Anexa 4.

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Greening pharmaceutical applications of liquid chromatography through using propylene carbonate–ethanol mixtures instead of acetonitrile as organic modifier in the mobile phases

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ABSTRACT

Substitution of acetonitrile (ACN) as organic modifier in mobile phases for liquid chromatography by mixtures of propylene carbonate (PC) and ethanol (EtOH) may be considered a greener approach for pharmaceutical applications. Such a replacement is achievable without any major compromise in terms of elution order, chromatographic retention, efficiency and peak symmetry. This has been equally demonstrated for reverse phase (RP), ion pair formation (IP) and hydrophilic interaction liquid chromatography (HILIC) separation modes. The impact on the sensitivity induced by the replacement between these organic solvents is discussed for UV–vis and mass spectrometric detection. A comparison between Van Deemter plots obtained under elution conditions based on ACN and PC/EtOH is presented. The alternative elution modes were also compared in terms of thermodynamic parameters, such as standard enthalpy (ΔH^0) and entropic contributions to the partition between the mobile and the stationary phases, for some model compounds. Van't Hoff plots demonstrated that differences between the thermodynamic parameters are minor when shifting from ACN/water to PC/EtOH/water elution on an octadecyl chemically modified silicagel stationary phase. As long as large volume injection (LVI) of diluents non-miscible with the mobile phase is a recently developed topic having a high potential of greening the sample preparation procedures through elimination of the solvent evaporation stage, this feature was also assessed in the case of ACN replacement by PC/EtOH.

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1. Introduction

The green analytical chemistry concept was introduced in the late nineties [1]. It refers to reduction or elimination of hazardous chemicals from the analytical processes, equally obtaining high throughput and saving energy, without any compromise of the method's performance criteria [2]. Because of its widespread application in chemical analysis and use of high amounts of hazardous organic solvents, liquid chromatography (LC) is a technique with increased impact risks on environment and human health [3]. Important efforts have been paid to quantify the greenness of a wide range of organic solvents [4,5]. Most LC solvents are volatile organic compounds (VOCs) that can easily disperse in the environment, many of them exhibiting both acute and chronic toxicity. Environmental, health and safety concerns (EHS) as well as the life cycle assessment (LCA) is the main criteria used for evaluating the greenness degree of an organic solvent. EHS properties of a solvent may include its ozone depletion potential, biodegradability, toxicity and flammability [6]. Two main directions are currently explored for transforming chromatography in a green approach [7]: (a) reduction of solvent consumption through reducing columns internal diameters (from analytical to narrow or even micro bore ranges) and particle sizes (from 5 to 3 or even sub-2 μm)[8,9]; (b) replacement of acetonitrile and/or methanol in the mobile phases by less harmful and environmental friendly alternatives such as water [10], ethanol or *iso*-propanol [11], and carbon dioxide (either in sub-critical or supercritical states)[12,13]. Propylene carbonate (R,S-4-methyl-1,3-dioxolan-2-one) is a carbonate ester derived from propylene glycol, synthesized by means of more or less green processes [14–17], often used as a polar aprotic solvent in analytical chemistry and organic synthesis [18–20]. It is commercially available as HPLC grade solvent with reasonable prices only as a racemic mixture. The uses of propylene carbonate (PC) and methanol (MeOH) for replacement of acetonitrile (ACN) in reversed phase liquid chromatography (RPLC) was recently reported [21–24]. However, the referenced works mainly

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chromatographic separation, and if possible, its addition should be avoided.

4. Conclusions

Acetonitrile, as organic modifier of mobile phases, may be successfully replaced by propylene carbonate alone or premixed with ethanol. Reverse phase, ion pair and HILIC separation mechanisms may be applied by shifting from acetonitrile to propylene carbonate/ethanol mixtures. Conversion from optimized conditions under acetonitrile elution to propylene carbonate/ethanol elution is simple and direct. The two elution alternatives also behave similarly when considering the tolerability against inorganic buffers. Due to a reduced mass transfer of analytes in propylene carbonate based mobile phases, optimal flow rates (necessary for reaching maximum of efficiency) are lower compared to acetonitrile based mobile phases. Thermodynamic parameters describing partition of analytes between mobile and stationary phases are similar when shifting from acetonitrile to propylene carbonate/ethanol. The possibility of making large volume injection of samples made in diluents non-miscible with the mobile phase may be equally considered for acetonitrile and propylene carbonate, without significant differences. Replacement of acetonitrile by propylene carbonate/ethanol mixtures in liquid chromatography is affordable and should be considered as a step toward greening analytical chemistry, with some compromise in terms of performance criteria. The compromise refers mostly to eluent's miscibility, to the pressure drop and to the increased duration of the separation to obtain maximum of efficiency.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpba.2012.11.045.

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