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Ionic liquids as superior solvents for headspace gas chromatography of residual solvents with very low vapor pressure, relevant for pharmaceutical final dosage forms

Gerhard Laus[a], Max Andre[b,*], Gino Bentivoglio[a], Herwig Schottenberger[a]

[a] Faculty of Chemistry and Pharmacy, University of Innsbruck, Innrain 52a, 6020 Innsbruck, Austria
[b] Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria

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ABSTRACT

1-*n*-Butyl-3-methylimidazolium dimethyl phosphate (BMIM DMP) was identified as the most suitable ionic liquid as solvent for the headspace gas chromatographic analysis of solvents with very low vapor pressure such as dimethylsulfoxide, *N*-methylpyrrolidone, sulfolane, tetralin, and ethylene glycol in a realistic matrix of commonly used excipients (carboxymethylcellulose, magnesium stearate, guar flour, and corn starch) in pharmaceutical products. Limits of quantification and limits of detection were in the low microgram per gram range. The detection of traces of sulfolane in a real sample of tablets containing the drug cefpodoxim proxetil demonstrated the applicability of the method.

1. Introduction

The determination of residual solvents in pharmaceutical products, as required by regulatory authorities, is of tremendous importance in quality control. Recently, a database for identification of residual solvents in pharmaceuticals has been established [1,2], and a fast gas chromatography (GC) technique [3] and a two-dimensional GC method [4] have been reported. Headspace (HS) equilibration is certainly the method of choice, and it has been incorporated into the major pharmacopoeias. Thus, the influence of dimethylsulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMA), benzyl alcohol (BA), 1,3-dimethyl-2-imidazolinone (DMI) and water as matrix in headspace gas chromatography (HSGC) has been investigated [5]. As a downside, these matrices preclude the analysis of high-boiling solvents. HSGC of residual solvents in an undisclosed matrix in water–DMF has been reported [6]. Next, solid-phase microextraction of residual solvents has been employed, although from another secret model drug substance [7]. However, residual solvents with very low vapor pressures, such as *N*-methylpyrrolidone, sulfolane, ethylene glycol, and tetralin, which are 'to be limited' according to the guideline of the International Conference on Harmonization (ICH Q3C) and the U.S. Pharmacopoeia, cannot be readily analyzed by known methods [8]. The limited applicability of HSGC for very high boiling residual solvents is stated expressively in the U.S. Pharmacopoeia.

The advent of ionic liquids (ILs) in general analytical chemistry [9–11], separation techniques [12], and sample preparation [13] has brought new possibilities and opportunities. ILs are ideal for HS application due to their negligible vapor pressure. Consequently, the application of ILs for headspace single drop microextraction of organochlorine pollutants and aromatic hydrocarbons in aquatic environments [14–21], for solid-phase microextraction of organic solvents in paints using a disposable IL-coated fiber [22] and for the determination of partition coefficients [23] has been reported. The use of ionic liquids as actual solvents of samples for HSGC of reaction mixtures [24] as well as residual solvents has been demonstrated recently [25,26]. Volatile impurities in ILs, a problem either due to thermolysis or remnants from the synthesis, have been analyzed [27]. However, at least volatile remnants from the synthesis are commonly removed by vacuum treatment. The first part of the problem is readily solved by selecting a thermally stable IL.

In our previous work [25], we used task-specific ILs for the HSGC analysis of acidic, basic and neutral volatile residual impurities in pharmaceutical ingredients. The objective of the present work was the evaluation of ILs for the analysis of residual solvents in pharmaceutical matrices in general. One of the exceptional benefits of some ILs is their capability to dissolve carbohydrate-derived excipients [28–30] which are insoluble in common solvents. We have attempted to identify an IL which combines these advantageous

* Corresponding author. Fax: +43 5338 200 2463.
E-mail address: max.andre@sandoz.com (M. Andre).

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properties and to demonstrate its suitability for routine HSGC trace analysis of residual solvents in pharmaceutical products.

Among the analytes studied, only ethylene glycol was found to react with the carbohydrate matrix and, therefore, had to be converted into a non-reactive derivative.

2. Experimental

2.1. Reagents and standards

Dimethylsulfoxide (DMSO, bp 189 °C, vapor pressure 80 Pa at 25 °C [31]), 1-methyl-2-pyrrolidone (NMP, bp 202 °C, vapor pressure 45 Pa at 25 °C [32]), sulfolane (bp 285 °C, vapor pressure 9 Pa at 30 °C [33]), 1,2,3,4-tetrahydronaphthalene (tetralin, bp 207 °C, vapor pressure 52 Pa at 25 °C [34]), ethylene glycol (EG, bp 198 °C, vapor pressure 12 Pa at 25 °C [35]), 1,2-butanediol (BD, bp 196–197 °C, vapor pressure 9 Pa at 25 °C [35]), dimethylformamide (DMF), and phenylboronic acid were purchased from Aldrich. 1-Butyl-3-methylimidazolium dicyanamide, 1-allyl-3-butylimidazolium chloride, 1-butyl-3-methylimidazolium acetate, 1-ethyl-3-methylimidazolium acetate, were prepared by known methods [36] or purchased from Aldrich. The ionic liquid 1-*n*-butyl-3-methylimidazolium dimethyl phosphate (BMIM DMP) was synthesized according to two known procedures [37,38]. The ILs were stirred at 100 °C overnight under vacuum to remove volatiles prior to use and stored under argon. Biocef tablets were produced by Sandoz GmbH, Austria.

2.2. Chromatographic system

The analyses of the solutes were performed on a polysiloxane fused-silica capillary column (J&W Scientific; DB-624, length 60 m, inner diameter 0.25 mm, film thickness 1.4 μm; the 60 m column was used to assure high resolution for studying the thermal degradation of ILs). A GC 6890 (Hewlett Packard) gas chromatograph equipped with a mass selective detector HP 5973 (Hewlett Packard) was used. The carrier gas was helium (99.999% purity) with a constant pressure of 138 kPa (20 psi) and a split ratio of 25:1. The initial temperatures of the capillary column was set to 120 °C (150 °C for ethylene glycol) for 5 min. The temperature gradient was set to 15 °C/min, and the final temperature was 250 °C for 20 min. The mass selective detector used electron impact (EI^+, 70 eV) ionization and was operated in the single ion monitoring (SIM) mode, monitoring the following masses: for DMSO 63 *m*/*z*, 78 *m*/*z*; for NMP 71 *m*/*z*, 98 *m*/*z*, 99 *m*/*z*; for tetralin 104 *m*/*z*, 132 *m*/*z*; for sulfolane 56 *m*/*z*, 120 *m*/*z*; for 2-phenyl-1,3,2-dioxaborolane (derivative of EG) 147 *m*/*z*, 148 *m*/*z*; for 4-ethyl-2-phenyl-1,3,2-dioxaborolane (derivative of BD) 147 *m*/*z*, 176 *m*/*z*. The temperature of the column interface into the detector was 150 °C, and the temperature of the ion source was 230 °C. For headspace sampling, a PE TurboMatrix40 headspace autosampler (PerkinElmer) was used. The temperature of the needle, the transfer line, and the oven was set at 200 °C. The injection time was 0.1 min, pressurizing time 1 min, and the column pressure 207 kPa (30 psi).

2.3. Stability of ionic liquids

A linear temperature program from 50 to 250 °C has been applied to assess the volatile degradation products of the ILs by GC after 15 min in the absence or presence of matrix at different incubation temperatures from 160 to 200 °C. A high resolution GC–MS analysis in the scan mode was used to evaluate the interference by degradation products after incubation at 200 °C. The acetate-containing ILs exhibited very low stability. Without further quantification, the fewest interferences were observed for BMIM DMP. The corresponding chromatograms in the SIM mode showed no interfering peaks in the retention windows of the target analytes.

2.4. Matrix

As a standardized matrix of excipients, 25 mg each of magnesium stearate, carboxymethylcellulose, guar flour, and corn starch was dissolved in 1.0 mL of the IL. The matrix was only slightly soluble in the chloride- or phosphate-containing ILs at room temperature but clearly soluble at temperatures between 160 and 200 °C. The matrix was insoluble in the dicyanamide IL. Solubility in the acetate-containing ILs was not tested because their low stability already precluded their use.

2.5. Standard solutions

100 mg of each analyte (DMSO, NMP, tetralin, sulfolane) was mixed and dissolved to 10 mL with DMF. Of this stock solution, 50–350 μL (in steps of 50 μL) were diluted to 1 mL with DMF. In the same manner, standard solutions of EG and BD were prepared in DMSO. These diluted solutions were used to spike the samples with respect to the matrix mass.

2.6. Sample preparation

1.0 mL of BMIM DMP and 100 mg of matrix were added into a 20 mL headspace vial (Chromacol) and spiked with 10 μL of a solution of the analytes in DMF to the respective concentration. The vials were tightly sealed using PTFE coated silicon rubber septa and aluminum crimp caps and incubated at 200 °C for 15 min with shaking.

2.7. Derivatization procedure

1.0 mL of BMIM DMP, 100 mg of benzeneboronic acid and 100 mg of matrix were added into a 20 mL headspace vial, spiked with 10 μL of a solution of EG and BD (as internal standard) in DMSO to the respective concentration. The vials were tightly sealed and incubated at 200 °C for 15 min with shaking. Reaction conditions were optimized with respect to highest response and repeatability. Lower temperature (180 °C) gave lower response. Longer reaction time (20 min) did not change the result, whereas a reaction time of 10 min was insufficient as indicated by low response.

2.8. Sulfolane in commercially available Biocef (Sandoz) tablets

1.0 mL of BMIM DMP and 100 mg of ground tablet, containing the antibiotic cefpodoxim proxetil, were added into a 20 mL headspace vial, sealed and incubated at 200 °C for 15 min with shaking. In a second experiment, the sample was spiked with sulfolane at the limit concentration of 160 $\mu g\,g^{-1}$.

3. Results and discussion

3.1. Ionic liquids

A relevant and significant methodical advancement for practical routine analytical requirements of pharmaceutical products would be dissolving the entire final pharmaceutical dosage form in the HSGC solvent, thus avoiding tedious extractive sample preparations from tablets. Only a very limited number of ILs have been identified in the literature to be capable of dissolving carbohydrate and cellulosic [39–41] pharmaceutical excipients. Therefore, several ILs known to dissolve cellulose were evaluated for their applicability in HSGC, especially with respect to stability at high temperatures, as described in Section 2. Most ILs exhibited unacceptable levels of