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Greener organic solvents in analytical chemistry

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The paper presents the most recent advances in analytical applications of greener organic solvents. Substitution of problematic solvents with more benign organic ones is much easier than shifting to technique applying alternative solvents, such as ionic liquids or supercritical fluids. In the area of liquid chromatography greener mobile phases, much attention is given to application ethanol or acetone instead of acetonitrile. Solvent-based extractions more often include the application of bio-based organic solvents, such as esters, alcohols or terpenes. All solvents applied in analytical sciences should be carefully assessed before their application.

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Introduction

Green chemistry is the concept formulated by Paul Anastas and is aimed at the reduction of negative impact of chemical processes products and substrates [1]. Green chemistry is not branch-specific but chemistry-wide, so chemists from all areas make efforts to get closer toward sustainable chemistry. The twelve principles of green chemistry is guidance on creation of more environmentally benign chemistry. The fifth principle directly refers to solvents application and states that "The use of auxiliary substances (i.e. solvents) should be made unnecessary whenever possible and, when used, innocuous" [2].

Green analytical chemistry (GAC) [3,4] proposes many possibilities to avoid or apply alternative, more innocuous solvents. The solventless processes applied in analytical laboratories are carried mainly at the stage of sample preparation. These include application of gas extraction techniques, either in static or dynamic mode and solid-phase microextraction. Also solvents that are alternatives to traditionally used in various analytical operations contribute to GAC. Ionic liquids [5], supramolecular solvents [6], deep eutectic solvents [7] can be the basis of analytical extractions. Supercritical fluids apart from contributing to greener extractions, make the chromatographic separations less environmentally problematic than liquid chromatography usually offers [8].

However, for some processes there are no substitutes available, in other processes organic solvents are used because of analysts' habits or are applied in standard procedures or are just convenient to be used. All these reasons make phase-out of organic solvents impossible and they will be still applied in analytical laboratories. Therefore, it is required to develop procedures based on greener organic solvents. It is much easier to change organic solvent for another, greener organic solvent than switching to completely different technology introduced together with shifting to more alternative solvent (in more general sense that just organic solvent) or solventless technique.

The aim of this paper is to present the latest achievements in the area of application of green organic solvents in analytical extraction and chromatographic separation processes. As in many reviews the stress is usually put on the minimization of solvent consumption the aim of this paper is to focus on the application of greener types of solvents.

Greenness of organic solvents

Organic solvent that is preferable in terms of greenness should be characterized by favourable environmental, health and safety (EHS) properties [9]. The tools that assist in choosing green organic solvents are solvent selection guides (SSGs) [10], the most of them developed by pharmaceutical industry companies. SSGs apply EHS information about solvents and each assessed solvent is labelled with colour accompanied with phrase score — from "recommended" through "problematic" and "hazardous" to "highly hazardous". Recently, SSGs focus on including, novel solvents, usually ethers, esters or alcohols, that are not yet fully characterized in terms of various greenness criteria, but are considered green [11,12] The application of solvents in analytical chemistry is different from the needs of pharmaceutical industry. Pharmaceutical industry pays attention to solvents that are very seldom applied in analytical laboratories, like nitromethane, sulfolane, dimethyl acetamide or dimethylsulfoxide [13]. The SSG specific for analytical chemists has not been developed yet. There is a need to propose such tool that would include assessment of solvents that are applied in analytical laboratories and are usually covered by pharmaceutical SSGs. Another aspects specific for assessment of solvents used in analytical laboratories are different waste solvents disposal practices (due to different volumes of wastes) and potentially increased occupational exposure than may take place during sample handling. However, it should be stated that the parameters that should be considered during solvent greenness assessment for analytical application have not been defined yet [14]. Recent review on SSGs shows that their results to certain degree differ, suggesting that greenness of solvent is often a matter of discussion [15].

Greener organic solvents as mobile phase

Liquid chromatography requires relatively large amounts of high-purity organic solvents as mobile phase. The first step towards greening of liquid chromatography was shift from normal phase, which applied nonpolar, toxic solvents, to reversed phase chromatography. The composition of mobile phase can be successfully changed from dichloromethane containing, to isopropyl alcohol in heptane or mixture of ethyl acetate with ethanol in heptane [16]. The change to less toxic mobile phase allowed to successfully separate neutral, acidic and basic compounds.

Reversed phase liquid chromatography, typically applies methanol, ethanol, acetonitrile, acetone, ethyl acetate, tetrahydrofuran or their mixtures or their mixtures with water. Out of these solvents ethanol, acetone and ethyl acetate are preferentially applied in terms of greenness and some efforts are made to substitute with them, acetonitrile and methanol that are more toxic [17]. Acetonitrile can be also successfully substituted with propylene carbonate or its mixture with ethanol, without deterioration of chromatographic analytical results [18]. Ethanol, as one of the least toxic organic mobile phase constituents, is preferentially selected with respect to acetonitrile but its drawback is relatively high viscosity [19]. Acetone is another greener substitute in relation to acetonitrile, while their separation performance are statistically similar [20]. Much effort is also done to increase the content of water in the mobile phase. The application of polyethylene glycol stationary phase allowed for good separation of four basic and acidic compounds with water containing 0.04% of triethylamine as mobile phase [21]. Water-based mobile phase was applied in high temperature liquid chromatography with only 0.85 mL of ethanol consumed per chromatographic run for determination of sweeteners in beverages [22]. Application of mobile phase temperatures above 110 °C reduces the problem of high viscosity of water or ethanol—water mixtures.

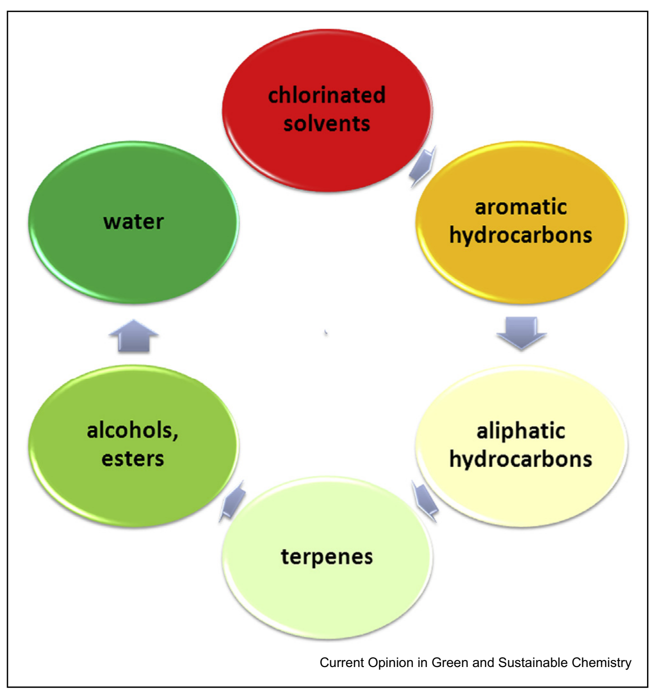
Less attention is paid to application of greener solvents in normal phase liquid chromatography as the general trend is to apply reversed phase systems, whenever possible. As some analytes, that are nonpolar and nonvolatile (i.e. lipids), are determined with normal phase systems, it is essential to work on greener solvents application in this area. Hexamethyldisiloxane, cyclopentyl methyl ether, 2-methyltetrahydrofuran and isopentyl acetate were successfully used as mobile phase constituents when liquid chromatographic separation of lipids was performed [23]. They substituted more problematic mobile phase constituents — chloroform and aliphatic hydrocarbons. This paper rises another important aspect of searches for green alternative solvents for analytical applications. D-limonene, probably like many other alternative solvents, is not available in high purity grade, what makes its potential analytical applications greatly limited, if not impossible.

The second strategy towards reduction of risks related to liquid chromatographic separations is the miniaturization of columns dimensions so that less of mobile phase is required. Combination of both approaches to reduce amount of mobile phase and to reduce its environmental impact should bring the most desired outcome.

Greener organic solvents as extraction agents

Organic solvents are historically the first choice for the extraction of various types of organic compounds from various matrices. For some examples of groups of solvents applied for analytical extractions see Figure 1.

Figure 1



The greenness preference of historically and presently applied solvents in extraction processes.

Therefore, liquid phase microextraction techniques are willingly developed. Various modes liquid-based microextraction techniques, like hollow fibre microextraction, dispersive liquid–liquid microextraction or single drop microextraction usually require only sub- millilitre amounts of organic solvents [24]. Systematic selection of solvents with simultaneous consideration of environmental and analytical performance aspects during dispersive liquid–liquid microextraction method optimization, has been recently presented [25]. Multicriteria decision analysis allows to compare the overall performance of possible binary solvents systems combinations to pick green and efficient solvents.

One of the directions in application of greener solvents for extraction processes is utilization of bio-based organic solvents, instead of petrochemistry derived ones. The basic characteristics of selected bio-based solvents is presented in the Table 1. Bio-based solvent that is relatively well described, it is obtained with many processes from many sources and its production is already implemented is (bio)ethanol [26]. The other bio-based solvents originate from chemical groups of alcohols, esters, ethers and ketones [27], all of them are characterized by potential applicability in chemical analyses. Ethyl lactate as bio-based and benign solvent was applied for the determination of total petroleum hydrocarbons in soil samples [28]. The another examples of bio-based solvents applied for purification of membrane proteins instead of chloroform–methanol mixture are 2-methyltetrahydrofuran and cyclopentylmethyl ether [29].

D-limonene is solvent derived from citrus waste as one of many valuable products [30] and it gained relatively much attention in analytical sciences. It has been used instead of more toxic and petroleum-derived toluene in water determination procedure [31]. In another procedure, aimed at microwave-assisted Soxhlet determination of fats and lipids, D-limonene was successfully replacing more environmentally problematic n-hexane [32]. Another application is extraction simvastatin from human blood plasma and large volume injection (100 μL) to HPLC [33]. Terpenes can be treated as environmentally problematic as they are characterized by high potential for tropospheric ozone formation and are relatively toxic to aquatic organisms [34].

Table 1

Characteristics of bio-based solvents applied in analytical sciences.

	D-limonene	Ethyl lactate	Glycerol
CAS Number	5989-27-5	97-64-3	56-81-5
Molecular weight [g mole^{-1}]	136	188	92
Density at 25 °C [g cm^{-3}]	0.84	1.03	1.26
Water solubility at 25 °C [mg dm^{-3}]	4.6	472800	Miscible
Vapour pressure [Pa] at 25 °C	200	160	~0
log k_{OW} at 25 °C	4.45	−0.19	−2.32
Inhalation LC_{50} [ppm]	5000	1120	n.a.
Fish LC_{50} [mg dm^{-3}]	0.72	320	5800
Oral LD_{50} [mg kg^{-1}]	4400	2500	25000
log bioconcentration factor	2.67	0.5	0.5

The applications of bio-based solvents in strictly analytical applications are still limited. More solutions have been developed in the area of bioactive substances extraction from plant material. These solutions need some more research to be applied in analytical sciences for assurance that solvent is of adequate purity and to characterize the extraction efficiency. Such solvents not yet widely applied in analytical extractions are ethyl lactate [35], glycerol, furfural, furans or cyrene and others [36]. On the other hand, to some applications bio-based reagents applied in chemical analyses do not have to be refined [37]. Similarly solvents for certain applications do not have to be ultrapure, under the condition that solvent contaminants are not analytes or interferences.

Conclusions

Developers of analytical procedures often claim that solvents used for the extraction and liquid chromatography separation processes are green but these statements are not supported by evidence. Analysts that wish to apply green solvents should follow recent trends in green or bio-based solvents development from other branches of chemistry. One of the trends that will gain more attention in analytical sciences is the application of solvents originating from renewable sources. The other trend is the shift from utilization of environmentally hazardous, non polar solvents to more green, polar ones, including esters, ethers and alcohols. There are just few solvents that can be treated as widely accepted as green but there are numerous examples of greener solvent substitutes for different analytical processes.

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