VOL. 11, NO. 3, FEBRUARY 2016 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

# PREDICTING THE SOLUBILITY OF PHARMACEUTICAL COMPOUND IN IONIC LIQUIDS USING COSMO-RS MODEL

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## ABSTRACT

One conventional way to address the poor solubility of drugs in order to increase their performance is to use excipients polar organic solvents. However, the use of such organic solvents has many drawbacks. They are often volatile, flammable and toxic. Pharmaceutical ingredients must be free from all such traces. So in this work, we have showed that we can use ionic liquids (ILs) as a replacement for conventional solvent in pharmaceutical industries. The solubility of Acyclovir in ILs was studied within two cations groups of ILs (Ammonium, Pyridinium) and sixteen anions using COSMOtherm-X software at room temperature and atmosphere pressure. COSMO-RS (Conductor like Screening Model for Realistic Solvents) program allows the prediction of many properties of pure fluids, fluid mixtures, and solutions. The results showed that the solubility of Acyclovir in ammonium-based ILs is relatively higher than other studied ILs. Considering ammonium salts examined in this work, tetramethylammonium-acetate [$N_{1111}$] [OAc], trimethylethylammonium-acetate [$N_{1112}$] [OAc] and dimethylethylpropylammonium-acetate [$N_{1123}$] [OAc] are excellent solvents. Due to the increasing of side alkyl chain (methyl) and proper solubility toward the drug compound, makes them suitable for further studies.

**Keywords:** COSMO-RS, acyclovir, ionic liquid, Ammonium-based cations, Tmole-X.

## INTRODUCTION

Ionic liquids (ILs) are compounds which structures can be easily modified to allow for tailoring physico-chemical properties of ILs to meet the requirements for a specific task or application [1]. Most importantly, the properties regarded as the viscosity, hydrophobicity, density and solubility of ILs can be tuned by selecting different combinations of cations and anions, to customize ILs for specific demands. They have advantageous thermal stability [2, 3] and solvent power [3, 4, 5].

Due to the high interest in the application of ILs, ternary ammonium-based ionic liquids were synthesized as a novel and economic class of ILs [6]. Recently, their low lipophilicity advantageous in terms of its environmental impact [7] in comparison with other pyridinium and pyrrolidinium-based ionic liquids was reported. As consequence they possess low toxic effect towards the organisms [8]. Ammonium-based ILs were presented as air and moisture-stable compounds with high thermal stability.

Pharmaceutical compounds are chemical substances characterized by the specific properties towards a human body. Acyclovir or Aciclovir is a guanosine analogue antiviral medication. It is primarily used for the treatment of herpes simplex virus infections, chickenpox and shingles. Other uses include: prevention cytomegalovirus infections following transplant and infections due to Epstein-Barr virus [10]. The production of these particular compounds usually generates high quantities of residues. Sheldon's E-factor, defined as the mass ratio of waste to desired product, typically reaches E factors of 25-100 for the pharmaceutical industry, the highest among the oil refining, and the bulk or fine chemicals sectors [11]. For this reason, attention is focused in the development of pharmaceutical processes in waste minimization and in assessing its current status in the broad context of green chemistry and sustainability. Particularly, the pharmaceutical industry is seeking for solutions to the problem of waste generation in chemicals' manufacture. Hazardous organic solvents may be replaced by green solvents, which are advantageous especially in terms of volatility and flammability. Ionic liquids (ILs) have proven their sustainable applications in reactions [12, 13] and separations [14] mostly due to their unique tunable properties. Furthermore, they were successfully used in the formation of emulsions in ionic liquid-in-oil systems for drug processing [15].

This work is focused on screening of several ionic liquids as alternative solvents for the drug compound (Acyclovir).

## Method

### Screening

Due to the structure of Acyclovir (Figure-1), chosen ILs must be highly polar, hydrophilic, short alkyl chain, biocompatible and most importantly, they have to be non-toxic. In this work, we used COSMO-RS model for

predicting the solubility of Acyclovir in ILs. COSMO-RS (short for Conductor like Screening Model for Real Solvents) is a quantum chemistry based equilibrium thermodynamics method with the purpose of predicting chemical potensial (μ) in liquids. It processes the screening charge density σ on the surface of molecules to calculate the chemical potential μ of each species in solution. Temperature and pressure were considered at room temperature (25°C) and 1atm respectively. Cation groups including: Ammonium, Pyridinium; and sixteen anions were chosen. Complete list of cations and anions is available in tables [1-3]. It, s necessary to mention that we chose this ILs regarding to the availability of them in the COSMOtherm-X data-base.

**Table-1.** List of pyridinium-based ILs.

| No. | Cations |
|---|---|
| 1 | Pyridinium |
| 2 | 4-methyl-n-butylpyridinium |
| 3 | 4-methyl-n-butylpyridinium |
| 4 | 1-[2-[2-(2-methoxyethoxy)ethoxy]ethyl]pyridinium |
| 5 | 1-butyl-3,5-dimethyl-pyridinium |
| 6 | 1-butyl-3,4-dimethyl-pyridinium |
| 7 | 1-butyl-3-ethyl-pyridinium |
| 8 | 1-butyl-3-methyl-pyridinium |
| 9 | 1-butyl-4-(dimethylamino)-pyridinium |
| 10 | 1-butyl-pyridinium |
| 11 | 1-ethyl-2,6-dimethylpyridinium |
| 12 | 1-ethyl-3-hydroxymethyl-pyridinium |
| 13 | 1-ethyl-3-methylpyridinium |
| 14 | 1-ethyl-pyridinium |
| 15 | 1-hexyl-3,5-dimethylpyridinium |
| 16 | 1-hexyl-3-methyl-4-(dimethylamino)pyridinium |
| 17 | 1-hexyl-3-methyl-pyridinium |
| 18 | 1-hexyl-4-(dimethylamino)pyridinium |
| 19 | 1-hexyl-4-methyl-pyridinium |
| 20 | 1-hexyl-pyridinium |
| 21 | 1-methyl-pyridinium |
| 22 | 1-octyl-pyridinium |
| 23 | 1-(phenylmethyl)pyridinium |
| 24 | 1-tert-butyl-pyridinium |
| 25 | 3-methyl-1-octyl-pyridinium |
| 26 | 4-(dimethylamino)-1-ethylpyridinium |
| 27 | 4-methyl-n-butylpyridinium |
| 28 | 4-methyl-1-octyl-pyridinium |
| 29 | n-(3-hydroxypropyl)pyridinium |
| 30 | n-(3-sulfopropyl)pyridinium |
| 31 | 4-methyl-n-butylpyridinium |

**Table-2.** List of ammonium-based ILs.

| No. | Cations |
|---|---|
| 1 | tetramethylammonium |
| 2 | bis(2-methoxyethyl)ammonium |
| 3 | butyl-diethanolammonium |
| 4 | Butyltrimethylammonium |
| 5 | Diethanolammonium |
| 6 | di-ethyl-di-isopropylammonium |
| 7 | dimethylethanolammonium |
| 8 | dodecyl-dimethyl-3-sulfopropylammonium |
| 9 | ethyl-dimethyl-2-methoxyethylammonium |
| 10 | ethyl-dimethyl-propylammonium |
| 11 | heptyltrimethylammonium |
| 12 | methyl-trioctyl-ammonium |
| 13 | n-butyl-n-propyl-n,n-dimethylammonium |
| 14 | n-hexyl-n,n,n-triethylammonium |
| 15 | octyltrimethylammonium |
| 16 | tetradecyltrimethylammonium |
| 17 | tetra-ethylammonium |
| 18 | tetra-methylammonium |
| 19 | tetra-n-butylammonium |
| 20 | tetrapropylammonium |
| 21 | tributylmethylammonium |
| 22 | triethylheptylammonium |
| 23 | triethyloctylammonium |
| 24 | triethylpentylammonium |
| 25 | trimethylethylammonium |
| 26 | hexyltrimethylammonium |
| 27 | Tetramethylammonium |

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ARPN Journal of Engineering and Applied Sciences



**Table-3.** List of anions.

| No. | Anions |
|---|---|
| 1 | Trifluoromethane-sulfonate |
| 2 | Acetate |
| 3 | Bromide |
| 4 | Chloride |
| 5 | Ethylsulfate |
| 6 | Iodide |
| 7 | Salicylate |
| 8 | Trifluoroacetate |
| 9 | Nitrate |
| 10 | Hexafluorophosphate |
| 11 | Dihydrogen-phosphate |
| 12 | Dicyanamide |
| 13 | Toluene-4-sulfonate |
| 14 | Hydrogensulfate |
| 15 | Dimethylphosphate |
| 16 | Bis((trifluoromethyl)sulfonyl)imide |

Since Acyclovir was not included in the COSMOtherm-X data-base, though we needed another software to generate the molecular structure of Acyclovir and then add it to the data base. For this purpose, we used Tmole-X software. We generated Acyclovir molecule with available various methods in software for several times and we chose the structure which had the smallest HOMO_LUMO gap. (However the gap is smaller, the result will be better, which means the molecule generated properly)

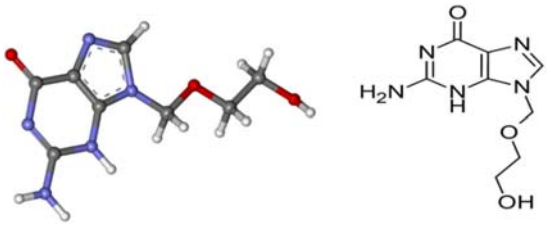
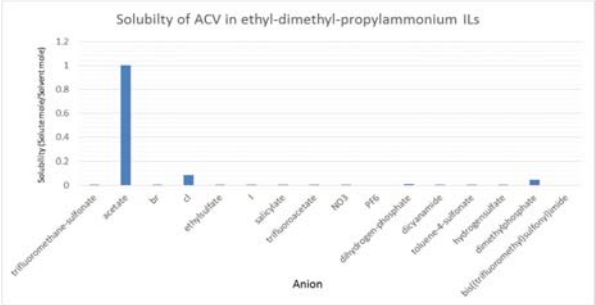


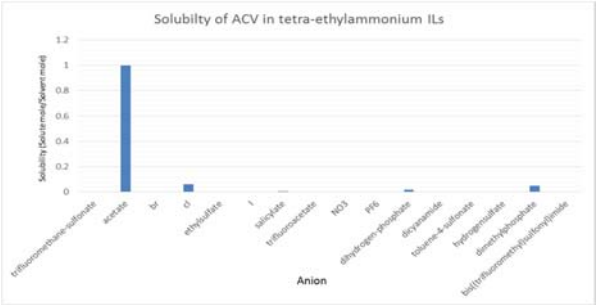

**Figure-1.** Acyclovir molecular structure.

Due to the huge amount of data, we decided to demonstrate only good results in this article. Five groups of ammonium-based ILs and three groups of pyridinium-based ILs showed better results rather than other cations. So it can be seen in the Figure. [2-3], acetate with all groups of these selevted cations gives us very good results. As it is obvious, the solubility of Acyclovir in the cation groups which they are combined with acetate is nearly to 1 mole of solute per mole of solvent. Also we got proper results with the chloride, bromide and nitrate. Certainly, special care should be paid in selection of IL because the toxicity of ILs depends significantly on their cation and the alkyl side chain. Generally, ILs synthesized with imidazolium cation is more toxic than phosphonium and ammonium based ILs. ILs with the benign cholinium cation was found to be highly biocompatible. For example, the cholinium alkanoates were less toxic than their corresponding sodium salts.

On the other hand, the toxicity of ILs increases dramatically with the increase in the length of side chain. Hence, bulky cholinium, phsophonium or ammonium based ILs with the shorter side chains on the cation core would be safer/more useful ILs for pharmaceutical use.

Accordingly, we decided to select ammonium-based ionic liquids: tetramethylammonium-acetate, trimethylethylammonium-acetate and ethyl-di-methylammonium-acetate (Figure. [4-6]) as good and proper solvents for Acyclovir because of several reasons. First, we can investigate the alkyl-chain effect in future studies. Furthermore low lipophilicity of ammonium advantageous in terms of its environmental impact [17] in comparison with other pyridinium and pyrrolidinium-based ionic liquids. Most likely, ammonium-based ILs possess low toxic effect towards the organisms [18]. Also Ammonium-based ILs were presented as air and moisture-stable compounds with high thermal stability.



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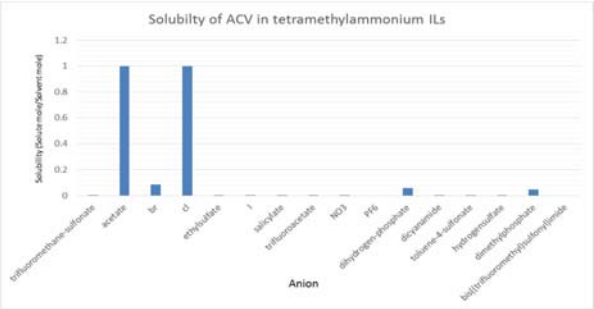
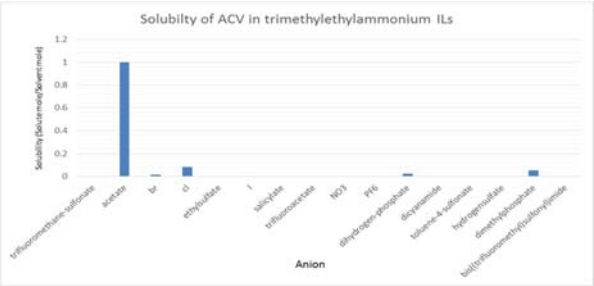


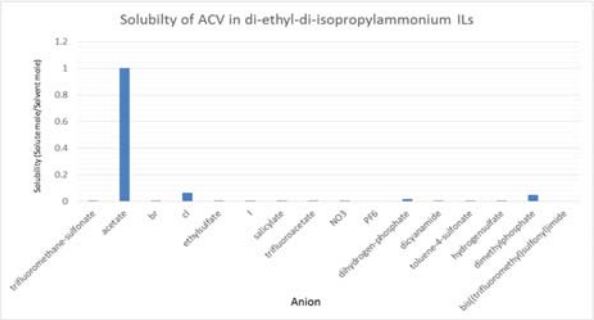
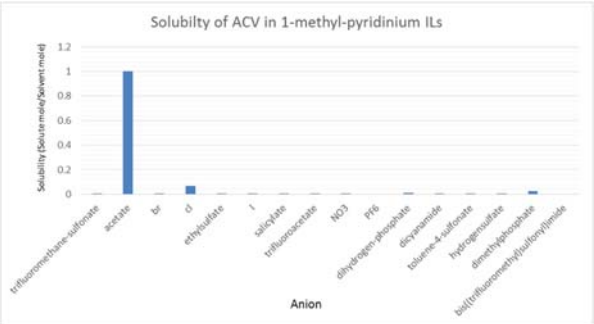
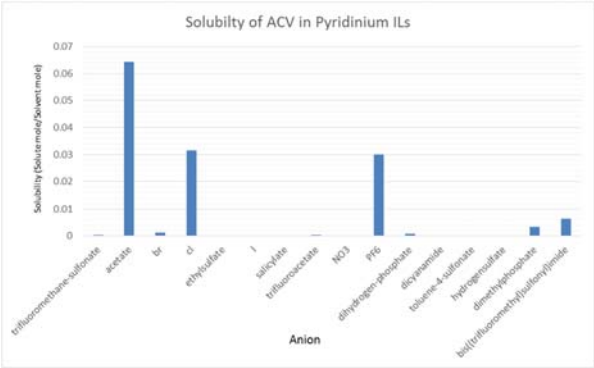




**Figure-2.** Solubility of Acyclovir in ammonium-based ILs.



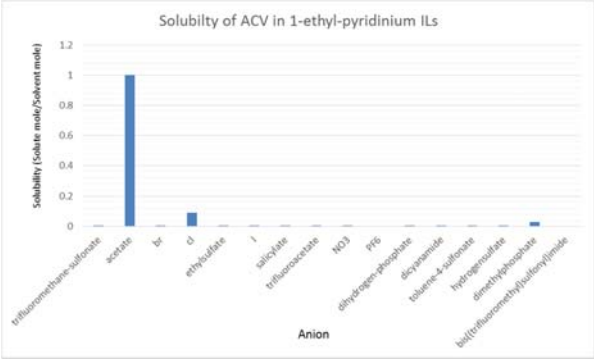




**Figure-3.** Solubility of Acyclovir in pyridinium-base ILs.

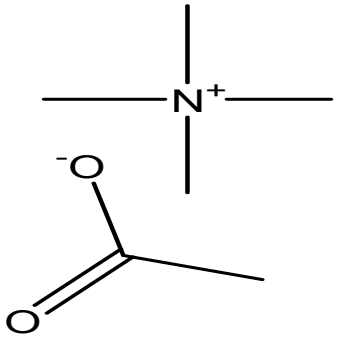


**Figure-4.** Structure of tetramethylammonium-acetate.

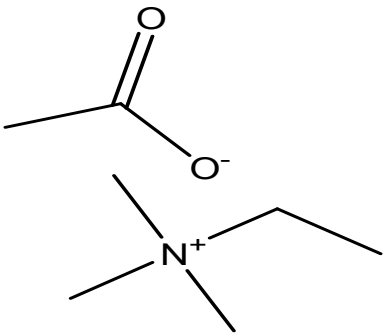


**Figure-5.** Structure of trimethylethylammonium-acetate.

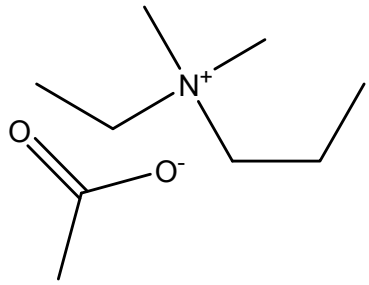


**Figure-6.** Structure of dimethylethylpropylammonium-acetate.

## CONCLUSIONS

Regarding to the conventional drug (Acyclovir) solvents problems like high toxicity, flamibility and Volatility, our data shows that we can hope in finding a novel solvent which is free from all such traces. Our promising data shows that we can use ILs as a solvent for pharmaceutical compounds. Among studied ILs, tetramethylammonium-acetate [$N_{1111}$] [OAc], trimethylethylammonium-acetate [$N_{1112}$] [OAc] and dimethylethylpropylammonium-acetate [$N_{1123}$] [OAc] showed to be adequate solvents for Acyclovir. In the future works, we are going to validate our modeling data by experimental results.

## ACKNOWLEDGEMENT

This work is financially supported by Centre of Research in Ionic Liquids (CORIL), University Teknologi PETRONAS (UTP) in Malaysia. The authors acknowledge Dr. Lethesh and all the research officers in CORIL for their helpful guidance and discussions.

## REFERENCES

[1] M. Moniruzzaman and M. Goto. 2011. "Ionic liquids: future solvents and reagents for pharmaceuticals," Journal of chemical engineering of Japan, vol. 44, pp. 370-381.

[2] C. I. Melo, R. Bogel-Łukasik, M. N. da Ponte, and E. Bogel-Łukasik, 2013. "Ammonium ionic liquids as green solvents for drugs," Fluid Phase Equilibria, vol. 338, pp. 209-216.

[3] A. D. dos Santos, A. R. Morais, C. Melo, R. Bogel-Łukasik, and E. Bogel-Łukasik, 2013. "Solubility of pharmaceutical compounds in ionic liquids," Fluid Phase Equilibria, vol. 356, pp. 18-29.

[4] V.I. Parvulescu, C. Hardacre, 2007. Chem. Rev. 107: 2615-2665.

[5] E. Bogel-Lukasik, S. Santos, R. Bogel-Lukasik, M. Nunes da Ponte. 2010. J. Supercrit. Fluids. 54: 210-217.

[6] M. Smiglak, A. Metlen, R.D. Rogers. 2007. Acc. Chem. Res. 40: 1182-1192.

[7] H. Zhao, S.Q. Xia, P.S. Ma. 2005. J. Chem. Technol. Biotechnol. 80: 1089-1096.

[8] W.L. Hough, M. Smiglak, H. Rodriguez, R.P. Swatloski, S.K. Spear, D.T. Daly, J. Pernak, J.E. Grisel, R.D. Carliss, M.D. Soutullo, J.H. Davis, R.D. Rogers. 2007. New J.Chem. 31: 1429–1436

[9] H.L. Ngo, K. LeCompte, L. Hargens, A.B. Mcewen. 2000. Thermochim. Acta. 357: 97-102.

[10] U. Domanska, R. Bogel-Lukasik. 2005. J. Phys. Chem. B. 109: 12124–12132.

[11] C. Lourenco, C.I. Melo, R. Bogel-Lukasik, E. Bogel-Lukasik. 2012. J. Chem. Eng. Data. 57: 1525–1533.

[12] E. Bogel-Lukasik, C. Lourenco, M.E. Zakrzewska, R. Bogel-Lukasik. 2010. J. Phys. Chem. B 114: 15605-15609.

[13] J.M. Crosthwaite, S.N.V.K. Aki, E.J. Maginn, J.F. Brennecke. 2004. J. Phys. Chem. B 108: 5113–5119.

[14] A. Forte, E. Bogel-Lukasik, R. Bogel-Lukasik. 2011. J. Chem. Eng. Data. 56: 2273-2279.

[15] Makowska, E. Dyoniziak, A. Siporska, J. Szydlowski. 2010. J. Phys. Chem. B. 114: 2504-2508.

[16] R. Bogel-Lukasik, D. Matkowska, E. Bogel-Lukasik, T. Hofman. 2010. Fluid Phase Equilib. 293: 168-174.

[17] J. Ranke, S. Stolte, R. Stormann, J. Arning, B. Jastorff. 2007. Chem. Rev. 107: 2183-2206.

[18] Y. Deng, P. Besse-Hoggan, P. Husson, M. Sancelme, A.M. Delort, P. Stepnowski, M. Paszkiewicz, M. Golgbiowski, M.F.C. Gomes. 2012. Chemosphere. 89: 327-333.