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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 organic 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].
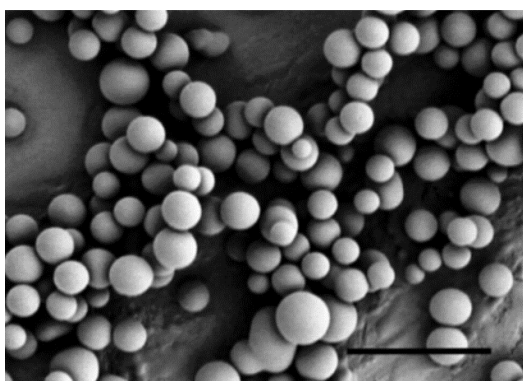

Figure 1. SEM image of Insulin precipitated from DMSO by the GAS process [6]

- 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].
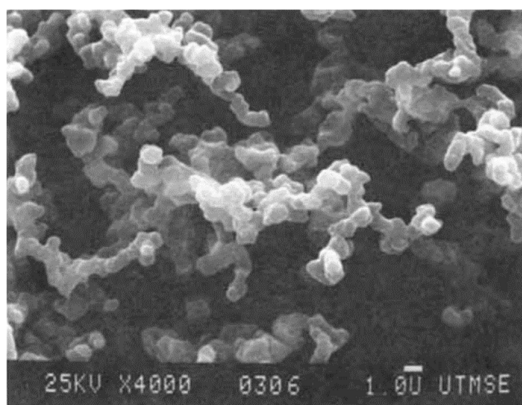

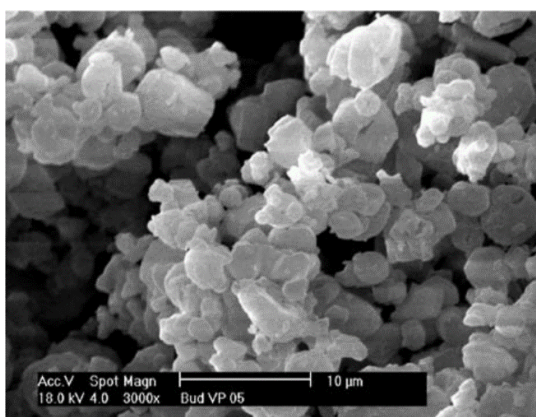**Figure 2.** SEM image of polystyrene micronized by the PCA process at 225bar and 40°C [7]

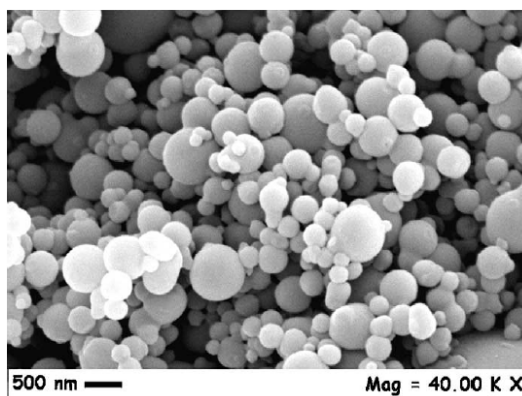**Figure 3.** SEM image of Budesonide micronized by the ASES process at 85bar and 40°C [8]

Figure 4. SEM images of micronized Cefonicid precipitated from DMSO at 150bar, 40°C [9]
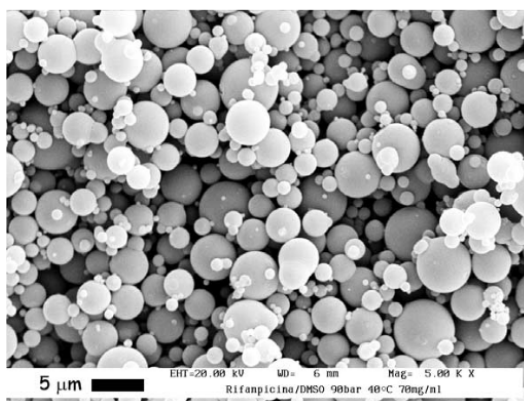
Figure 5. SEM images of Rifampicin micronized from DMSO at 90bar, 40°C [10]

- 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].
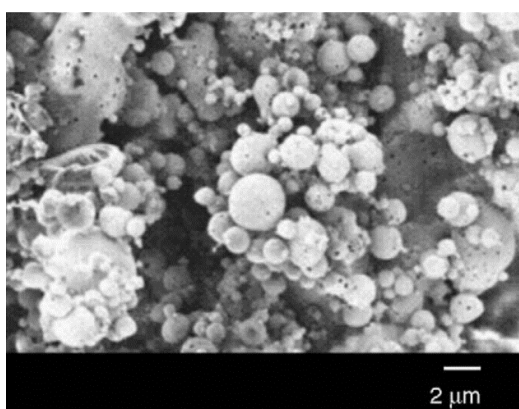

Figure 6. SEM image of cyclosporine micronized by the PGSS process at 200bar and 25°C [11]

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:
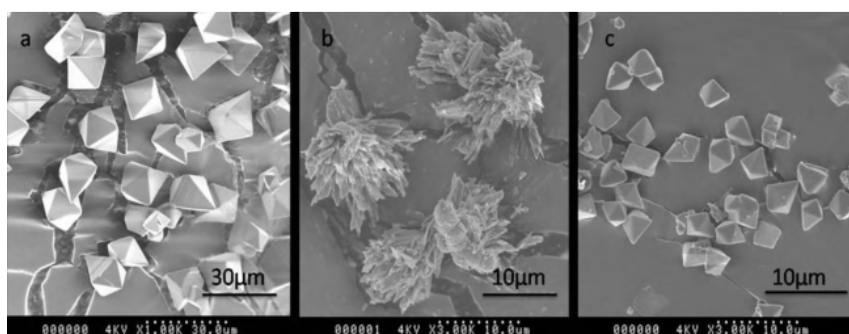

Figure 7. Griseofulvin precipitated by SBW at 20bar: a) 140°C; b) 160°C; and c) 170°C [14]
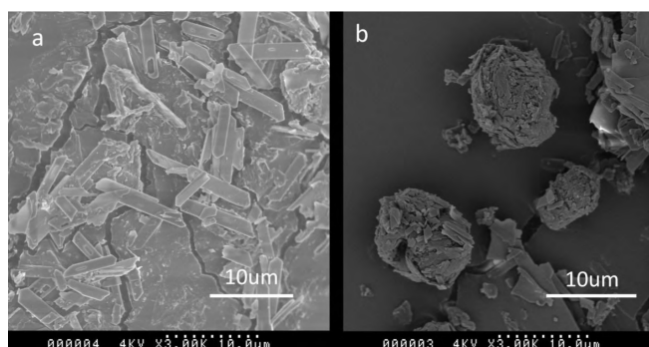

Figure 8. Naproxen precipitated by SBW at 20bar: a) 140°C; and b) 170°C [14]
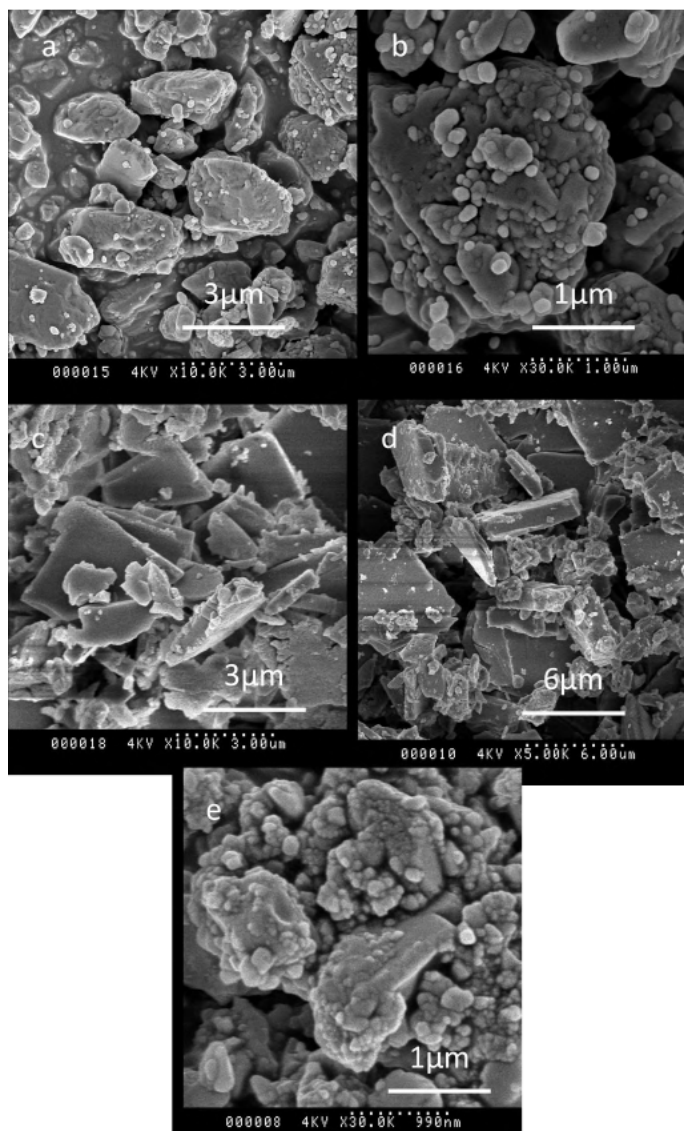
Figure 9. SEM images of a) raw budesonide; budesonide precipitated by SBW at b) 200°C; c) 130°C with 20%v/v ethanol fraction; d) 150°C with 20%v/v ethanol fraction; and e) 160°C with 10%v/v methanol fraction [14]

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**
Ammoeng 110	Albumin, lysozyme, myoglobin, trypsin	[23]
1,3-dialkylimidazolim bromide	Albumin, trypsin, cytochrome c, γ-globulin	[24]
1-butyl-3-methylimidazoli-um chloride, K2HPO4	Albumin, transferrin	[25]
Extraction of Hormones, Alkaloids and Vitamins		
Type of ILs	**Material Extracted**	**Reference**
1-methyl-3-butylimidazolium chloride, K_2HPO_4	Testosterone, epitestosterone	[26]
1,3-dialkylimidazolium chloride	Caffeine, nicotine	[27]
1-hexyl-3–methylimidazolium chloride, K_2HPO_4	Vitamin B12	[28]
Butyl-methyl-imidazolium chloride, K_3PO_4 or KH_2PO_4	Quinine	[29]
Extraction of Antibiotics		
Type of ILs	**Material Extracted**	**Reference**
1-butyl-3-methylimidazolium tetrafluoroborate, NaH_2PO_4	Penicillin G	[30]
1-butyl-3-methylimidazolium tetrafluoroborate	Asazithromycin, mydecamycin	[31]
1-butyl-3-methylimidazolium tetrafluoraborate, Na_2CO_3	Roxithromycin	[32]
1-butyl-3-methylimidazolium tetrafluoroborate, $(NH_4)_2SO_4$	Sulfadimidine	[33]
Type of ILs	**Material Extracted**	**Reference**
1-butyl-3-methylimidazolium tetrafluoraborate, NaH_2PO_4	Acetylspiramycin	[34]
1-butyl-3-methylimidazolium tetrafluoroborate, $Na_3C_6H_5O_7$	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].

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