RESEARCH ARTICLE

Rheological and Thermal Behavior of Choline-based Deep Eutectic Ionic Liquid and its Impact on a Poorly Soluble Drug Model

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ABSTRACT

Objective: This study was conducted to prepare a deep eutectic ionic liquid based on choline chloride and malonic acid (Maline) in different molar ratios and evaluate the maline properties to designate the best ratio for solubilizing risperidone, a poorly soluble drug model.

Method: Malines were prepared using choline chloride and malonic acid in 1:0.8, 1:0.9 and 1:1 molar ratios. The characterization of malines involved pH rating, rheological test and thermal behavior using DSC. In addition to estimating the interactions that occur between the choline chloride and malonic acid to form the malines theoretically using the computational prediction program Mercury and experimentally by ^{1}H-NMR and FTIR.

Results: This study shows that all malines (M1-M3) represents an acidic pH and high viscosity with a non-newtonian behavior (shear thinning property) at low temperature while a Newtonian behavior (shear rate-independent) at high temperatures. In malines (M1-M3) thermograms, the absence of pure compounds melting point peaks with a glass transition temperature at -14°C that confirms the DES property. FTIR and ^{1}H-NMR results represent a hydrogen bond formation between choline chloride and malonic acid and further between maline and risperidone which is similar to the computational prediction. Maline (M1) with molar ratio of 1:1 had a preferable solubilizing effect on risperidone reaching 20.5 mg/mL, while in (M2) (1:0.9) reaches 13.6 mg/mL, and in (M3) reaches 11.9 mg/mL.

Conclusion: Maline (M1) was chosen as the optimum molar ratio to form a deep eutectic ionic liquid that successfully enhances risperidone solubility and boosts its bioavailability.

Keywords: Choline chloride, Deep eutectic ionic liquid, Ionic liquid, Maline, Malonic acid, Risperidone.

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INTRODUCTION

Recently, a novel class of environmentally benign and tailored made solvent called ionic liquid (ILs) has been utilized as solvent, co-solvent and/or materials in the fields ofpharmaceutical drug delivery and active pharmaceutical ingredient (API) formulation due to their unique and tunable physicochemical and biological properties such as low melting point, chemical and thermal stability, low vapor pressure and widely tunable properties with regard to polarity, hydrophobicity, andsolvent miscibility.[1,2] These properties results from a matchless combination of molecular characteristics of their constitutive ions. Using ILs can notably improve the pharmacokinetic and pharmacodynamic properties of drugs and is widely used in medicine, chemistry and nanotechnology industries. ILs are compounds that consist of ions with a melting point below 100ºC.[3] They are organic salts that combine an organic cation and an organic/inorganic anion. These salts have been classified into four categories, according to the cation present in these ILs: dialkylimidazolium, N-alkyl-pyridinium, phosphonium, or alkyl ammonium cation. Imidazolium-based ILs are the most studied among these classes due to their high stability, low viscosity and relatively easy synthesis. However, in drug delivery field, they have exhibited some limitations since they have shown high toxicity. In contrast, the quaternary ammonium-based ILs, such as the choline-based ILs, have been described as less toxic, so they have been considered as "green" ILs. This fact puts them at the forefront as more suitable for applications in the pharmaceutical field.[4]

Among the pharmaceutical applications of ionic liquid, it is applied to prepare ionic liquid-in-oil micro emulsions with biocompatible choline carboxylic acids to improve the

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transdermal delivery of acyclovir composing a hydrophilic IL (choline formate, choline lactate,or choline propionate) as the non-aqueous polar phase and a surface-active IL (choline oleate) as the surfactant in combination withsorbitan laurate in a continuous oil phase.[5]

The development of a highly effective oral insulin formulation using choline and geranate (CAGE) ionic liquid significantly enhanced paracellular transport of insulin, while protecting it from enzymatic degradation and interacting with the mucus layer resulting in its thinning. Leading to a significant decrease in blood glucose levels, which were sustained for longer periods.[6]

Also, an ionic-liquid-based paclitaxel preparation which were composed of PTX/cholinium amino acid ILs/ethanol/ Tween-80/water, with a significant enhancement in the solubility of PTX provide a potentially safer alternative to cremophor EL as an effective formulation for cancer treatment giving fewer hypersensitivity reactions.[7]

The choline based ionic liquid can form a deep eutectic solvent when mixed with distinct components which typically interact *via* strong hydrogen bonding, forming deep eutectic solvents that are also known as deep eutectic ionic liquids (DEILs). They are mixtures of substances with a significantly lower melting point than any of its single components, which is the most important feature of DES.[8] On the other hand, the IL was considered as the parents of DES. Some authors estimate DES to be a subclass of ILs, and sometimes they consider these terms interchangeable.[9]

DES typically formed by mixing a quaternary ammonium salt (*e.g.* choline chloride) and a hydrogen bond donor (HBD) (*e.g.,* urea or carboxylic acid), was found to have relative physicochemical properties of room temperature ionicliquids but without metal salt-associated draw-backs, with few reports studying their performability as a solvent to dissolve certain poorly water-soluble drugs.[10] A significant drug solubility enhancement was obtained upon using deep eutectic solvents based on glycolic acid and choline chloride (up to 6700 folds) on selected basic poorly water-soluble drugs.[10]

The model drug risperidone (RSD) is a class II BSC (low soluble highly permeable) which is a benzisoxazole derivative psychotropic agent; it is a selective monoaminergic antagonist, approved by the United States Food and Drug Administration for the treatment of schizophrenia, bipolar disorder and irritability in children and adolescents ages. It is practically insoluble in water, soluble in methanol and exhibits a pH-dependent solubility.[11]

The aim of this work is to prepare choline chloride-based deep eutectic ionic liquid (DEIL) with malonic acid and named Malines, as well as investigate and evaluate its rheological and thermal activity to optimize its properties for solubilizing RSD to be used as a potential drug delivery system that may improve drug miscibility, diffusivity and hence its bioavailability.

MATERIALS

Choline chloride, malonic acid and RSD were purchased from Hangzhou Hyper chemicals, China. Methanol was purchased from Thomas Baker, India

METHODS

Preparation of DEILs, Malines

To prepare DEILs, choline chloride and malonic acids were mixed at different molar ratios as shown in Table 1. The mixtures were sealed in vials and heated in water bath at 80ºC until homogenous solutions were formed. Subsequently, each sample was stored at room temperature and at refrigeration temperature for 48 hours. Only those samples that remained liquid were further tested.[10,12,13]

Computational Structural Prediction for the H-bonding Design of Maline Components and Maline with RSD

Using ConQuest and Mercury, two programs have been developed for searching the Cambridge Structural Database (CSD) and visualizing database entries. Conquest provides building queries, searching the CSD and structure parameters such as distance and angle. Mercury import and visualize all the structures and the associated parameters providing an interactive interface connecting data analysis such as spreadsheets, statistics and plotting of results.[14-16]

Malines pH Determination

Each samples that succeeded to remain liquid (malines M1-M3) was mixed with corresponding volume of deionized water. The freshly prepared solutions were kept at room temperature for period of 30 minutes, and the pH was measured using Pen pH meter (Kedide instrument, china). Then every solution was placed in a water bath and heated to 37ºC for further pH measurement.[17,18]

Saturated Solubility Determination

The saturated solubility of risperidone in each of the prepared DEILs (malines M1-M3)was determined by adding excess

Table 1: Mixtures of choline chloride and malonic acid (Malines)

DEILS (Malines)	*Choline chloride molar ratio*	*Malonic acid molar ratio*
M1	1	1
M2	1	0.9
M3	1	0.8
M4	1	0.7
M5	1	0.6
M6	1	0.5

amount of RSD into screw vials containing 5 mL of each maline. The tubes were closed and placed in water bath at 25 and 37ºC for 48 hours. The samples were withdrawn at several time intervals (1, 2, 4, 6, 12, 24, and 48 hours). Aliquots were filtered by 0.45 µm filter syringe and diluted using methanol. After making a calibration curve for RSD in each maline, the drug concentration was then calculated from the UV absorbance using UV spectroscopy at λ_{max} of RSD (279 nm).[19,20]

Thermal Behavior of DEILs by DSC

An approximate amount between 5 to 10 mg of nitrogen dried sample of each of the DEILs (malines M1-M3) was placed into the aluminum hermetic pan and covered with the lid, and the DSC analysis was carried out using (Mettler Toledo DSC823e). The thermal behavior was also carried for choline chloride, malonic acid, and RSD from 0 to 400°C, while from 25 to 80°C for DEILs and for the drug with DEILs (M1, M2, M3) and for M1 containing RSD and the heating rate of 1–10°C/min.[21]

Compatibility Study by FTIR Spectroscopy

A sample of 4 mg of pure RSD powder, choline chloride, and malonic acid was mixed each one separately with dry potassium bromide and pressed in the form of a disc. The IR spectroscopy also applied for DEILs (malines M1-M3), and RSD in maline (M1). The disc was analyzed by FTIR spectroscopy (at a range of 4000 to 400 cm^{-1}) using Shimadzu FTIR-8400S.[22,23]

H^1-NMR Determination for Maline (M1)

The test carried out for choline chloride, malonic acid, maline (M1),and RSD in maline(M1) on a Bruker AVANCE 500 spectrometer operated at room temperature. The samples were prepared on 5 mm NMR tubes using deuterated methanol (MEOD) as solvent.[13]

Rheological Tests

The rheological properties of DEILs (malines M1-M3) and for M1 containing RSD were evaluated using a rotational rheometer (Physica MCR 302, Anton Paar) at 25°C. The rheometer offers different geometries (concentric cylinder, cone-and-plate and parallel-plate) with DG27 double gap concentric cylinder measurement system to determine the viscosity. This rheometer characterized by high precision and accuracy. A Peltier temperature system embedded in the measuring chamber. To ensure accurate results, the rheometer was calibrated, then rheological tests were programmed *via* a computer-controlled rheocompass software (Anton Paar).[24]

Flow Curve

The flow curves could be measured by either controlled shear rate or controlled shear stress. Upon low shear behavior interpretation, the shear rate was varied inthe range (2 to 100s^{-1}) and shear stress was measured. For the presentation of the data, flow curve will be presented by plotting the shear stress against the shear rate,and the viscosity (Pa.s) is the slope of this curve.[25,26]

Temperature Sweep Test

This test shows the temperature dependence of the viscosity. A constant shear rate of 50 s^{-1} was used to shear the samples, and the temperature was decreased from 40 to -10°C with a slope of 2°C /min.[24]

RESULTS AND DISCUSSION

DEILs Preparation (Malines)

After preparing the DEILs (Malines M1-M3) by mixing choline chloride and malonic acids at different molar ratios and storing each maline at room and refrigeration temperatures, only malines with molar ratio of 1:1, 1:0.9 and 1:0.8 (M1, M2 and M3), respectively succeeded to remain liquid in both temperatures. Since maline formed from a complexation between a hydrogen bond accepter (choline chloride) and a hydrogen bond donor (malonic acid). Therefore, lowering molar ratio of hydrogen bond donor (malonic acid) influences the formation and the stability of malines.[27] Only the optimal ratio of the hydrogen bond acceptor and hydrogen bond donor may lead to the eutectic mixture and depends on the component's mutual hydrogen bonding abilities.[28] The only maline M1-M3 formed stable deep eutectic ionic liquids and were selected for further investigations.

Maline Computational Structural Prediction

According to conquest-mercury program, maline could be formed by two probable hydrogen bonds existed with different lengths and angles as shown on (Figure 1A and 1B). An H-bond formed between the chloride of choline chloride and the hydroxyl group of malonic acid with distance of 2.281Å. The other H-bond occurs between the hydroxyl group of choline in choline chloride and the carbonyl group of malonic acid with distance of 1.919Å. These results suggested the formation of a weak to moderate hydrogen bonding corresponding to the liquid state, and the H-bond angles of 158.252° and 161.508°, respectively, implies the stability of these hydrogen bond as they are close to the 180°.[29,30]

Regarding the intermolecular H-bonding that exist between maline and RSD (as shown in Figure 1C and D), the most likely H- bonds occured between the benzyl fluoride of RSD and the hydroxyl group of maline with distance of 2.747Å, and between the ammonium N6 of RSD and the hydroxyl group of maline with length of 2.100Å.

These results also indicated the formation of weak hydrogen bonding corresponding to the liquid state. Furthermore, the H-bond angleof the ammonium N6 of RSD and the hydroxyl group of maline proposed more stable bond with 157.160° than H- bonds occur between the benzyl fluoride of RSD and the hydroxyl group of maline with angle of 111.053°.[29,30]

Figure 2 shows the suggested H-bonding of maline components (between choline chloride and malonic acid) as well as H-bonding of RSD with maline M1.

Malines pH Determination

The pH is an important physical property and has an essential influence on chemical reactions and on DEILs applications. The results in Table 2 indicate the acidic pH value of maline due

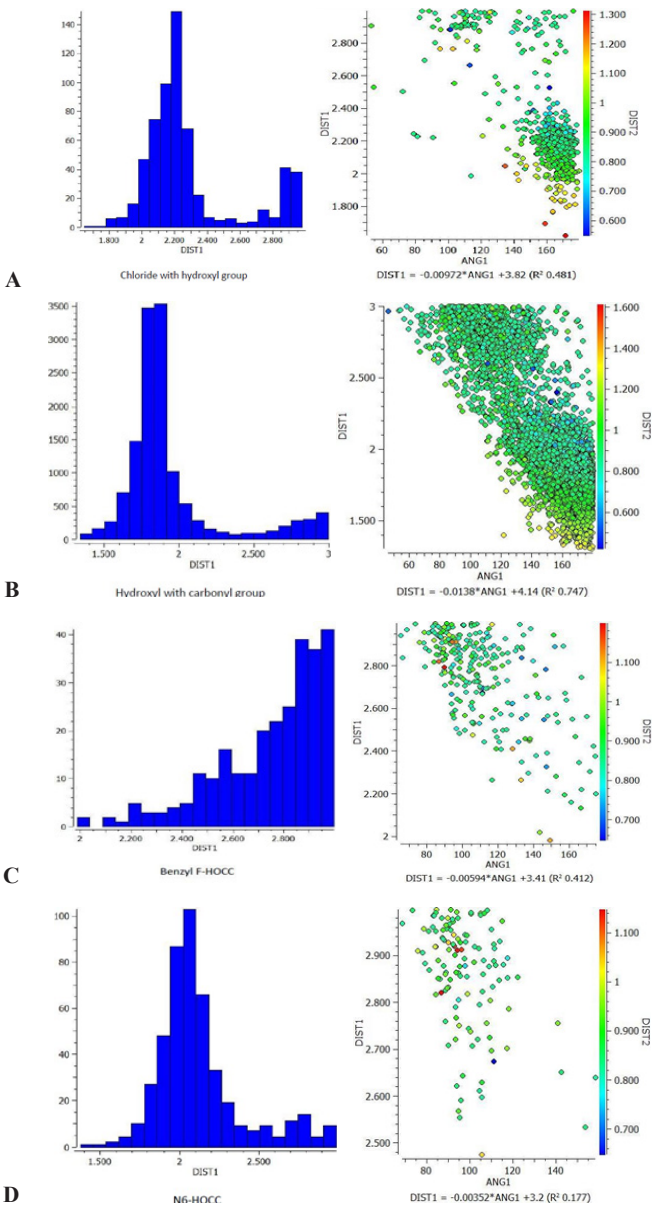

Figure 1: H-bond distance and angle prediction chart: (A)Chloride of chloine chloride with hydroxyl of malonic acid. (B) hydroxyl of chloine in choline chloride with carbonyl of malonic acid (C)benzyl fluoride of risperidone with hydroxyl of maline and (D) ammonium of risperidone with hydroxyl of maline.

to the nature of the malonic acid (hydrogen bond donor), and the pH values decreased with increasing temperature. Same pH behaviors were observed with several deep eutectic solvents.[17] However, there are no significant differences in the pH values of the malines (M1-M3) at room and body temperature.

Saturated Solubility of RSD in Malines

RSD solubility was evaluated in malines (M1-M3), and was found to be soluble in all the tested malines (Table 3). The highest solubility was recorded in 1:1 choline chloride/ malonic acid (M1) where the saturated solubility of the drug in M1 was significantly ($p \leq 0.5$) higher than its solubility in M2 and M3 where it was 20.5 mg/mL at 25°C and 5.6 mg/

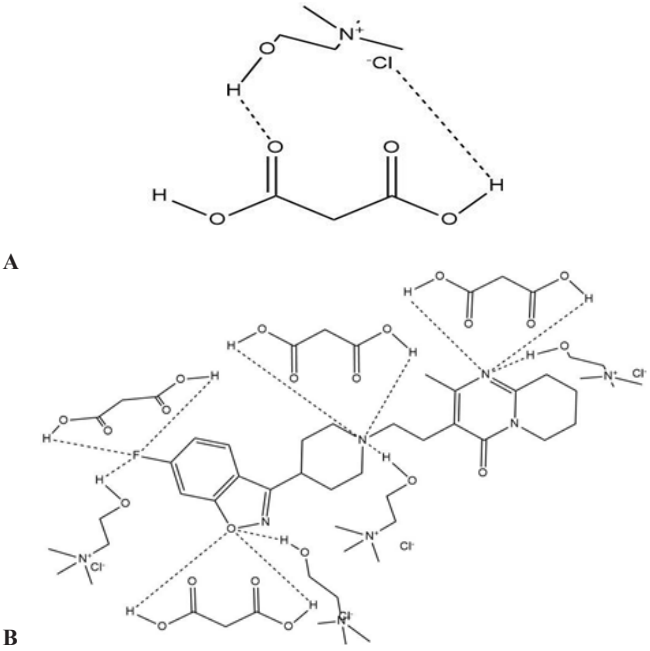

Figure 2: Predicted H bonding between: (A) Choline chloride and Malonic acid (Maline structure (B) Risperidone and Maline.

mL at 37ºC. While saturated solubility of RSD in M2 and M3 were 13.6 mg/mL at 25°C and 0.23 mg/mL at 37ºC; and 11.86 mg/mL at 25○C and 2.69 mg/mL at 37ºC, respectively. These values is much higher than the reported solubility of the drug in water, *i.e.,* 2.8 µg mL^{-1} at 25○C and 5 µg mL^{-1} at 37°C.[31,32] Therefore, maline (M1) was chosen for the solubilization of RSD. The high solubility of the drug in maline (M1) due to the formation of stronger hydrogen bonding. The reduction in solubility at 37ºC was due to the changes in H-bonding that occur with temperature increasing.[30] The same results were reported utilizing different DES for lidocaine solubilization,[33] and studying carbohydrates solvation in various choline chloride-based deep eutectic solvents.[34,35]

Thermal Behavior of DEILs by DSC

Since melting point depression is one of the most obvious properties of DEILs, the DSC analysis provides an effective technique to track the thermal behavior of the formed DEILs. The thermogram of choline choride (Figure 3A) revealed an endothermic peak near 302°C indicating the crystalline nature of choline chloride.

Also, a sharp endothermic peak near 135°C specifying malonic acid. These outcomes are in agreement with the reported melting point data for choline chloride and malonic acid.[36, 37]

It is clearly shown in Figure 3B that all malines showed no peak corresponding to the melting points of the choline chloride and malonic acid, and no thermal events were observed. Instead, a glass transition temperature presented near -14°C which confirmed that these DEILs are supramolecular complexes *via* strong hydrogen bonding with the liquid state over a broad temperature range. The same results were observed with other deep eutectic solvents based on choline chloride and carboxylic acid.[13]

Table 2: Malines pH values

Maline	*pH at 25ºC*	*pH at 37ºC*
M1	1.90	1.60
M2	1.98	1.79
M3	2.00	1.90

Table 3: Solubility of risperidone in malines.

Respirdone in	*At 25°C*	*At 37°C*
	Concentration (solubility) mg/mL ± SD	*Concentration (solubility) mg/mL ± SD*
1:1 (M1)	20.46 ± 1.082	5.64 ± 0.355
1:0.9 (M2)	13.61 ± 1.705	0.23 ± 0.135
1:0.8 (M3)	11.86 ± 1.859	2.69 ± 0.240

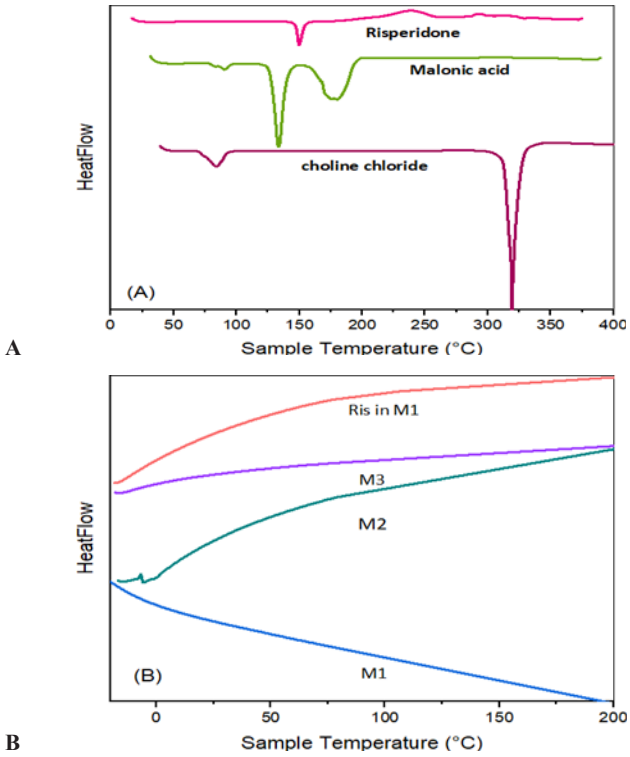

Figure 3: Dsc thermogram of :(A) Choline chloride, Malonic acid, risperidone (B) Maline M1, M2,M3,and risperidone in M1.

RSD showed a sharp melting endotherm at 171ºC as presented in Figure 3A and aligned with its melting point.[19] The thermogram of RSD in the maline(M1) revealed that the presence of RSD did not significantly affect the main glass transition temperature of the maline. However, the melting endotherms of risperidone itself no longer existed indicating its complete solubilization. In fact, the absence of RSD melting endotherm underlines the ability of DEILs to maintain the drugs in the soluble form up to temperatures that are lower than their melting points.[38]

Compatibility Test by FTIR Spectroscopy

FTIR is a compelling analytical technique that decides the functional groups present in the prepared malines and identifies the structure of chemical bonds with extreme sensitivity to hydrogen-bonding interactions.[12] IR spectrum of maline is a frequency combination of choline chloride and malonic acid, except a specific frequency shifting as presented in Table 4.

In Figure 4, choline chloride showed a sharp peak near 3271.38 cm^{-1}, revealing the OH group.[39] The OH stretching region of malonic acid as a typical carboxylic acid stretching that form hydrogen-bonded dimer rings, with a strong broad overlapping bands centered at frequencies between 2945 and 3153 cm^{-1}.

In addition, a strong broad peak near1708.99 cm^{-1} referred to the carbonyl stretching region of malonic acid. The broad nature of this peak reflected two dimer rings with almost equal hydrogen strength. These values are comparable to the wave numbers recorded in previous study.[40]

After maline formation, the vibrational mode of the carbonyl stretching region of malonic acid observed in Figure 4, shifted from 1708.99 cm^{-1} toward a higher wave number 1732 cm^{-1} and considerably became less intense. This indicates that these carbonyl groups are free in maline.

Furthermore, the -OH groups of malonic acid in malines (M1, M2 and M3) appear as a broad peak due to the liquid and the amorphous nature of maline which makes the sharper peaks overlap. This broad peak was observed at a higher wave number near 3340 cm^{-1}, representing weaker hydrogen bonds formed than pure malonic acid cyclic dimers. All these results was harmonized with the reported data of choline chloride/ malonic acid DEILs FTIR analysis.[39,40]

RSD showed a sharp peak at 1651 cm^{-1} related to the carbonyl group in its structure.[19] Once dissolving RSD in

Table 4: FTIR Spectrum stretching

Substance	*Functional group*	*Stretching (cm^{-1})*
Choline chloride	OH	3271
Malonic acid	OH, C=O	2945-3153, 1708.9
Maline (M1, M2 and M3)	C=O, O=H	1732.13, 2926-3340
Risperidone	C=O	1651
Risperidone in maline	C=O	1726, 1633

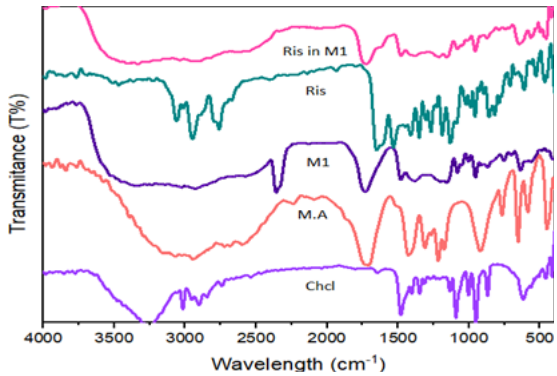

Figure 4: FTIR spectra of (—)Choline chloride, (—)Malonic acid,(—) Maline(M1), (—)Risperidone, (—) risperidone in maline(M1).

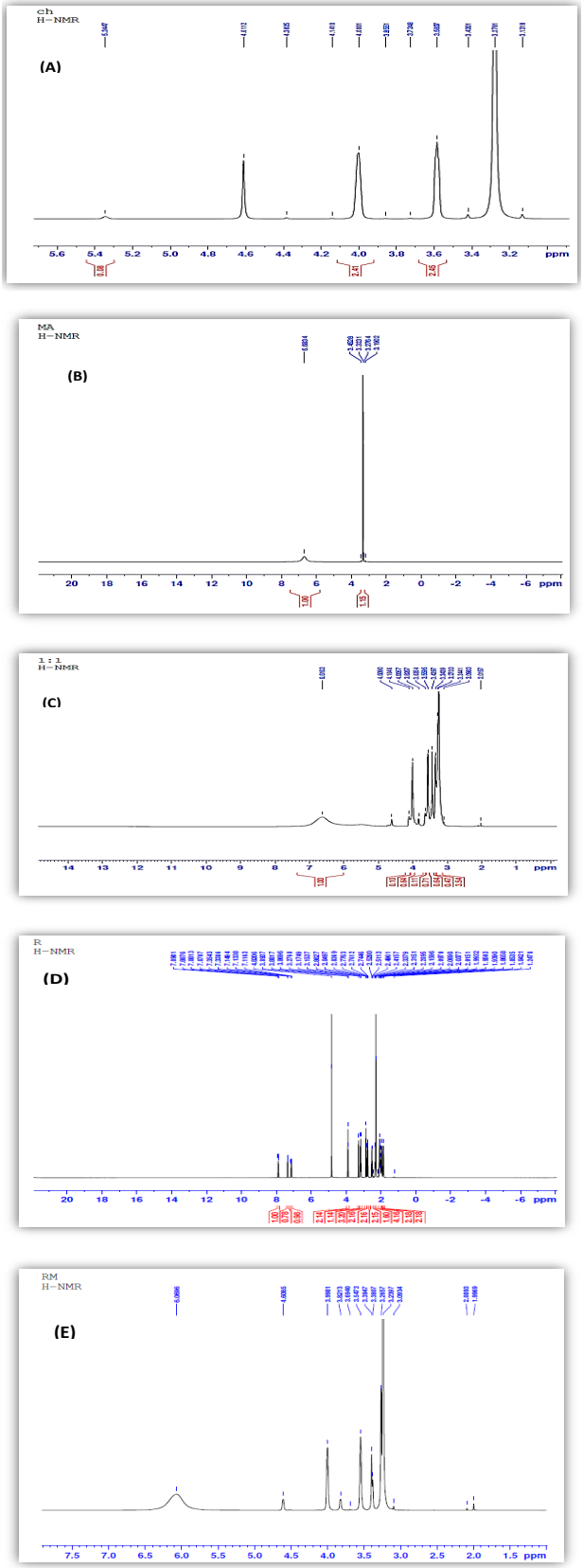

Figure 5: H^1-NMR spectroscopy of (A) choline chloride, (B) malonic acid, (C) maline (M1)1:1, Risperidone. (E) Risperidone in M1.

maline (M1), the IR spectrum demonstrated a shift in the carbonyl stretching regions of both maline (M1) and RSD. These shifts occured from 1732 to 1726 cm^{-1} for maline, and from 1651 to 1633 cm^{-1} for RSD. These shifting were due to the formation of further hydrogen bonding between the maline (M1) and RSD, which resulted in absorption at lower wave numbers, comparable behavior was observed using different DES with different drugs.[38,41,42]

Maline ^{1}H-NMR Determination

^{1}H-NMR spectroscopy is a valuable technique to study the hydrogen-bonding interactions that could occur upon maline formation. The pure compounds (choline chloride and malonic acid) along with maline (M1) were analyzed. Figure 5 shows that after maline generation, there was a chemical shift occured from 6.68 ppm in malonic acid for OH to 6.61 ppm, and from 3.27 ppm in choline chloride for OH to 3.24 ppm. This may confirm the formation of complex anions (formed between the malonic acid and the chloride anion), which interacted with the choline cation. This hydrogen bonding between the chloride anion and the acidic protons in malonic acid was suggested earlier in the computational prediction (Figure 2A). Same results was observed with other choline chloride based DESs.[43,44]

Upon adding risperidone to maline (M1), Figure 5E shows a chemical shift that appeared from 6.61 ppm in maline (M1) for OH to 6.06 ppm implying a hydrogen bonding formation at this postion.

Rheological tests

Rheological studies assist the characterization of substances by understanding their flow properties. The flow curves of the malines (M1 (1:1), M2 (1:0.9) and M3 (1:0.8)) and the viscosity-shear rate curves were estimated. During these experiments, the shear was pre-setted with a logarithmic increase and the measuring-point duration was logarithmically decreased throughout the experiment from 30 to 2 s from first to last measuring point. The flow curves of malines (Figure 6), showed that the shear stress for all malines increased with the increase in the shear rate interval. The gradual increase in shear stress does not intersect with the origin point (zero point at Y axis); therefore, all the samples (M1, M2 and M3) exhibited a non-Newtonian behavior (pseudoplastic) at room temperature conditions, as compared with imidazolium based ionic liquid.[45]

Similarly, M1 with RSD showed the same behavior of increasing the shear stress with the increase in the shear rate interval, indicating no effect of adding RSD to M1.

In general, viscosities of DEILs are higher than water, most molecular solvents and molten salts.[46] It is mainly affected by the chemical nature of the DEILs components, hydrogen bond accepter and hydrogen bond doner (HBA/HBD) molar ratio, temperature and the water content. The high viscosity of DEILs is often attributed the presence of an extensive hydrogen-bonding network between the components.[47,48] The shear rate curve (Figure 7) shows that at low shear rates (2–20s^{-1}) as the

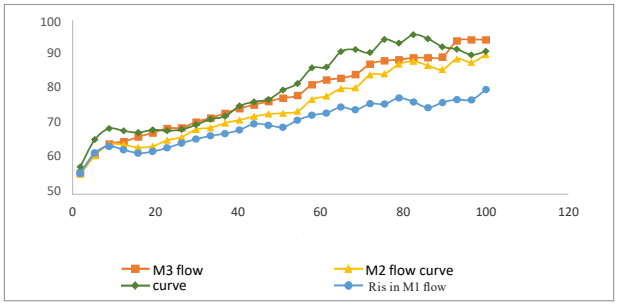

Figure 6: Flow curve of malines

shear rate increased, malines tend to illustrate a non-uniform viscosity profile, and the apparent viscosity decreased from 8.1, 6 and 6.4 to 2,1.5 and 1.8 Pa·s for M1, M2 and M3, respectively with no significant differences between them. Thus, presenting a shear-thinning property which is non-Newtonian behavior (shear rate dependent). But as the shear rate approached $20s^{-1}$ (and above) the viscosity became independent on the shear rate and a Newtonian plateau was observed at a viscosity of approximately 1.6, 1.3 and 1.7 ± 0.1 Pa·s for M1, M2 and M3, respectively. Thus, they can be considered as Newtonian fluids at the high shear rates. This possible shear thinning behavior could be attributed to the different magnitude of H-bonding leading to aggregated or sponge-like structure which starts breaking with increasing shear rate until the viscosity shows a nearly Newtonian behavior, same results observed with other ionic liquid such as 1-ehyl- 3-methylimidazolium tosylate [emim][TSO] and DES such as choline chloride:citric acid and citric acid:glucose.[45,49]

Similar result was observed for maline M1 with RSD as there was an initial viscosity decline at range from 2 to around 20 s^{-1} from 6.5 to 1.3 Pa.s, followed bya Newtonian plateau at a viscosity of 1.2 ± 0.1 Pa.s, indicating that addition of RSD has no effect on maline viscosity.

Temperature Sweep

Temperature sweep curves presented in Figure 8, express that as the temperature increased, the viscosity decreased for all malines (M1, M2, M3). This could be explained due to the weakening of the van der waals and hydrogen bond interaction upon increasing temperature. These DEILs exhibited a Newtonian behavior at high temperature, because high temperatures increase their molecules mobility

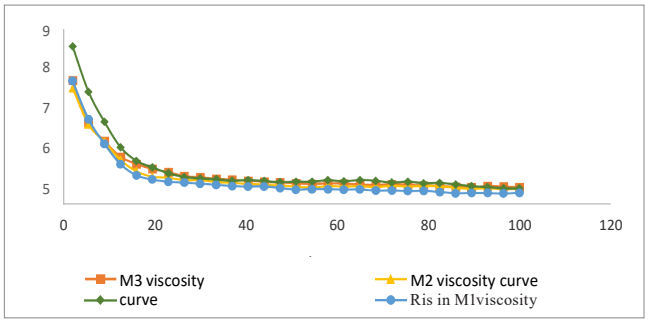

Figure 7: viscosity- shear rate curve for malines.

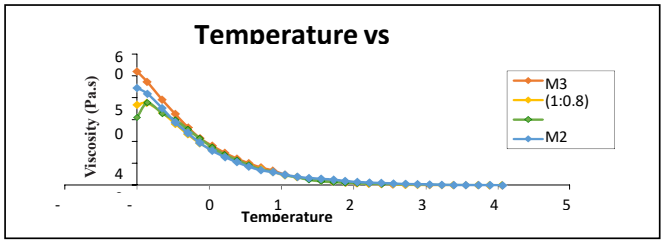

Figure 8: Temperature-sweep (temp-viscosity) relations for malines.

that eventually increases their fluidity.[44] This behavior was similar to reported DES such as ChCl:glucose and ChCl:sorbitol.[50]

Moreover, malines viscosity decrease as a function of temperature can be wellrepresented by the logarithm form of the Arrhenius equation:

$$\ln \eta = \ln \eta\infty + Ea/RT$$

η is the shear viscosity
η∞ is the viscosity at infinite temperature
Ea is the flow activation energy
R is the ideal gas
T is the absolute temperature.

Since the activation energy (Ea) is the energy that must be exceeded for the molecules to step past each other in the fluid, above Ea value, the molecules step past each other loosely, which is related to the interactions originating in the fluid, thus, indicates the high fluid viscosity.[24]

From Figure 9, the Ea/R values were determined from the slope of ln η versus 1/T(as presented in table), indicating that all malines (M1, M2 and M3) possess almost same activation energy implying that they have similar extent of intermolecular interactions within each maline.

The experimental viscosity readings were suited Arrhenius equation with satisfactory (R^2 linearity values of > 0.98). Therefore, this equation can be reliable to evaluate the DEILs viscosity.[24]

Furthermore, upon addition of RSD to maline (M1), no effect on viscosity ofmaline was observed in the Arrhenius

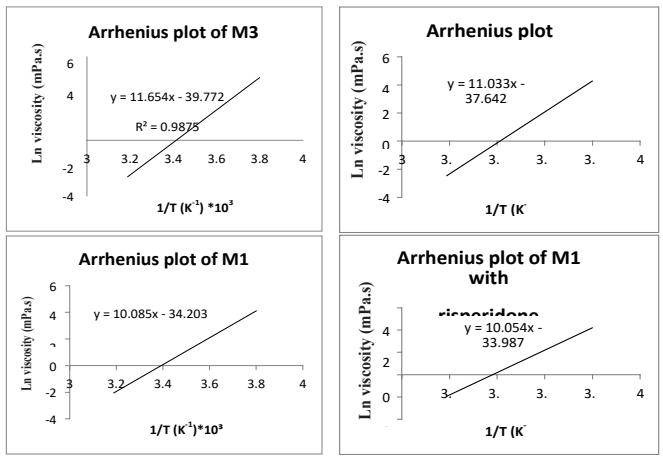

Figure 9: Arrhenius plots (The effect of temperature on the viscosity) for malines (M1, M2 and M3) and risperidone in maline (M1).

plot. This could be further evidence for the absence of effect of RSD on maline viscosity and behavior.

CONCLUSION

A deep eutectic ionic liquid based on choline chloride and malonic acid (maline) has been successfully enhanced RSD solubility. It was attributed to the hydrogen bonding that occurs between maline and RSD that was suggested theoretically by mercury program and confirmed experimentally. Such Deep Eutectic Ionic Liquid (DEIL) composed of choline chloride-malonic acid (maline) may act as alternative solvent for RSD to improve its solubility and absorption. Therefore, maline with RSD can be a potential candidate to prepare a suitable oral dosage form with reduced dose, and improved bioavailability leading to reduced side effects.

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