Neoteric Media as Tools for Process Intensification

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Abstract. Process intensification (PI) is a commonly used term in the chemical processing industry. When the concept of PI was first introduced in the late 1970s within the Imperial Chemical Industries (ICI) company, the main impetus was to reduce the processing cost without impairing the production rate. Neoteric media present as alternatives in chemical processing include gas-expanded liquids, ionic liquids, subcritical water, and combination of gas-expanded liquids and ionic liquids. The applications of neoteric media include particle engineering for improved bioavailability, controlled release of therapeutic implants, pharmaceutical formulations, extraction of natural products, nano-carriers for drug delivery, sterilisation of implants, and chemical reactions. This paper provides an overview of the use of these neoteric media.

1. Introduction
Neoteric can be defined as new or recent. Neoteric media in this context involves those media that are new and recently under extensive research such as gas-expanded liquids (GXLs), ionic liquids (ILs), subcritical water or superheated water, and combination of GXLs and ILs. The environmental and economic burdens from waste generation resulted from excessive usage of conventional solvents in chemical reactions is the main factor for the introduction and extensive investigation of neoteric media. Conventional solvents are commonly used in industries and laboratories for various applications which include synthetic chemistry, separations, coatings and cleaning. The annual amount of solvent waste produced is up to million tonnes and is generally being released to the environment [1]. Conventional solvents are mostly carcinogenic, and toxic to human health. Besides, they also cause disruption of ecosystems by depleting the ozone layer and resulting in tropospheric smog from chemical reactions. Although there are safety and controlled measures to regulate the use of the conventional solvents, the operations are generally lengthy and time consuming. Hence, neoteric media have emerged as a promising green alternative to conventional solvents in chemical processes [2].

The ideal alternative solvent media has to be able to achieve the following in comparison with the conventional solvents:

- retain the significant characteristics of the replaced conventional solvent such as polarity and solubility of reactants;
- increase or maintain process safety;
- be able to operate at similar or milder operating conditions;
- retain or increase product quality;
• be economically viable.

2. Neoteric Data

2.1. Gas-Expanded Liquids
A gas-expanded liquid (GXL) is a mixed solvent composed of a compressible gas and an organic solvent at pressure and temperature that are below the critical point of the mixed solvent. Among the compressible gases, carbon dioxide (CO$_2$) is the most commonly used in GXL studies, which is generally known as CO$_2$-expanded liquids (CXL). A CXL is able to combine benefits of both dense CO$_2$ and organic solvents, specifically good solvation abilities coupled with gas-like solubility and mass transfer properties. In addition, CXL has advantages environmentally by replacing organic solvents with CO$_2$ and being able to operate at milder operating conditions than supercritical CO$_2$ [3]. Most traditional or ganic solvents such as methanol, hexane, and dimethylformamide are able to dissolve large amounts of CO$_2$ and expand volumetrically. Hence, the mixture of organic solvents and CO$_2$ can experience significant changes in physical properties compared with the pre-expanded state [1]. The volumetric expansion is dependent on the mole fraction of CO$_2$ present in the liquid phase [3]. Gas-expanded liquids are commonly used for particle formation, chemical reactions and materials processing. There are various methods to produce fine and homogeneous particles using GXL. Fine particles find applications in pigments, food, cosmetics, and pharmaceutical compounds. The processes involving GXL or CXL for particle formation include:

• Gas Anti-Solvent (GAS)
In a GAS process, CO$_2$ is used to expand a solution of solute in organic solvent in a vessel. The solvent expansion decreases the solute solubility where its precipitation point is achieved. The associated organic solvent is then extracted by a continuous flow of CO$_2$. The resulting precipitate is then collected upon depressurization where the precipitate is separated from the expanded solvent [1, 4, 5]. A scanning electron microscopy (SEM) image of Insulin precipitated from dimethyl sulfoxide (DMSO) by the GAS process is illustrated in figure 1 [6].

![Figure 1. SEM image of Insulin precipitated from DMSO by the GAS process [6]](image)

• Precipitation with Compressed Anti-Solvent (PCA)/Aerosol Solvent Extraction System (ASES)
In the PCA process, a solution of solute in organic solvent is sprayed into a CO$_2$ pressurised vessel. Solvent expansion occurs rapidly and induces precipitation of fine solute particle. Subsequently, the remaining organic solvent is washed from the precipitated particles with CO$_2$ [1, 3]. An example of particle formation by the PCA process in which polystyrene was micronized at 225bar and 40°C is shown in figure 2 [7].
In an ASES process, a solution of solute in organic solvent is expanded and dissolved into supercritical CO$_2$. The procedure can be undertaken with CO$_2$ continuously flowing through the vessel concurrently or counter-currently with the organic solution to extract the organic solvent from the vessel [5]. Figure 3 is a SEM image of Budesonide micronized at 85bar and 40°C [8]. Figure 4 illustrates Cefonicid precipitated from DMSO at 150bar and 40°C [9]. Figure 5 is a SEM image of Rifampicin precipitated from DMSO at 90bar and 40°C [10].

**Figure 2.** SEM image of polystyrene micronized by the PCA process at 225bar and 40°C [7]

**Figure 3.** SEM image of Budesonide micronized by the ASES process at 85bar and 40°C [8]

**Figure 4.** SEM images of micronized Cefonicid precipitated from DMSO at 150bar, 40°C [9]
• Particles from Gas-Saturated Solution (PGSS)

Solid solute is melted by CO$_2$ expansion and sprayed into a vessel at atmospheric pressure via a nozzle. The rapid depressurization and cooling induce fine particle precipitation [1, 3, 11]. Figure 6 illustrates an example of cyclosporine micronized at 200bar and 25°C [11].

Apart from particle formation, GXL or specifically CO$_2$-expanded liquid (CXL) has advantages for hydrogenation reactions, such as safety, reaction performance, and catalysis reactions. A mixture of CO$_2$ and H$_2$ has been demonstrated to be as chemically effective as pure H$_2$ at the same pressure, and is a safe alternative option. In addition, accidental fires and explosions can be prevented with the presence of CO$_2$ in the mixture. The choice of expansion gas played a role in affecting the rate of hydrogenation [12]. The solvent expansion methods for H$_2$ generation are more commonly used in asymmetric hydrogenations for homogeneous catalysed reactions. It was reported that CO$_2$-expanded ILs are better at dissolving H$_2$ and H$_2$ is likely to diffuse rapidly into the liquid phase. With this combination, H$_2$ becomes more available to reactions in the IL, hence, improving rates and reaction selectivity [1].

Figure 5. SEM images of Rifampicin micronized from DMSO at 90bar, 40°C [10]

Figure 6. SEM image of cyclosporine micronized by the PGSS process at 200bar and 25°C [11]
2.2. Subcritical Water

As many chemical industries shift towards sustainability, water has become popular in many chemical and separation processes [13-15]. The strong hydrogen-bond cohesive energy between the water molecules leads to low solubility of hydrophobic compounds in water. However, the hydrogen-bond in water weakens at elevated temperature, which causes an increase of the solvating power of water for hydrophobic compounds [15]. Hence, materials such as ionic and polar compounds can be extracted using water at temperature above its ambient boiling temperature while non-polar materials can be extracted at higher temperature or at near-critical condition [16].

The term “subcritical water (SBW)” is generally used to describe water heated below its critical temperature and held at a pressure that retains its liquid state. The solvating power of subcritical water is particularly dependent on temperature and polarity. Therefore, subcritical water has increasing solvating power for various non-polar compounds with increasing temperature [15].

Subcritical water has become a popular research subject by researchers in recent years as it can be used as an alternative solvent to organic solvents for particle engineering of hydrophobic compounds, particularly Active Pharmaceutical Ingredients (APIs). The dissolution rates of APIs in the human body can be enhanced by modifying the morphology and size of APIs. Subsequently, APIs have a higher chance of reaching the targeted drug reception site. Furthermore, the efficiency of some APIs can be improved when their particle sizes are reduced, which could potentially reduce both the drug dosage required as well as the risk of adverse side effects [14]. A few examples of APIs micronized by SBW are illustrated in figure 7, figure 8 and figure 9:

**Figure 7.** Griseofulvin precipitated by SBW at 20bar: a) 140°C; b) 160°C; and c) 170°C [14]

**Figure 8.** Naproxen precipitated by SBW at 20bar: a) 140°C; and b) 170°C [14]
Figure 9. SEM images of a) raw budesonide; budesonide precipitated by SBW at b) 200°C; c) 130°C with 20% v/v ethanol fraction; d) 150°C with 20% v/v ethanol fraction; and e) 160°C with 10% v/v methanol fraction [14]

It has been observed that smaller particles are formed at higher temperatures of SBW. The morphology and size of APIs can be tailored accordingly by the working conditions such as temperature, co-solvents involvement, and concentration of the materials. Subcritical water has been proven to be a useful alternative and tunable solvent for particle engineering. It is a promising tool to move industry processes towards sustainability.

2.3. Ionic Liquids

Ionic liquids (ILs) are organic salts that are in liquid state below 100°C or at ambient temperature. As ILs have low, or negligible vapour pressure, they are good solvent alternatives in replacement of toxic organic solvents for a wide range of polar organic compounds and a few aromatic hydrocarbons [17-20]. The physical and chemical properties of ILs are tunable (by selecting the cation and anion constituents). Consequently, ILs are described as “designer solvents”. Their potential as
environmentally benign solvents to replace volatile organic solvents in chemical processes such as separation or extraction, purification, and reaction media in biochemical and chemical catalysis has been demonstrated. As ILs have low volatility, they can significantly improve the environmental impact and contamination in chemical processes. Ionic liquids are electrical conducting electrolytes, hence, they are particularly useful in electric batteries applications. Ionic liquids also find useful applications in gas handling processes as a transport medium for reactive gases, pharmaceutical production, extraction of natural and synthetic compounds, natural gas purification, carbon dioxide capture, heat transfer and storage media for solar thermal energy systems, and as dispersing agents in paints [1].

Ionic liquids are commonly used in extraction processes [21, 22]. Various types of ILs used in different extraction processes are listed in Table 1.

Table 1. Use of different types of ionic liquids in extraction of proteins, alkaloids, vitamins and antibiotics

| Extraction of Protein | Type of ILs                                | Material Extracted                          | Reference |
|-----------------------|--------------------------------------------|---------------------------------------------|-----------|
|                       | Ammonium 110                               | Albumin, lysozyme, myoglobin, trypsin       | [23]      |
|                       | 1,3-dialkylimidazolium bromide             | Albumin, trypsin, cytochrome c, y-globulin  | [24]      |
|                       | 1-butyl-3-methylimidazolium chloride, K2HPO4 | Albumin, transferrin                        | [25]      |

| Extraction of Hormones, Alkaloids and Vitamins | Type of ILs                              | Material Extracted                          | Reference |
|------------------------------------------------|------------------------------------------|---------------------------------------------|-----------|
|                                                 | 1-methyl-3-butylimidazolium chloride, K2HPO4 | Testosterone, epitestosterone               | [26]      |
|                                                 | 1,3-dialkylimidazolium chloride          | Caffeine, nicotine                          | [27]      |
|                                                 | 1-hexyl-3-methylimidazolium chloride, K2HPO4 | Vitamin B12                                 | [28]      |
|                                                 | Butyl-methyl-imidazolium chloride, K2PO4 or KH2PO4 | Quinine                                    | [29]      |

| Extraction of Antibiotics | Type of ILs                              | Material Extracted                          | Reference |
|---------------------------|------------------------------------------|---------------------------------------------|-----------|
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, NaH2PO4 | Penicillin G                             | [30]      |
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, Na2CO3 | Asazithromycin, mydecamycin                | [31]      |
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, (NH4)2SO4 | Roxithromycin                             | [32]      |
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, Na2C6H5O7 | Sulfamididine                             | [33]      |
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, Na2C6H5O7 | Acetylspramycin                           | [34]      |
|                           | 1-butyl-3-methylimidazolium tetrafluoroborate, Na2C6H5O7 | Chloramphenicol                           | [35]      |

In addition, ILs are useful for extracting metal ions. Such application usually involves addition of special ligands to increase the affinity of strongly hydrated ions to the hydrophobic ILs phase. The most commonly used ILs for this purpose are 1-alkyl-3-methylimidazolium hexafluorophosphate, tetrafluoroborate and bis (trifluoromethylsulphonyl) imide [21, 36, 37].

As for catalytic reactions, chloroaluminate (III) ionic liquids are particularly powerful solvents [17]. The Friedel-Crafts reaction is a classical synthesis reaction for commercial fragrance molecules such as Traseolide® (5-acetyl-1,1,2,6-tetramethyl-3-isopropylindane) and Tonalid® (6-acetyl-1,1,2,4,4,7-...
hexamethyltetralin) [38, 39]. Ionic liquids are also being applied to the acetylation of anthracene [17]; isomerisation of polyethylene [40], stearic acid or methyl stearate [17], and oleic acid or methyl oleate [17]; dimerization and oligomerisation of olefins [41, 42]; chlorination of alkenes to produce dihaloalkanes [43]; hydrogenation of cyclohexene [44]; esterification [17]; aromatic alkylation reactions [17]; and pharmaceutical synthesis [45].

2.4. Combination of Gas-Expanded Liquids and Ionic Liquids

Since decades ago, supercritical fluids (SCF) are popular in catalysis and reaction engineering as homogeneous reaction media. Subsequently, multiphasic systems that involve a liquid phase and a compressed supercritical or subcritical gas phase have been studied [46]. Biphasic systems comprising GXL and IL at temperature and pressure below the critical conditions have recently captured the attention of researchers for the lower investment costs as simpler equipment compared to operations in SCF. Combining GXL and IL, for example, can significantly change the viscosity of the IL rich mixture [1, 47] and improve mass transfer [48].

Generally, the solubilities of ILs in CO$_2$ are low, even at high pressures. Hence, the CO$_2$ phase is free from contamination by IL in any biphasic system that involves IL and CO$_2$. Ionic liquids have been reported to have low volumetric expansion with CO$_2$ and to behave like polymers in both solubility and volumetric expansion properties [3]. As compressed CO$_2$ reduces the viscosity of ILs, the ion mobility of the ILs is subsequently increased, which leads to higher conductivity [1, 20].

3. Conclusion

The neoteric media are under extensive research both in academia and industry. They are considered as “green solvents” and as a potential replacement for volatile organic solvents. The applications of neoteric media have been summarised in the present article. Neoteric media are believed to present advantages in current chemical processes. In fact, some have been applied commercially [2].

References

[1] Jessop, P.G. and Subramaniam, B., 2007. Gas-expanded liquids. Chem. rev., 107 (6), p.2666-2694.
[2] Welton, T., 2015, November. Solvents and sustainable chemistry. In Proc. R. Soc. A 471 (2183) p. 20150502. The Royal Society.
[3] Scurto, A.M., K. Hutchenson, and B. Subramaniam, Gas-expanded liquids: Fundamentals and applications, in ACS Symp. Ser. 2009, American Chem. Soc. J. p. 3-37.
[4] Jung, J. and M. Persut, Particle design using supercritical fluids: Literature and patent survey. The J. of Supercritical Fluids, 2001. 20 (3): p. 179-219.
[5] Pasquali, I., Bettini, R. and Giordano, F., 2006. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. European J. of Pharmaceutical Sci., 27 (4), p. 299-310.
[6] Thiering, R., Dehghani, F., Dillow, A. and Foster, N.R., 2000. Solvent effects on the controlled dense gas precipitation of model proteins. J. of Chem. Technol. and Biotechnology, 75 (1), p. 42-53.
[7] Dixon, D.J., Johnston, K.P. and Bodmeier, R.A., 1993. Polymeric materials formed by precipitation with a compressed fluid antisolvent. AIChE J., 39 (1), p.127-139.
[8] Steckel, H., Pichet, L. and Müller, B.W., 2004. Influence of process parameters in the ASES process on particle properties of budesonide for pulmonary delivery. European J. of Pharmaceutics and Biopharmaceutics, 57 (3), p.507-512.
[9] Reverchon, E. and De Marco, I., 2004. Supercritical antisolvent micronization of Cefonicid: thermodynamic interpretation of results. *The J. of Supercritical Fluids*, 31 (2), p. 207-215.

[10] Reverchon, E., De Marco, I. and Della Porta, G., 2002. Rifampicin microparticles production by supercritical antisolvent precipitation. *Int. J. of Pharmaceutics*, 243 (1), p.83-91.

[11] Tandya, A., Dehghani, F. and Foster, N.R., 2006. Micronization of cyclosporine using dense gas techniques. *The J. of Supercritical Fluids*, 37 (3), pp.272-278.

[12] Thomas, C.A., Bonilla, R.J., Huang, Y. and Jessop, P.G., 2001. Hydrogenation of carbon dioxide catalyzed by ruthenium trimethylphosphine complexes Effect of gas pressure and additives on rate in the liquid phase. *Canadian J. of Chem.*, 79 (5-6), p.719-724.

[13] Canıaz, R.O. and Erkey, C., 2014. Process intensification for heavy oil upgrading using supercritical water. *Chem. Eng. Res. and Design*, 92 (10), p.1845-1863.

[14] Carr, A.G., Mammucari, R. and Foster, N.R., 2010. Solubility, solubility modeling, and precipitation of naproxen from subcritical water solutions. *Ind. & Eng. Chem. Res.*, 49 (19), p. 9385-9393.

[15] Teoh, W.H., Mammucari, R., Vieira de Melo, S.A. and Foster, N.R., 2013. Solubility and solubility modeling of polycyclic aromatic hydrocarbons in subcritical water. *Ind. & Eng. Chem. Res.*, 52 (16), p. 5806-5814.

[16] Brunner, G., 2009. Near critical and supercritical water. Part I. Hydrolytic and hydrothermal processes. *The J. of Supercritical Fluids*, 47 (3), p.373-381.

[17] Earle, M.J. and K.R. Seddon, Ionic Liquids: Green Solvents for the Future, in Clean Solvents. 2002, American Chem. Society J. p. 10-25.

[18] Hulsbosch, J., De Vos, D.E., Binnemans, K. and Ameloot, R., 2016. Biobased Ionic Liquids: Solvents for a Green Processing Industry. *ACS Sustainable Chem. & Eng.*, 4 (6), p. 2917-2931.

[19] Marsh, K.N., Deev, A., Wu, A.C., Tran, E. and Klamt, A., 2002. Room temperature ionic liquids as replacements for conventional solvents--A review. *Korean J. of Chem. Eng.*, 19 (3), p. 357-362.

[20] Pollet, P., Davey, E.A., Ureña-Benavides, E.E., Eckert, C.A. and Liotta, C.L., 2014. Solvents for sustainable chemical processes. *Green Chem.*, 16 (3), p.1034-1055.

[21] Flieger, J., E. Grushka, and A. Czajkowska-Zelazko, 2014. Ionic liquids as solvents in separation processes. *Austin J. Anal. Pharm. Chem* 1 (2): p. 1-8.

[22] Salar-García, M.J., Ortiz-Martínez, V.M., Hernández-Fernández, F.J., de Los Ríos, A.P. and Quesada-Medina, J., 2017. Ionic liquid technology to recover volatile organic compounds (VOCs). *J. of Hazardous Mat.*, 321, p. 484-499.

[23] Dreyer, S., Salim, P. and Kragl, U., 2009. Driving forces of protein partitioning in an ionic liquid-based aqueous two-phase system. *Biochemical Eng. J.*, 46 (2), p. 176-185.

[24] Pei, Y., Wang, J., Wu, K., Xuan, X. and Lu, X., 2009. Ionic liquid-based aqueous two-phase extraction of selected proteins. *Separation and Purification Technol.*, 64 (3), p. 288-295.

[25] Du, Z., Yu, Y.L. and Wang, J.H., 2007. Extraction of Proteins from Biological Fluids by Use of an Ionic Liquid/Aqueous Two-Phase System. *Chem. - A European J.*, 13 (7), p. 2130-2137.

[26] He, C., Li, S., Liu, H., Li, K. and Liu, F., 2005. Extraction of testosterone and epitestosterone in human urine using aqueous two-phase systems of ionic liquid and salt. *J. of Chromatography A*, 1082 (2), p. 143-149.

[27] Freire, M.G., Neves, C.M., Marrucho, I.M., Lopes, J.N.C., Rebelo, L.P.N. and Coutinho, J.A., 2010. High-performance extraction of alkaloids using aqueous two-phase systems with ionic liquids. *Green Chem.*, 12 (10), p. 1715-1718.

[28] Berton, P., Monasterio, R.P. and Wuilloud, R.G., 2012. Selective extraction and determination of vitamin B 12 in urine by ionic liquid-based aqueous two-phase system prior to high-performance liquid chromatography. *Talanta*, 97, p. 521-526.

[29] Flieger, J. and Czajkowska-Żelazko, A., 2015. Aqueous two phase system based on ionic liquid for isolation of quinine from human plasma sample. *Food Chem.*, 166, p. 150-157.
[30] Qingfen, L., Xuesheng, H., Yuhong, W., Ping, Y., Hansong, X., Jiang, Y. and Huizhou, L., 2005. Extraction of penicillin G by aqueous two-phase system of [Bmim] BF4/NaH2PO4. *Chinese Sci. Bulletin*, **50** (15), p. 1582-1585.

[31] Han, J., Wang, Y., Kang, W., Li, C., Yan, Y., Pan, J. and Xie, X., 2010. Phase equilibrium and macrolide antibiotics partitioning in real water samples using a two-phase system composed of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate and an aqueous solution of an inorganic salt. *Microchimica Acta*, **169** (1-2), p. 15-22.

[32] Li, C.X., Han, J., Wang, Y., Yan, Y.S., Xu, X.H. and Pan, J.M., 2009. Extraction and mechanism investigation of trace roxithromycin in real water samples by use of ionic liquid–salt aqueous two-phase system. *Analytical Chimica Acta*, **653** (2), p. 178-183.

[33] Yu, C., Han, J., Wang, Y., Yan, Y., Hu, S., Li, Y. and Ma, C., 2011. Ionic liquid/ammonium sulfate aqueous two-phase system coupled with HPLC extraction of sulfamidimidine in real environmental water samples. *Chromatographia*, **74** (5-6), p. 407-413.

[34] Wang, Y., Han, J., Xie, X.Q. and Li, C.X., 2010. Extraction of trace acetylspiramycin in real aqueous environments using aqueous two-phase system of ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate and phosphate. *Central European J. of Chem.*, **8** (6), p. 1185-1191.

[35] Han, J., Wang, Y., Yu, C.L., Yan, Y.S. and Xie, X.Q., 2011. Extraction and determination of chloramphenicol in feed water, milk, and honey samples using an ionic liquid/sodium citrate aqueous two-phase system coupled with high-performance liquid chromatography. *Analytical and Bioanalytical Chem.*, **399** (3), p.1295-1304.

[36] Zhao, H., Xia, S. and Ma, P., 2005. Use of ionic liquids as ‘green’ solvents for extractions. *J. of Chem. Technol. and Biotechnology*, **80** (10), p.1089-1096.

[37] Zaijun, L., Junkang, L. and Xiulan, S., 2011. Ionic Liquid As Novel Solvent For Extraction And Separation In Analytical Chem. INTECH Open Access Publisher.

[38] Earle, M., Seddon, K. and Adams, C., 1998. Friedel–Crafts reactions in room temperature ionic liquids. *Chem. Communications*, (19), p. 2097-2098.

[39] Boon, J.A., Levisky, J.A., Pflug, J.L. and Wilkes, J.S., 1986. Friedel–Crafts reactions in ambient-temperature molten salts. *The J. of Organic Chem.*, **51**(4), p. 480-483.

[40] Adams, C.J., Earle, M.J. and Seddon, K.R., 2000. Catalytic cracking reactions of polyethylene to light alkanes in ionic liquids. *Green Chem.*, **2** (1), p. 21-24.

[41] Ellis, B., Keim, W. and Wasserscheid, P., 1999. Linear dimerisation of but-1-ene in biphasic mode using buffered chloroaluminate ionic liquid solvents. *Chem. Communications*, (4), p. 337-338.

[42] Chauvin, Y., Olivier, H., Wyrrvalski, C.N., Simon, L.C. and de Souza, R.F., 1997. Oligomerization of 1-butene Catalyzed by Nickel Complexes Dissolved in Organochloroaluminate Ionic Liquids. *J. of Catalysis*, **165** (2), p. 275-278.

[43] Green, L., Hemeon, I. and Singer, R.D., 2000. 1-Ethyl-3-methylimidazolium halogenoaluminate ionic liquids as reaction media for the acylative cleavage of ethers. *Tetrahedron Letters*, **41** (9), p. 1343-1346.

[44] Suarez, P.A., Dullius, J.E., Einloft, S., De Souza, R.F. and Dupont, J., 1996. The use of new ionic liquids in two-phase catalytic hydrogenation reaction by rhodium complexes. *Polyhedron*, **15**(7), p. 1217-1219.

[45] Earle, M.J., McCormac, P.B. and Seddon, K.R., 2000. The first high yield green route to a pharmaceutical in a room temperature ionic liquid. *Green Chem.*, **2**(6), p. 261-262.

[46] Hintermair, U., Leitner, W. and Jessop, P., 2010. Expanded Liquid Phases in Catalysis: Gas-expanded Liquids and Liquid–Supercritical Fluid Biphasic Systems. *Handbook of green Chem*.

[47] Blanchard, L.A., Gu, Z. and Brennecka, J.F., 2001. High-pressure phase behavior of ionic liquid/CO2 systems. *The J. of Physical Chem. B*, **105** (12), p.2437-2444.
[48] Keskin, S., Kayrak-Talay, D., Akman, U. and Hortaçsu, Ö., 2007. A review of ionic liquids towards supercritical fluid applications. *The J. of Supercritical Fluids*, 43 (1), p.150-180.