.11	1,165.61	0.064	10.07	18.88
3	[C3eim][BF_4]	226.03	266	3.68	377.65	1,196.31	0.052	15.62	29.92
4	[C5mmim][Br]	247.18	350	2.54	270.50	1,162.50	0.052	11.75	19.34
5	[C3mim][Cl]	160.65	334	3.68	265.34	1,008.86	0.040	11.87	24.35
6	[C3mim][Ac]	184.24	253	3.68	265.34	1,008.85	0.169	12.04	21.04
7	[C5mmim][BF_4]	254.08	269	2.54	328.03	1,139.60	0.068	13.57	21.05
8	[C4mmim][BF_4]	240.05	290	3.11	294.56	1,165.61	0.055	13.03	21.04
9	[C3mmim][BF_4]	226.03	314	3.68	261.10	1,076.53	0.045	12.98	20.55

4. Conclusion

In conclusion, this study was able to develop an improved ionic liquid design framework for phytochemical extraction. The framework applied for the extraction of flavonoid extraction from *O. aureus* using microwave-assisted extraction method. Based on the framework, list of potential candidates of ionic liquid were generated and selected for performance evaluation. Predictive models were then introduced in the process performance and validation stage to predict yield of phytochemical extracted. The models introduced associate with the advanced extraction methods of flavonoids and phenolic acid extraction using microwave-assisted extraction can predict the yield of the product. Based on the case study, the improved framework was able to screen out potential ionic candidates based on selected extraction process. This framework simplifies user by saving time and cost to identify the type of ionic liquid as well as extraction methods that suitable for the extraction process. The framework can be further improved by including other type of extraction methods such as ultrasonic-assisted extraction; and incorporating other molecules into the ionic liquid database.

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