

The Importance of Acetonitrile in the Pharmaceutical Industry and Opportunities for its Recovery from Waste

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Supporting Information

ABSTRACT: Acetonitrile is regarded as a key solvent in the pharmaceutical industry. However, the volatility in acetonitrile supply in recent years, coupled with its relatively poor environmental profile, has presented significant challenges to its use in manufacturing processes and laboratories. This study investigates the importance of acetonitrile in the pharmaceutical industry and critically examines several options for reducing the exposure of the industry to future supply problems whilst also improving its life cycle management. The physicochemical properties of acetonitrile were compared with other typical process solvents and the Conductor-like Screening Model (COSMO) surfaces and sigma profiles were used to help explain the favorable solvation behaviour of acetonitrile. Several options for the replacement or recovery and recycle of acetonitrile were critically examined in the contexts of environmental, technical, and economic feasibility. Azeotropic distillation was found to be the most likely approach to recovering acetonitrile from aqueous waste streams. Several potential breaking agents were assessed against a range of selection rules based on residue curve maps, determined using the Universal Functional Activity Coefficient (UNIFAC) method, and potential processing issues. A range of ionic liquids were screened via the predictive Conductor-like Screening Model for Realistic Solvation (COSMO-RS) approach and several promising candidates were identified. Experimental vapor–liquid equilibria studies were carried out, confirming the feasibility of ionic liquid-enhanced azeotropic distillation as a novel approach to acetonitrile recovery.

1. INTRODUCTION

Acetonitrile (MeCN) is a core solvent in the chemical industries, particularly the pharmaceutical industry, where the global demand accounts for over 70% of the total market.¹ The high popularity of MeCN is due to its excellent solvation ability with respect to a wide range of polar and nonpolar solutes, and favorable properties such as low freezing/boiling points, low viscosity, and relatively low toxicity. Several key properties of MeCN are shown in Table 1 along with similar solvents.^{2–5} Currently the pharmaceutical and fine chemical industry has two major uses of MeCN: (a) laboratory use, particularly as a mobile phase in liquid chromatography analytical techniques,⁶ and (b) as an industrial process solvent, for example, in the manufacturing of antibiotics.⁷ Due to the need for very high purity solvents in analytical techniques such as high performance liquid chromatography (HPLC), laboratories tend to use “Analar” grade MeCN, whilst industrial applications favor “technical grade” MeCN due its lower cost. In both cases, the solvent is very highly refined in terms of purity, typically >99.9% for Analar and >99.5% for technical grade.

The vast majority of MeCN is manufactured as a byproduct of acrylonitrile production. During the period 2008 to 2009, issues associated with the MeCN supply position were raised as a major concern within the pharmaceutical industry. With a limited demand for acrylonitrile as a result of the world economic downturn,⁸ the supply of MeCN was reduced significantly, probably by at least 50% in 2008, although figures are difficult to determine accurately. There was a further shortfall in 2009, and once again it was difficult to predict

where the supply would bottom out. During the shortfall period, supply costs were typically increased, peaking at 6 times the normal cost. Such volatility in price caused interruptions in the normal supply chain as a number of operators reviewed their positioning in the market. This had a major impact on the pharmaceutical industry, with drastic measures, such as stringent stock control, prioritisation of use, and sourcing solvent for intermediate suppliers, for example, being taken to mitigate their supply problems in the short term. All new sources of MeCN on the market had to undergo user requirement trials to ensure no detrimental impact on the process or product.

In addition to supply volatility, MeCN presents further challenges to its industrial use. A general solvent selection review⁹ recently concluded that there are major issues associated with MeCN use in the pharmaceutical industry such as difficulties in dealing with waste MeCN and its poor scoring with regard to life cycle management. Therefore, the recent volatility in supply of MeCN combined with environmental challenges presents the industry with a major incentive to develop new, more sustainable approaches to MeCN use. Herein is presented a review of the options for MeCN conservation in use, including a technical assessment based on experimental and predictive analysis.

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Table 1. Key properties of MeCN for use as a solvent in the pharmaceutical industry in comparison with other polar solvents²

property	MeCN	MeOH	THF	DMSO	DMF	NMP	DCM	[C ₄ mim][BF ₄]	water
MW	41.5	32.04	72.11	78.14	73.09	99.13	84.93	226.03	18.02
normal boiling point (°C)	81.6	64.50	67.0	189.0	153.0	202.0	39.7	nonvolatile	100.0
kinematic viscosity* (10 ⁶ m ² /s) at 20 °C	0.49	0.75	0.62	2.0	0.98	1.62	0.33	86 ^a	1.00
miscibility with water	misc.	misc.	misc.	misc.	misc.	misc.	immisc.	misc.	n/a
dielectric constant at 20 °C	35.94	32.66	7.58	46.45	36.7	32.20	8.93	11.7 ^b	80.10
log <i>P</i>	-0.34	-0.74	0.46	-1.35	-1.01	-0.38	1.25	-2.44 ^c	n/a
GSK SHE issue categorisation ⁹	life cycle, waste	no issue	EHS red flag	reactivity and stability	EHS red flag	EHS red flag	EHS red flag	n/a	no issue

^aReference 3. ^bReference 4. ^cReference 5.

2. WHY IS MeCN SUCH A GOOD SOLVENT?

As alluded to previously, MeCN is regarded as a good solvent because of its ability to dissolve a wide variety of fine chemical and pharmaceutical ingredients, with an acceptable environmental profile, even though a sustainable supply cannot be guaranteed. It has, therefore, tended to be a favored solvent by process chemists, although, for some manufacturing processes, its relatively high cost would be regarded as contributing unduly to the cost of production. MeCN is also relatively inert, due to the strong C–C bond which can only be hydrolysed under extreme conditions, making it an excellent reaction solvent.

The Conductor-like Screening Model (COSMO) σ -profile¹⁰ is a useful qualitative tool in explaining the solvent properties of molecules, as shown in Figure 1 for four different solvents:

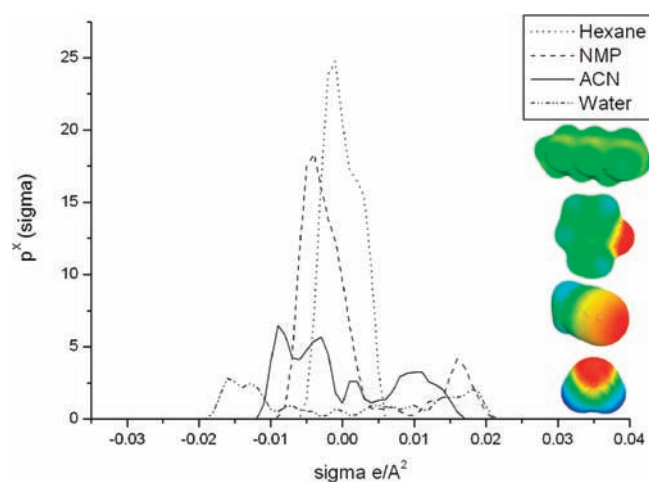


Figure 1. Comparison between the COSMO σ -profiles and σ -surfaces for water, MeCN, hexane, and *N*-methyl-2-pyrrolidone.

MeCN, water, NMP, and hexane. The σ -profile is a statistical representation of the surface charge distribution on a given molecule as determined from the quantum-based COSMO calculation,¹¹ and it is possible to use the profiles to interpret the likelihood of a molecule to form strong coulombic interactions with a wide variety of compounds. This is illustrated via comparison with a strong dielectric, such as water, and a nonpolar molecule, such as hexane. The abscissa of the profile describes the electron density of the molecular surface with positive values, indicating a high electron density and electronegativity, whilst negative values indicate low electron density, or electropositive regions. The ordinate describes the relative areas of molecular surface possessing

such electron densities. Notice the narrow profile of hexane, which is centred on the 0.00 σ value, illustrating the nonpolar nature of the compound. The σ -profile of hexane ranges from -0.5 to $+0.6$ e/A², with a maximum at -0.1 e/A² arising from the hydrogens, and a shoulder at about $+0.2$ e/A² arising from the exposed surfaces of carbon atoms. The σ -profiles of other alkanes look very similar, and mainly differ in height due to the differences in the total surface area. Thus, the moderate electron density of the functional groups can be recognised in the sigma surface plot via green colour coding. Similarly, if one considers the profile for water, the two hydrogen atoms can be identified by the peak at around -0.015 e/A², whilst the electronegative oxygen is highlighted at around $+0.015$ e/A². In the colour coding of the surfaces these regions can be recognized as deep blue and deep red, respectively. The symmetry of the water profile is very important as this implies partner contact surfaces for each area on adjacent water molecules. Symmetry indicates high molecular affinity within a pure compound and hence water “likes itself” very much, resulting in a high boiling point. Qualitatively, the σ -profile for MeCN lies amidst the two extremes mentioned. The electronegative nitrogen atom is illustrated by the peak around $+0.01$ e/A², whilst the electropositive hydrogen atoms are shown via the peaks located around 0.0075 e/A². Furthermore, the peak at approximately 0.0025 e/A² highlights the central nonpolar carbon atom of the molecule. Once again, these regions can be identified on the sigma surface plot as deep red, light blue, and green, respectively. Neglecting the obvious steric differences, both water and MeCN possess similar charge silhouettes. The possession of such a charge distribution results in balance of both moderate and more pronounced polarities highlighting the versatility of the compound to dissolve a range of polar and nonpolar media. From Table 1, the solvent with the physicochemical properties most similar to MeCN, such as dielectric, log *P* and miscibility, is *N*-methyl-2-pyrrolidone (NMP). The downside of NMP is that it has a relatively high boiling point and is difficult to recover from aqueous waste, requiring abatement largely by incineration. NMP is also a solvent whose hazard rating is under close review and tends to require more precautions to be taken as more is understood about its systemic mode of action.⁹

3. REVIEW OF THE OPTIONS FOR DEALING WITH THE MeCN SUPPLY PROBLEM

Given the challenges faced by the pharmaceutical industry as a result of MeCN supply problems in recent years, several options exist for minimising the impact of the volatile market supply. These have been drawn up within the context of the hierarchy of waste minimisation as given in EU Directive 2008/

98/EC,¹² and are summarised in Table 2. A number of hybrid options associated with the main options are also shown in

Table 2. Strategies for tackling the MeCN supply problem in the context of the waste minimisation hierarchy, technical feasibility, and economic feasibility

Strategy	EU Waste Hierarchy classification	Technical feasibility	Economic feasibility
(a) Do nothing	Disposal. Not sustainable as an option; relies on the status quo.	No technical effort required.	Volatility on price control likely to be out of control.
(b) New manufacturing routes to MeCN (internal or external)	Disposal. Supports the existing manufacture; however, not a very sustainable approach.	Processing route requires excellent SHE standards.	Difficult to compete with MeCN available from acrylonitrile process.
(c) External recycling of MeCN	Recycle. Energy and breaking solvent may be necessary.	Technical capability available at all scales, although cGMP may be an issue.	Use of toll conversion should make this relatively easy to achieve.
(d) Internal recycling of MeCN	Recycle. As above.	May require a column with a large number of contacting stages.	Process plant availability and access could be a problem.
(e) Reduce MeCN usage (utilising alternative solvents, solvent-free synthesis or alternative separation techniques)	Prevention. Longer term, removal of MeCN from processes is the most sustainable option, providing good alternatives can be established.	Culture change required, especially at the organic process synthetic chemistry level.	Longer term economic feasibility should be better.

Table 2. MeCN sent for recycle is a complex mixture of solvents and other agents. Technically, the best short-term solution to the supply shortage of MeCN is to control and reduce usage and to examine if MeCN can be recycled for use in other manufacturing sectors to free up use of 'virgin' MeCN for the pharmaceutical industry.

Recycle and reuse is by far the most popular activity for managing MeCN supply and demand. The method that has reached commercial potential is azeotropic distillation, although a number of other more novel techniques such as membrane filtration and pervaporation have had some limited success.

A multistage column will have the capability to recover MeCN using a breaking agent. However, following the guidelines¹³ issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), solvents classified as ICH Class 3 (low toxicity potential) or, perhaps, Class 2 (solvents to be limited) would be preferred. A number of current good manufacturing practice (cGMP) hurdles need to be overcome to reuse MeCN. From a sustainability point of view, the most powerful corporate social responsibility approach would be to review previous activity in MeCN supply and reuse. The waste hierarchy can be applied in order of preference: prevent, minimise, reuse, recycle, energy recovery and disposal to the MeCN supply and use. Prevention is almost impossible due to the physical property characteristics of MeCN for analytical and process use.

In terms of minimising MeCN consumption within analytical science, focus has been centred on the development of novel

HPLC methods which avoid MeCN use entirely. Alcohols such as methanol^{14–16} and ethanol¹⁷ have been proposed for a number of limited systems. In this manner the pharmaceutical industry can also moderate its laboratory use of MeCN. However, the versatility of MeCN is impossible to reproduce with other such solvents over a wide range of systems.

4. RELEVANT PREVIOUS RESEARCH ON MeCN REPLACEMENT OR RECOVERY

In the past two decades, significant efforts have been taken to investigate and develop technologies for dealing with the sustainability issues associated with MeCN use in the pharmaceutical industry. The research and technological developments can be subcategorised into four main areas: solvent substitution; recycle using azeotropic distillation; recycle using physical separations; novel manufacturing processes. For convenience, these have been summarized in Table 3, with further explanation given under the subheadings below. A further section on more recent developments using predictive approaches to identifying possible approaches to MeCN recovery is also included.

4.1. Solvent Substitution. The impact of the MeCN shortage led several researchers to investigate the replacement of MeCN in pharmaceutical HPLC applications with readily available and low cost alternatives such as methanol or ethanol. Whilst some success has been reported as described earlier, the studies are limited to a few isolated HPLC applications and the authors concede that, when available, MeCN remains the preferred mobile phase in such cases. Furthermore, due to their relatively high reactivities, methanol and ethanol would be inappropriate to replace MeCN in most applications as a reaction solvent.

There is a general movement within the SHE community to remove solvents that have specific issues; for example, in recent times, industrial use of dichloromethane has been significantly restricted in Europe due to safety concerns.¹⁸ Within industry, therefore, the view should be to largely remove MeCN from process development as early as possible to avoid any legacy issues that may occur with supply or other issues at later stages. From the point of view of the process chemist, however, this approach is seldom adopted because MeCN is such a useful reaction solvent for the reasons outlined earlier.

4.2. Azeotropic Distillation for MeCN Recovery. Several researchers have investigated the use of extractive and azeotropic distillation to achieve the recovery of MeCN from aqueous waste. Acosta-Esquijarosa et al.¹⁹ proposed a combined process of butyl-acetate solvent extraction followed by distillation. Using this technique the authors claimed an 83.4% recovery of MeCN with a purity of 98.51%. Gomez et al.²⁰ proposed novel methods using hybrid pervaporation-distillation units for MeCN recovery. This work did not cover the impact of the potential decomposition of butyl acetate to form butanol and acetic acid. From Table 4, it is possible to identify a number of azeotropes that will influence the quality of the separation of MeCN for butyl acetate e.g. BuOH/BuOAc, BuOH/HOAc and various other azeotropes if small amounts of water are formed. The azeotrope may also be broken via the use of an entrainer, i.e. an additive which shifts the thermodynamic equilibrium in such a way that the azeotrope is eliminated. Details on the processes and feasibility of such operations have been offered by Bernot et al.²¹ and Dussel and Sticklmair,²² whilst a complete overview of entrainer selection techniques for homogeneous azeotropic

Table 3. Overview of recent research reported in the literature on the replacement or recovery of MeCN

Research/Development Area	Method	Technical feasibility	Economic feasibility
(a) Solvent Substitution	Methanol HPLC ¹⁴⁻¹⁶	Only tested in a limited number of areas. More research needed to ensure management of change.	MeOH (£13.50)* < ethanol (£49.80)* < MeCN (£72.60)*
	Ethanol HPLC ¹⁷		
(b) Azeotropic Distillation for recycle	Entrainer Screening ²¹⁻²⁵	Well researched and understood however entrainer optimisation is difficult.	In line with strategy (b) and (c) of table 2
	Ionic Liquids ³³	Good reputation as azeotrope breakers however not tested for aqueous nitrile systems	Large amounts of expensive IL may be required.
	Salting Out ²⁶⁻²⁸	May present corrosion issues	Relatively low cost
	Sugaring Out ²⁹⁻³⁰	A promising and recent development area which requires further work.	Cheaper than salt
(c) Physical Separations for recycle	Pervaporation ³⁴⁻³⁶	Problems in producing commercially available and solvent stable membranes.	Low OPEX
	Pervaporation Distillation ²⁰	Problems with temperature and concentration polarisation effects.	Avoids use of entrainers which can prove difficult to purify and recycle.
(d) Novel Manufacturing Processes at Feasibility Stage	Amination of Ethanol ²⁸	Processing routes will require excellent SHE standards.	Probably only for HPLC grade
	Amoxidation of Ethane ⁴¹⁻⁴⁶		By product of natural gas thus large scale production could prove expensive.
(e) Commercial Manufacturing Processes in place	Pilot Plant ³⁸	Plant can produce around 4m ³ /week	HPLC grade only
	NITRALZ [®] ³⁹ AlzChem	In production	HPLC grade only

*HPLC grade (or equivalent) prices per litre from Sigma Aldrich.

Table 4. Azeotropic bubble points (°C at 1 atm) as predicted by UNIFAC² of solvent mixtures typically encountered in the recovery of MeCN. Shaded cells represent heterogeneous azeotropes

Solvent	H ₂ O		MeCN		Acetone		MeOH		Toluene		HOAc		MTBE		BuOAc		BuOH	
MECN	75.5																	
Acetone	56.0																	
MeOH	-	64.1	55.3															
Toluene	84.1	80.7	-	84.1														
HOAc	98.4	-	-	-	103.2													
MTBE	60.5	55.8	51.9	52.4	-	-												
BuOAc	90.7	-	-	-	-	116.6												
BuOH	92.7	-	-	-	104.7	117.7												

batch distillation has been given by Rodriguez-Donis et al.²³ The same group also investigated heterogeneous azeotropic distillation by using an acrylonitrile entrainer within aqueous MeCN batches yielding a recovery close to 80%.²⁴ However, due to the use of acrylonitrile, the coproduct of MeCN, this technique has little potential impact on MeCN shortage. To address this problem, the same researchers screened several alternative entrainers by simulating, *via* the Universal Functional Activity Coefficient (UNIFAC) method, the separation

of MeCN–water systems using heterogeneous batch distillation,²⁵ identifying two potential entrainers, hexylamine and butyl acetate, from various amines, alcohols, esters, ketones and aromatics.

“Salting out” involves the preferential solvation of salt ions in water at the expense of the tertiary component thus forcing the formation of biphasic systems. Ligette et al.²⁶ illustrated that MeCN–water phase separation can be induced at 25 °C with addition of NaCl. Building upon this, Gu and Shih²⁷ obtained a 60% recovery of MeCN from an aqueous HPLC effluent stream using a combination of phosphate salts and cooling to 4 °C. Zhang et al.²⁸ examined the extraction of platinum group metals (PGM) from aqueous solutions using NaCl–MeCN–diisopentyl sulphide to form a three-liquid-phase-system. The authors present the aforementioned as an optimum system for PGM recovery furthermore highlighting the adept ability of salts to induce phase separation in aqueous MeCN systems. However, one inconvenience when using this technique is the need to use a pH buffering agent to protect sensitive components such as enzymes, for example. The use of salts may also be problematic in that they, under certain conditions, may precipitate out of solution, leading to fouling problems in process equipment. Furthermore, the prospect of unwanted reactions with impurities and complications due to corrosion may negate the use of such additives. Such problems may be overcome via the use of dissimilar mass separating agents such as sugars. “Sugaring out” is another innovative technique which

operates in a similar fashion to salting out however the additive here is usually a monomeric sugar or disaccharide. In such systems the sugars preferentially hydrogen bond to the water molecules forcing the MeCN into a distinct phase. The concept was proven by Wang et al.²⁹ with glucose, fructose, xylose, arabinose, sucrose, and maltose; however, it was unsuccessful when using polysaccharides. When considering the partition of syringic acid and furfural the concentration of said components in the organic phase increased with sugar concentration. Glucose was the most effective of the sugars studied. Dhamole et al.³⁰ investigated the effect of glucose concentration, temperature and initial amount of MeCN on the sugaring out process to recover proteins from aqueous solutions. As a result, an 83% (v/v) MeCN enrichment of the organic phase was achieved at 6 °C and 0.012 mol fraction glucose. Sugars, however, carry the risk of microbial growth, which could present significant issues in pharmaceutical processing. Furthermore, like salts, sugars may precipitate from solution during processing and lead to fouling issues.

Traditional laboratory methods of subzero cooling (to approximately -20 °C) to crystallise out water for removal by filtration are associated with high operating costs. Hence, such techniques have arisen as a direct result of MeCN supply and demand in an aid to keep costs down by recycling the solvent internally in a cost-effective manner. That being said, the industrial applications of such techniques are highly attractive.

Ionic liquids have attracted significant attention recently as potential azeotrope breakers for a wide range of systems. They are essentially salts which are liquid at or near room temperature and are typically made up of organic cations and inorganic anions, thereby combining some of the properties of organic entrainers with those of inorganic salts. The advantages of ionic liquids include their negligible vapour pressures,³¹ making their separation and recycle of relatively straightforward, and the fact that their physical and thermodynamic properties can be tuned by varying the cation-anion combination and hydrocarbon chain lengths. It has been estimated that, theoretically, there are over 10⁶ possible ionic liquids, each with different physicochemical properties.³² Therefore, with the emergence of appropriate computational screening technologies, the potential exists to optimally design ionic liquids as azeotrope breakers for a given separations problem. Whilst the lack of extensive toxicity data for novel ionic liquids is a major barrier to their direct use in pharmaceutical processing in the short to medium term, they have potential to be used as azeotrope breakers where the MeCN is to be recycled externally to non-cGMP processes. A detailed review of the application of ionic liquids as azeotrope breakers has been recently published by Pereira et al.³³ Here the authors cite references for the use of ionic liquids as azeotrope breakers in a range of water + alcohol, water + THF, alcohol + ester, alcohol + ketone, alcohol + hydrocarbon, alcohol + halogen and aromatic + aliphatic systems, whilst also offering a comparison with published data regarding more conventional entrainers. Contrast is also made between azeotropic breaking and extractive distillation where appropriate. However, there is no published work on the use of ionic liquids for azeotropic distillation of water + nitrile systems, which is a clearly an area needing urgent attention.

4.3. Physical Separation Techniques for MeCN Recycle. As well as azeotropic distillation, other approaches have been reported for the separation of MeCN from water. For

example, Pfenning and Woermann³⁴ describe hyperfiltration experiments using phenolsulfonic acid (PSA) membranes for the separation of MeCN from water. More recent work on the use of commercial membrane based techniques for solvent dehydration has been reviewed by Hoof et al.³⁵ Whilst some promising results have been achieved, the major technological challenge in this area is producing membranes of sufficient robustness and chemical stability for commercial use.

Khayet³⁶ used the pervaporation process to successfully separate binary solutions of acetone-water, MeCN-water and ethanol-water as well as multicomponent systems using Sulzer Pervap 4060 membranes. More recently, Mandal³⁷ examined the separation of MeCN-water systems using Pervap 2202 and nanocomposite PVA-iron oxide membranes delivering up to 99% (wt) water in the permeate. Both papers suggest that this is an efficient and cost-effective separation technique. However, these methods have yet to achieve commercial viability.

4.4. Novel Manufacturing Processes. In addition to elimination of MeCN use or separation and recycle, many industrial and academic researchers have tried to bypass the MeCN supply chain problem by introducing a direct manufacturing process for MeCN. There are a number of commercial routes to synthesize MeCN and recently, Bayer³⁸ has developed a process for the manufacture of isocratic grade MeCN in a pilot plant with a capacity of around 4 m³ per week. NITRALZ³⁹ is another process for the direct synthesis where after an ammoxidation reaction, pressure swing distillation is utilized to manufacture up to 99.9% HPLC grade MeCN. Moreover several academic papers have been published highlighting novel manufacturing techniques. Zhang et al.⁴⁰ examined the amination of ethanol to MeCN over a Ni-doped Co/ γ -Al₂O₃ catalyst with MeCN being obtained with a yield >82% under the optimum reaction conditions (drying at 120 °C and calcining at 550 °C) for 720 h. Furthermore in 2011²⁸ the authors published the intrinsic kinetics of the process in a fixed bed reactor for the temperature range 613–643 K. A concise overview of previous developments in MeCN process development was also covered by the authors and shall not be reiterated here. However, one important area considers the use of ethane as a feedstock. Li and Armor^{41–45} have published a number of papers describing the ammoxidation of ethane to MeCN (eq 1) over a range of zeolite catalysts indicating that Co-ZSM-5, Co-beta, and Co-Nu-87 to be superior with ethane conversions of 38.2%, 35.3%, and 26.7% respectively.



In contrast, Rojas et al.⁴⁶ describe the ammoxidation of ethane over a niobium-modified NiO catalyst with a 19% MeCN yield. With further catalyst development and improvements in reaction yield, coupled with the increasing volatility in acetonitrile supply via the existing route, this novel approach has the potential to gain industrial importance.

4.5. Predictive Engineering Science Approach. The use of predictive tools in pharmaceutical process development is becoming increasingly important, particularly in the preliminary screening of solvent systems, to reduce costly and time-consuming experimental screening studies. Well-established group contribution approaches such as UNIFAC⁴⁷ have been found to work reasonably well when dealing with species containing the more common functional groups. However, where more “exotic” species are involved, as is often the case in pharmaceutical processes or in systems involving ionic liquids, UNIFAC cannot be applied due to the lack of group interaction

parameters for many functional groups. Quantum-based *a priori* approaches to thermodynamic prediction, such as COSMO-RS,¹⁰ have received significant attention in recent years, due to their wide-ranging applicability without the need for experimental data or group interaction parameters. Some work has been carried out recently to investigate the use of COSMO-RS for predicting the solubilities of pharmaceutical compounds⁴⁸ and ionic liquid-based systems.⁴⁹ However, despite the recent interest in COSMO-based approach for predicting phase equilibria, there has been very little attention in the literature given to its use in MeCN-containing systems.

5. CASE STUDY ON THE RECOVERY OF MeCN FROM THE MeCN–WATER–TOLUENE SYSTEM

MeCN–water–toluene is a ternary system that is typically encountered in the pharmaceutical industry and can be found in several registered processes. Initially a reaction takes place with MeCN as the reaction solvent. Separation of the organic and inorganic species is achieved by the addition of water to extract the inorganics. Since acetonitrile is fully miscible with water, it is then necessary to back-extract the acetonitrile, and any other organics, into toluene. The ternary liquid–liquid equilibria of the MeCN–water–toluene system at 20 °C is shown in Figure 2, illustrating typical Type I phase behaviour.

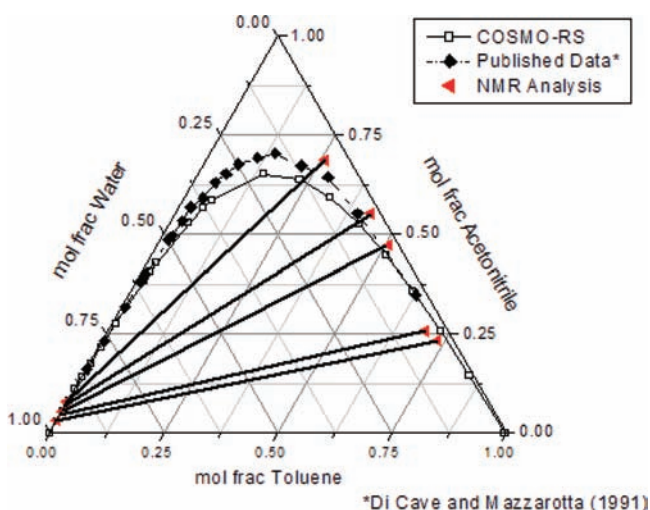


Figure 2. Liquid–liquid equilibria for the MeCN+water+toluene system at 20 °C determined from NMR analysis and COSMO-RS simulation and compared with literature values.⁵⁰

The figure also shows good agreement between data obtained in this experimental study, COSMO-RS prediction- and previously reported data⁵⁰ for the ternary system.

5.1. Distillation of the MeCN–Water–Toluene System.

Due to the formation of several azeotropes, this is a complex system from a separations perspective. The MeCN–water–toluene system has four azeotropes (see Tables 4 and 5) as follows:

- (i) MeCN and water (homogeneous)
- (ii) water and toluene (heterogeneous)
- (iii) MeCN and toluene (homogeneous)
- (iv) MeCN–water–toluene (heterogeneous)

MeCN and water form a homogeneous azeotrope when distilled. Therefore, in principle, if a breaking agent is introduced, it would be possible to continue distilling and

Table 5. Ternary azeotropes at 1 atm as predicted by UNIFAC² for mixtures involving impurity solvents typically encountered in the recovery of MeCN

components	bubble point (°C)	phase behaviour
H ₂ O–MeOH–MTBE	59.0	heterogeneous
H ₂ O–MeCN–MTBE	60.3	heterogeneous
H ₂ O–MeOH–toluene	65.4	heterogeneous
H ₂ O–MTBE–toluene	67.9	homogeneous
H ₂ O–MeCN–toluene	72.4	heterogeneous
H ₂ O–BuOH–toluene	83.1	heterogeneous
H ₂ O–HOAc–toluene	84.0	heterogeneous
H ₂ O–BuOAc–BuOH	90.1	heterogeneous

condensing until a relatively pure MeCN stream is achieved. However, this separation will also be influenced by the presence of other impurities in the feed stream. Reduction of water to extremely low levels will probably require an extra dehydration step which would be a slow and time-consuming distillation. The ternary azeotrope has the lowest boiling point at atmospheric pressure and, therefore, will come off first in a binary distillation. A number of other solvents that might be present in waste MeCN are shown in Tables 4 and 5.

5.2. Selection and Use of Azeotropic Breaking Agents.

The review of options for MeCN recovery from aqueous waste identified the use of azeotropic distillation as the approach with the greatest potential, in the short to medium term, to address problems in MeCN supply. To further examine the feasibility of this approach within the context of pharmaceutical processing, the following ICH Class 3 solvents were considered as breaking agents: acids (acetic and formic acid), ketones (acetone, methyl ethyl ketone, methyl isobutyl ketone), ethers (MTBE, diethyl ether), alcohols (1-propanol, 1-pentanol, 2-methyl-1-propanol, *n*-butanol, ethanol, 2-butanol, 2-propanol and 3-methyl-1-butanol), esters (methyl acetate, isopropyl acetate, *n*-butyl acetate, isobutyl acetate, ethyl acetate, ethyl formate, *n*-propyl acetate) and others (DMSO, *n*-pentane, *n*-heptane). Since batch distillation is the most commonly used approach to separation and purification in the pharmaceutical industry, these solvents were screened according to the practical entrainer selection rules and guidelines for heteroazeotropic batch distillation described by Skouras et al.⁵¹ and summarised below:

- Entrainer selection rule 1: “The entrainer should form a heteroazeotrope with one of the original components and/or a ternary heteroazeotrope.”
- Entrainer selection rule 2: “The vertex of the original component to be obtained in the still at steady-state should be connected with the steady-state reflux point of the entrainer-rich phase, with a distillation line in the direction of increasing temperature from the top of the column to the bottom.”
- Guideline 1: “The entrainer must not lead to the formation of maximum azeotropes with any of the original components.”
- Guideline 2: The entrainer should preferably not lead to the formation of a ternary saddle homoazeotrope.”

Two examples of the residue curve maps (RCM) generated for the (a) MeCN–water–MTBE system and (b) MeCN–water–*n*-propyl acetate system are shown in Figure 3 to illustrate the application of the entrainer selection rules. The first RCM illustrates that MTBE passes each of the entrainer rules and guidelines and, therefore, has potential for the

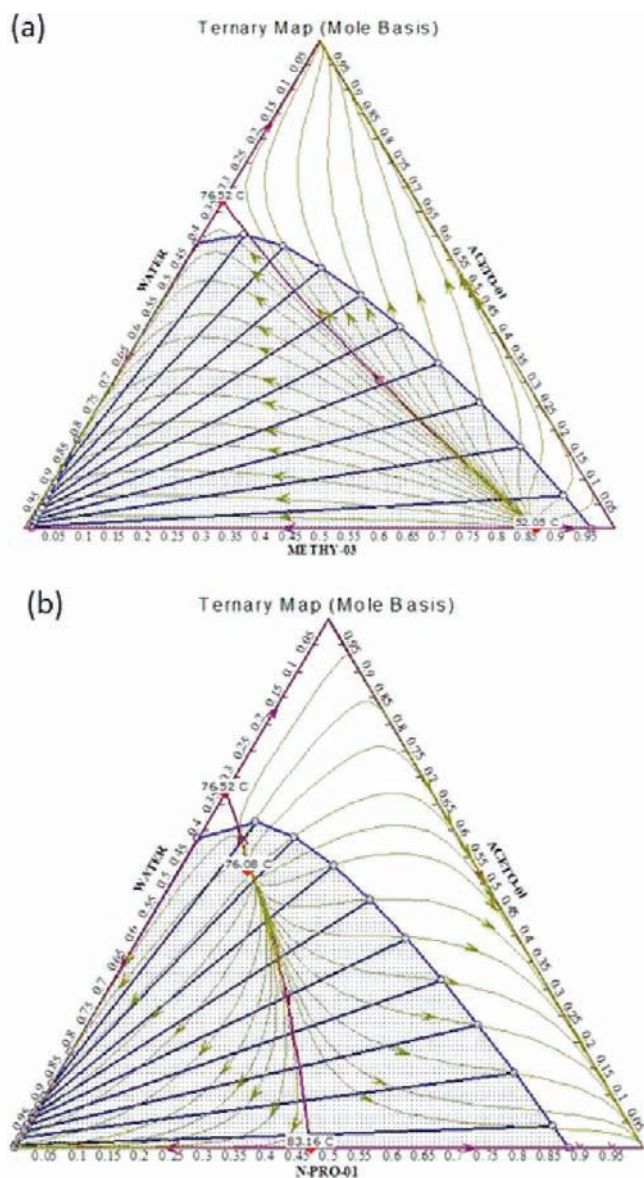
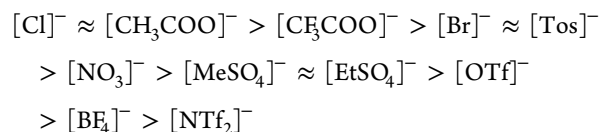


Figure 3. Residue curve maps for (a) MeCN–water–MTBE and (b) MeCN–water–*n*-propyl acetate generated using UNIFAC in Aspen Plus.

separation of MeCN and water. On the other hand, *n*-propyl acetate fails the second entrainer selection rule and is not suitable as an entrainer in this system. For brevity, the detailed results of the entrainer screening for several other ICH Class 2 and Class 3 solvents can be found in the Supporting Information. Three solvents emerged from the entrainer screening study as potential candidates: MTBE, *n*-pentane, and ethyl formate. Tables 4 and 5 provide information on the binary and ternary azeotropes for several mixtures involving water and/or MeCN to illustrate how a tactical separation of MeCN could be planned for a mixed-solvent system with MTBE and the previously investigated BuOAc. Due to the likely harsh environment in a multicomponent solvent distillation it is probably best to avoid esters due to hydrolysis. In the case of ethyl formate, under the wrong conditions carbon monoxide and hydrogen may be formed, presenting a significant safety issue. *n*-Pentane has not been considered

due to its relatively high volatility and special conditions needed to contain it.

5.3. Ionic Liquids As Alternative Azeotropic Breaking Agents. In the review of MeCN recovery options above, the use of ionic liquids as azeotropic breaking agents was identified as a previously unexplored route with significant potential. In this work, a range of 51 ionic liquids were initially screened, using the predictive COSMO-RS approach, for their ability to break the MeCN–water azeotrope. These ionic liquids were chosen as they are reasonably well characterised and can be purchased from major ionic liquid suppliers. The structures of these ionic liquids are shown in Chart 1. Initially, the vapor–liquid equilibria of the MeCN–water system were simulated at atmospheric pressure using the COSMO-RS method. In order to check the validity of the simulations, a series of VLE experiments were carried out using the apparatus shown in Figure 4, with the *x*-*y* plot for the experimental and predicted VLE shown in Figure 5. There is good agreement between the COSMO-RS model and the experimentally determined VLE values for the MeCN–water system, including the accurate detection of the azeotrope point at approximately 0.7 mol fraction MeCN and 351 K. On the basis of this validation, a series of simulations were performed on the VLE of the MeCN–water system with varying amounts of 51 different ionic liquids added. A summary of the results obtained from the predictive screening calculations is shown in Table 6. It is observed that the ability to break the MeCN–water azeotrope is strongly dependent on the anion of the ionic liquid. For example, with the series of $[\text{C}_4\text{mim}]^+$ based ionic liquids, the following general anionic trend is observed (from most effective to least effective):

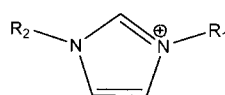
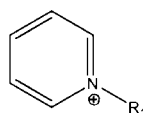
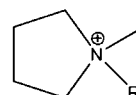
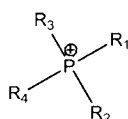
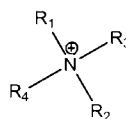


The observed order coincides with the inverse of the trend found in ionic liquid hydrophobicity, which studies⁵² have shown increases from $[\text{NTf}_2]^- > [\text{BF}_4]^- > [\text{I}]^- > [\text{Cl}]^-$. Furthermore, the decrease in azeotrope breaking ability with increasing cation length for ionic liquids based on the $[\text{BF}_4]^-$ anion mirrors the decrease in hydrophilicity with increasing chain length.⁵³ This indicates that the affinity of the ionic liquid towards water plays a crucial role in its ability to break the MeCN–water azeotrope. Comparison of the sigma surfaces for some of the anions investigated, shown in Figure 6, suggests that anions which contain areas of high electron density tend to be more suitable for breaking the azeotrope of the MeCN–water system. In addition to the ionic liquids screened, COSMO-RS was used to predict the azeotrope breaking ability of two common salts, $[\text{NH}_4][\text{Cl}]$ and $[\text{NH}_4][\text{CH}_3\text{COO}]$. The results coincide with the behaviour of ionic liquids containing the same anions however these ammonium salts can easily decompose to form HCl, ammonia or acetic acid, leading to corrosion issues.

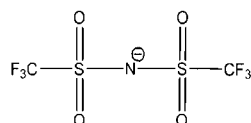
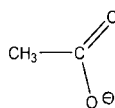
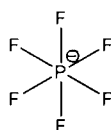
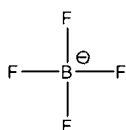
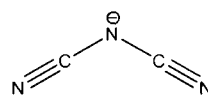
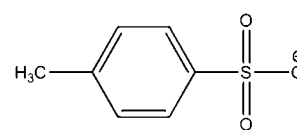
Whilst the effect of an ionic liquid on the VLE of the MeCN–water system is clearly the primary factor in determining the optimal breaking agent, cost is also a key consideration. The costs of ionic liquids vary widely, by several orders of magnitude, mainly due to their relative novelty and the lack of large scale processes for their manufacture. As an indication, relative costs based on typical laboratory prices of the various ionic liquids are also shown in Table 6, although

Chart 1. Structures of the cations and anions in the ionic liquids screened as azeotrope breakers for the MeCN–water system

Cations :

Imidazolium
[im]⁺Pyridinium
[Py]⁺Pyrrolidinium
[Pyr]⁺Phosphonium
[P]⁺Ammonium
[N]⁺

Anions :

Bis(trifluoromethylsulfonyl)imide
[NTf₂]⁻Acetate
[CH₃COO]⁻Chloride
[Cl]⁻Bromide
[Br]⁻Hexafluorophosphate
[PF₆]⁻Tetrafluoroborate
[BF₄]⁻Dicyanamide
[N(CN)₂]⁻Tosylate
[Tos]⁻

caution should be exercised since the relative bulk manufacturing costs of the ionic liquids may differ significantly from the relative laboratory prices. Other potential issues which may affect the suitability of specific ionic liquids for use as entrainers, such as high viscosity, corrosive nature or chemical instability, are also detailed in Table 6.

In order to provide some validation to the predictive screening results, three ionic liquids were chosen for experimental investigation. [P_{6,6,14}]Cl and [C₈mim]Cl were chosen due to their promising screening results, relatively low cost and ease of availability. To provide a validation at the other end of the scale, [N_{2,2,2,8}][NTf₂] was chosen as an ionic liquid which was not able to break the MeCN–water azeotrope. The VLE results are shown in Figure 5, Figure 7 and Figure 8 respectively. Due to the nonvolatile nature of ionic liquids, the VLE can be represented using a typical binary *x*–*y* plot for MeCN and water, rather than using the residue curve maps shown previously. In all cases, the results suggest that COSMO-RS is qualitatively useful in predicting the VLE data for the IL–MeCN–water systems. In the case of [C₈mim]Cl, the experimental data closely maps the VLE predictions. For [N_{2,2,2,8}][NTf₂], only one equilibrium point was experimentally determined, at a liquid phase composition of 0.9 mol fraction of MeCN, which illustrates that the azeotrope is not broken in the presence of the ionic liquid, thus corroborating the predictive screening results.

Table 7 summaries the previous discussion by identifying the leading options for the recovery of MeCN from the MeCN–water–toluene system. For recovery to take place at a manufacturing site then the best use of multipurpose plant is

required. To this end, maximising the relative volatility and simplicity of equipment in a cGMP environment, minimising the cost of breaking agent and guaranteeing process robustness will lead to the best solution. From Table 7, the best external solution is multistage distillation with or without a breaking agent whilst internally the better solution may be to use an ionic liquid in conventional batch processing equipment.

6. CONCLUSIONS

This study has highlighted the importance of MeCN in the pharmaceutical industry and illustrated the need for implementation of recovery and recycle steps to improve its environmental profile and reduce exposure to supply volatility. It has been demonstrated that it is possible and feasible to recover and recycle MeCN from aqueous waste streams and ensure that the use of this process solvent is sustainable from a corporate social responsibility viewpoint. Several Class 3 solvents have been identified as potential entrainers in the distillation of MeCN–water mixtures. A number of recommendations have been made that would be helpful to toll converters or commercial manufacturing organisations (CMO). It is unlikely that pharmaceutical grade MeCN can be manufactured and tactically recycled MeCN should be used in industries other than the pharmaceutical industry. Moreover, it has been demonstrated that the predictive science approach to the opportunities presented by MeCN sustainability allows novel technologies that are under development to be assessed quickly for viability and commercial success. In this way, the potential of ionic liquids as “designer” entrainers to enable the

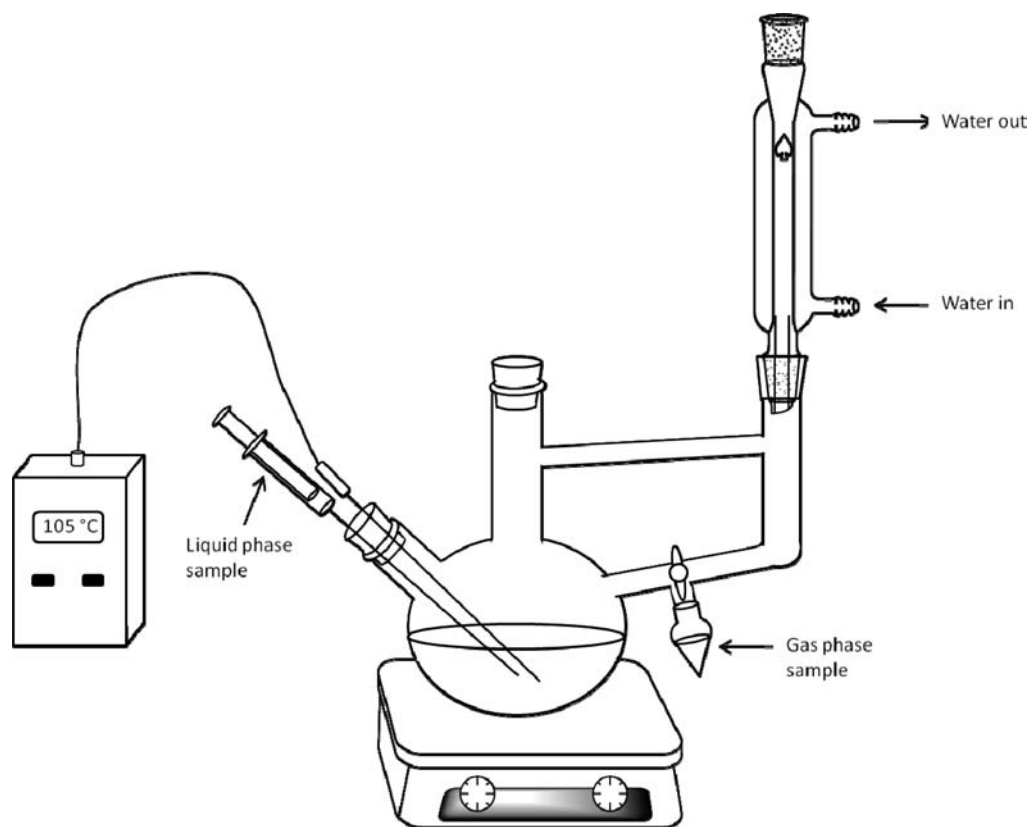


Figure 4. Experimental setup used to measure the VLE of the MeCN+water+IL system.

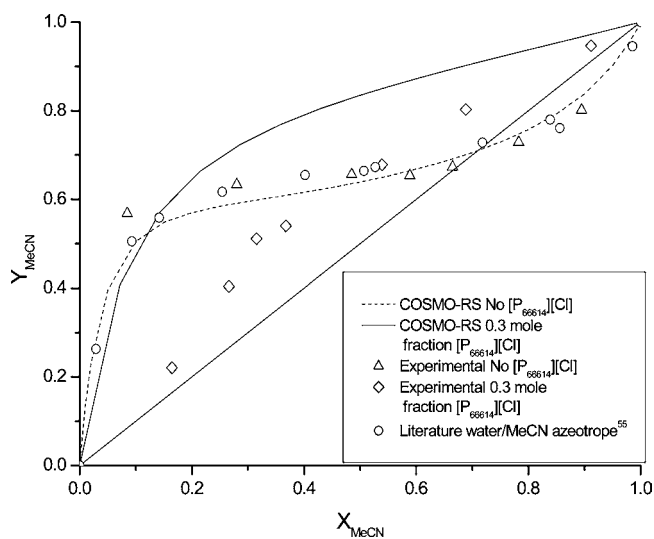


Figure 5. Experimental and COSMO-RS predicted VLE for the MeCN–water system with 0.3 mol fraction $[P_{6,6,6,14}][Cl]$ entrainer compared with the MeCN–water system with no entrainer obtained in this study and from literature.⁵⁵

recovery and recycle of MeCN has been illustrated. The need for further investigation into the relevant safety, environmental and processing implications of ionic liquids in pharmaceutical processes to establish their potential utility in the medium-to-long-term has been highlighted. Several alternative routes to manufacturing MeCN have also been highlighted and this approach merits further investigation to tackle the current supply issues associated with producing MeCN as a side product.

7. EXPERIMENTAL AND COMPUTATIONAL METHODOLOGY

MeCN and toluene used in the current study were obtained from Sigma Aldrich with purity in excess of 98%. $[P_{6,6,6,14}][Cl]$ was provided by Cytec and used as received. $[C_6mim][Cl]$ and $[C_8mim][Cl]$ were synthesised within QUILL by alkylation of 1-methylimidazole with the appropriate alkyl chloride according to previously reported procedures.⁵⁴ $[N_{2,2,2,8}][NTf_2]$ was synthesised within QUILL by the analogous reaction of triethyl amine with octyl iodide followed by the metathesis reaction with lithium bis(trifluoromethane)sulfonimide according to previously reported procedures.⁵⁴

VLE experiments were carried out to verify predicted results using the apparatus in Figure 4. This experimental setup was initially validated by measuring VLE for the MeCN–water system and comparing with data available in the literature⁵⁵ as shown in Figure 5. Furthermore, to validate the experimental setup for ionic liquid-containing systems, the VLE of the ethanol–water– $[C_6mim][Cl]$ system was measured and compared with literature data.⁵⁶ These results are shown in the Supporting Information. To obtain each point on the equilibrium curve, 50 mL of MeCN–water binary mixture with a known composition was weighed out using a Denver SI-234 balance and added to the VLE apparatus along with a stirrer bar. The flask was then placed in a heating block and fitted with a thermocouple and condenser. A 5 mL sample vial was fitted to the reflux tap to collect the condensed phase while the liquid phase was collected using a 5 mL syringe. The system was then insulated and heated to boiling point and allowed to reflux for 15 min, ensuring equilibrium was reached. After 15 min the temperature was recorded, and 2 mL samples were taken from both the liquid and condensed phases and allowed to cool. The

Table 6. Screening of several ionic liquids as entrainers for breaking the MeCN–water azeotrope

Cation	Anion	Min. mole fraction required to break azeotrope ^a	Cost of ILs £ (relative to [P ₆₆₆₁₄][Cl]) ^b	Issues
[P ₆₆₆₁₄] ⁺	[Cl] ⁻	0.1	1.0	Cheap and readily available
[C ₂ mim] ⁺	[Cl] ⁻	0.1	0.9	Solid at RT
[C ₄ mim] ⁺	[Cl] ⁻	0.1	1.3	Solid at RT
[C ₆ mim] ⁺	[Cl] ⁻	0.1	1.9	Viscous at RT
[C ₈ mim] ⁺	[Cl] ⁻	0.1	1.8	Viscous at RT
[C ₁₀ mim] ⁺	[Cl] ⁻	0.1	2.5	Viscous at RT
[C ₄ mPyrr] ⁺	[Cl] ⁻	0.1	6.9	
[C ₄ mPyrr] ⁺	[Cl] ⁻	0.1	3.8	
[N ₂₂₂₂] ⁺	[Cl] ⁻	0.1	n/a	
[N ₈₈₈₈] ⁺	[Cl] ⁻	0.3	19.8	
[C ₂ mPyrr] ⁺	[Cl] ⁻	0.1	n/a	
[C ₂ mim] ⁺	[Br] ⁻	0.2	1.4	Solid at RT
[C ₄ mim] ⁺	[Br] ⁻	0.2	1.3	
[C ₈ mim] ⁺	[Br] ⁻	0.2	n/a	
[P ₆₆₆₁₄] ⁺	[Br] ⁻	0.3	1.0	
[C ₄ mPyrr] ⁺	[Br] ⁻	0.3	3.8	
[C ₂ mim] ⁺	[CH ₃ COO] ⁻	0.1	2.0	
[C ₄ mim] ⁺	[CH ₃ COO] ⁻	0.1	1.8	
[C ₈ mim] ⁺	[CH ₃ COO] ⁻	0.1	n/a	
[C ₄ mim] ⁺	[CF ₃ COO] ⁻	0.15	n/a	
[C ₈ mim] ⁺	[CF ₃ COO] ⁻	0.15	n/a	
[N ₂₂₂₂] ⁺	[CF ₃ COO] ⁻	0.3	23.6	Corrosive
[C ₄ mPyrr] ⁺	[CF ₃ COO] ⁻	0.3	n/a	
[C ₂ mim] ⁺	[NO ₃] ⁻	0.2	n/a	Corrosive
[C ₄ mim] ⁺	[NO ₃] ⁻	0.2	9.3	
[C ₈ mim] ⁺	[NO ₃] ⁻	0.25	n/a	
[C ₄ mim] ⁺	[N(CN) ₂] ⁻	0.4	11.5	
[C ₂ mim] ⁺	[Tos] ⁻	0.2	4.1	Corrosive
[C ₄ mim] ⁺	[Tos] ⁻	0.2	8.6	Corrosive to carbon steel and copper
[C ₈ mim] ⁺	[Tos] ⁻	0.2	n/a	
[C ₂ mim] ⁺	[MeSO ₄] ⁻	0.3	2.6	Corrosive
[C ₄ mim] ⁺	[MeSO ₄] ⁻	0.3	1.0	
[C ₈ mim] ⁺	[MeSO ₄] ⁻	0.35	n/a	
[C ₂ mim] ⁺	[EtSO ₄] ⁻	0.3	0.7	Corrosive to copper and brass
[C ₄ mim] ⁺	[EtSO ₄] ⁻	0.3	n/a	
[C ₈ mim] ⁺	[EtSO ₄] ⁻			
[C ₄ mim] ⁺	[OctSO ₄] ⁻	0.5	2.9	
[C ₂ mim] ⁺	[BF ₄] ⁻	0.5	1.6	Potential to hydrolyse
[C ₄ mim] ⁺	[BF ₄] ⁻	0.6	1.0	Potential to hydrolyse
[C ₁₀ mim] ⁺	[BF ₄] ⁻	-	n/a	Potential to hydrolyse
[C ₂ mPyrr] ⁺	[BF ₄] ⁻	-	n/a	Potential to hydrolyse
[N ₂₂₂₂] ⁺	[BF ₄] ⁻	-	n/a	Potential to hydrolyse
[C ₂ mim] ⁺	[OTf] ⁻	0.6	1.6	
[C ₄ mim] ⁺	[OTf] ⁻	0.6	1.6	
[C ₂ mim] ⁺	[NTf ₂] ⁻	-	1.6	Does not break azeotrope
[C ₄ mim] ⁺	[NTf ₂] ⁻	-	1.7	Does not break azeotrope
[C ₆ mim] ⁺	[NTf ₂] ⁻	-	n/a	Does not break azeotrope
[N ₂₂₂₈] ⁺	[NTf ₂] ⁻	-	n/a	Does not break azeotrope
[NH ₄] ⁺	[CH ₃ COO] ⁻	0.1	n/a	Volatile at low pressures. Decomposes easily
[NH ₄] ⁺	[Cl] ⁻	0.1	n/a	Corrosive

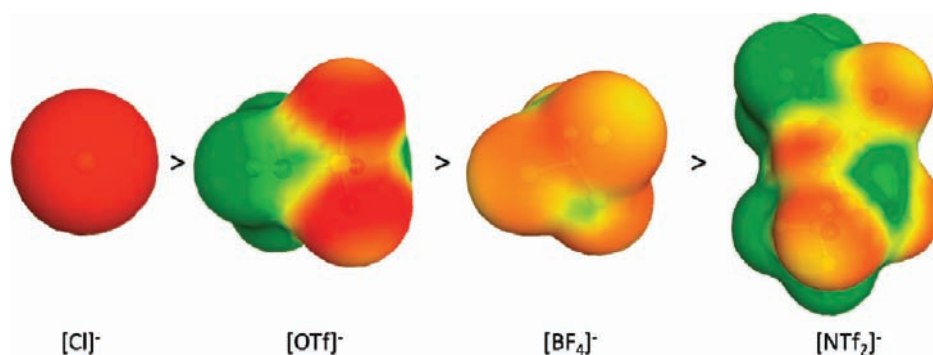


Figure 6. COSMO σ -surfaces for the anions $[\text{OTf}]^-$, $[\text{BF}_4]^-$, and $[\text{NTf}_2]^-$. The anions are ranked according to their ability to break the MeCN–water azeotrope as determined from the screening results.

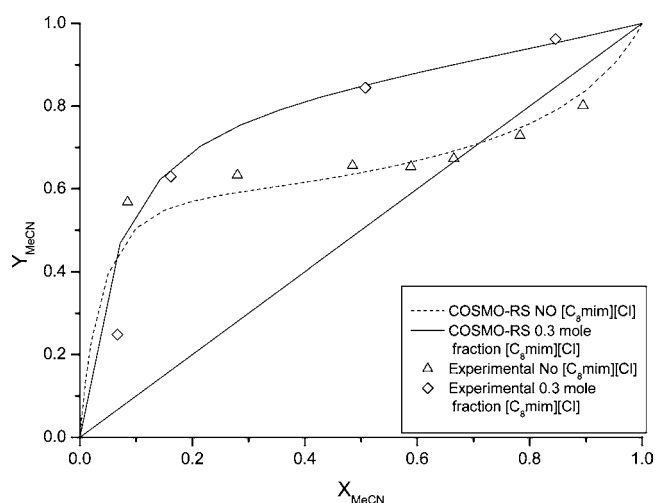


Figure 7. Experimental and COSMO-RS predicted VLE for the MeCN–water system with 0.3 mol fraction $[\text{C}_8\text{mim}][\text{Cl}]$ entrainer compared with the MeCN–water system with no entrainer.

content of the top and bottom phases were analysed by NMR using a Bruker 300 MHz spectrometer. A small amount from each sample collected was added to NMR tubes along with a deuterated DMSO probe and submitted for proton analysis.

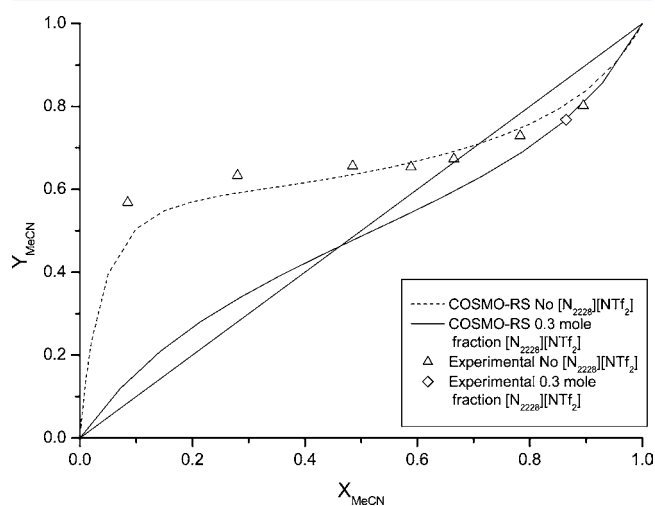


Figure 8. Experimental and COSMO-RS predicted VLE for the MeCN–water system with 0.3 mol fraction $[\text{N}_{2,2,2,8}][\text{NTf}_2]$ entrainer compared with the MeCN–water system with no entrainer.

Table 7. Performance comparison of the different methods for breaking the MeCN–water azeotrope

Breaking agent	Relative cost/per amount breaking agent	No operations	Relative volatility of MeCN*	Ease of externalisation	Robustness
None	N/A	Batch distillation	1	Easy at toll convertor	Ideally requires an excess of MeCN and > 20 theoretical plates.
BuOAc	Low	Extraction followed by batch distillation	4.1*	Easy	Yes – conventional processing with a number of vessels used. Stability of acetate may be an issue.
NaCl	Low	Separation followed by batch distillation	8.9	Easy	No – requires large quantities of salt and corrosion may be an issue.
Glucose	Medium	Separation followed by batch distillation	1.7	Medium	No – microbial growth may be an issue.
$[\text{C}_8\text{mim}][\text{CH}_3\text{COO}]$	High	Simple batch distillation	9.9	Availability of ionic liquid may be an issue in the short term	Yes – after development and may be possible to include ionic liquid in reaction phase.
$[\text{C}_8\text{mim}][\text{Cl}]$	High	Simple batch distillation	4.3	Availability of ionic liquid.	Yes – as above

* Average relative volatility of MeCN in BuOAc.

The composition of each sample was obtained by quantitative analysis of the integrated NMR spectra. The quantitative accuracy of NMR for the MeCN–water–IL system was verified by analysing a range of ternary mixtures of known composition and the uncertainty was estimated to be $\pm 5\%$.

Residue curve maps were generated using UNIFAC and UNIQUAC thermodynamic packages within Aspen Plus v. 7.2. COSMO calculations were performed on each individual ion or molecule using the TURBOMOLE⁵⁶ quantum chemistry package. Computations were carried out on the density functional theory (DFT) level, using the BP functional,^{57,58}

with a triple-valence polarised basis set (TZVP).⁵⁹ Where applicable, optimised radii⁶⁰ were used in the COSMO calculation (H = 1.30, C = 2.00, N = 1.83, O = 1.72, F = 1.72, S = 2.16, Cl = 2.05, Br = 2.16, I = 2.32); otherwise, 1.17xvdW radii were used. COSMO-RS thermodynamic predictions of VLE were generated using COSMOthermX software.

■ ASSOCIATED CONTENT

■ Supporting Information

Detailed results for entrainer screening of Class 2 and Class 3 solvents can be found in the Supporting Information spreadsheet. Also included are the experimental results for the water–ethanol–[C₆mim][Cl] system used to validate the VLE apparatus for systems containing ionic liquids. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ NOMENCLATURE

MeCN	acetonitrile
BuOH	butanol
BuOAc	butyl acetate
cGMP	current good manufacturing practice
COSMO-RS	Conductor-Like Screening Method for Realistic Solvation
DCM	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Immisc	immiscible
HOAc	acetic acid
MeOH	methanol
Misc	miscible
MTBE	methyl tertiary butyl ether <i>n</i> is the known number of protons contained within the functional group
NMP	<i>N</i> -methyl pyrrolidinone
SHE	Safety, Health and Environment
THF	tetrahydrofuran
UNIFAC	Universal Functional Activity Coefficient

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