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Review

Selective capillary coating materials for in-tube solid-phase microextraction coupled to liquid chromatography to determine drugs and biomarkers in biological samples: A review

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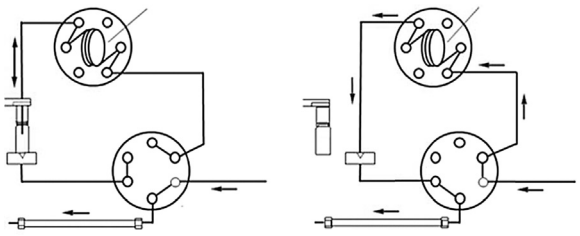
HIGHLIGHTS

- In-tube SPME-LC successfully determines drugs in biological samples.
- This review describes recently developments and applications of in-tube SPME-LC.
- Future trends and current technology used for the synthesis of selective sorbents.
- Selective sorbents enhance the selectivity and the sensitivity of the in-tube SPME-LC.

GRAPHICAL ABSTRACT



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ABSTRACT

In-tube solid-phase microextraction (in-tube SPME) coupled with high performance liquid chromatography (HPLC) or liquid chromatography coupled to mass spectrometry (LC-MS) successfully determines drugs or biomarkers in biological samples by direct sample injection or by simple sample treatment. This technique uses a capillary column as extraction device. Several capillaries (wall-coated open tubular, sorbent-packed, porous monolithic rods, or fiber-packed) with unique phases have been developed and evaluated, aiming to improve the efficiency and selectivity of the in-tube SPME-LC technique. This review describes new developments and applications occurred in recent years, and discusses future trends with emphasis on new extraction devices and current technology used for the synthesis of selective sorbents for bioanalysis, such as (*i*) polypyrrole, (*ii*) restricted-access materials, (*iii*) immunosorbents, (*iv*) molecular imprinting polymers, (*v*) monolithic polymers, and (*vi*) bi-functional materials.

Contents

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Maria Eugênia Costa Queiroz received her Ph.D. degree at the University of São Paulo-Brazil in 1996, and concluded a postdoctoral research fellow at the University of São Paulo – Brazil in 2001. In 2006, she worked with Professor Janusz Pawliszyn as a postdoctoral research fellow at the University of Waterloo (Canada), where she developed an immunoaffinity in-tube solid-phase microextraction coupled with liquid chromatography–mass spectrometry system to determine drugs in biological fluids. She works as Associate Analytical Chemistry Professor at the University of São Paulo, Ribeirão Preto Campus, Brazil. Her research interest is to develop selective sorbents, such as polypyrrole, restricted-access materials, immunosorbents, molecular imprinting polymers, monolithic polymers, and bi-functional materials to analyze drugs in biological fluids by both two-dimensional ultra-high liquid chromatography-tandem mass spectrometry and in-tube solid-phase microextraction coupled with liquid chromatography.

Dr. Lidervan de Paula Melo is a graduate in Chemistry from the Institute of Chemistry, UNESP, Brazil. He received his Ph.D. in 2012 from the University of São Paulo (USP) in Analytical Chemistry. At 2012 he initiated a postdoc. from USP, Brazil. He has worked with chromatographic techniques employing different detection systems (ultraviolet and sequential mass spectrometry). Dr. Lidervan de Paula Melo has experience in development of analytical methods and miniaturized sample preparation techniques (SBSE, intube SPME, and MEPS). He has recently developed extraction phases, molecularly imprinted polymers coated with restricted access materials, to determine parabens (chemical preservatives) in biological fluids.

1. Introduction

It is essential to quantitatively determine drugs and their metabolites or endogenous substances in biological samples (e.g., serum, plasma, urine, blood, and tissue) for a variety of bionalyses including (*i*) therapeutic drug monitoring, (*ii*) forensic toxicological analysis, (*iii*) screening for drugs of abuse, (*iv*) drug metabolism investigation, (*v*) diagnostic or prognostic purposes (biomarkers), and (*vi*) pharmacokinetic and drug development studies [1,2].

Therapeutic drug monitoring (TDM) refers to customizing the drug dosage during treatment of disease or condition. TDM helps to maintain plasma/serum drug concentrations within a targeted therapeutic range, thereby increasing therapeutic efficiency while reducing adverse side effects. In particular, TDM aids monitoring of drugs with narrow therapeutic ranges, drugs with marked pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and drugs known to cause therapeutic and adverse effects [3,4].

Screening for drugs of abuse is also valuable: it helps to monitor illicit drug consumption in dependent patients and avoids prescription of controlled drugs to patients who are not themselves drug-dependent. In addition, diagnosing maternal drug abuse, either during pregnancy or postpartum, can aid management of the neonate [5–7].

Many studies suggest that specific endogenous substances, such as neurotransmitters and peptide hormones, are correlated with pathological conditions and offer opportunities for potential clinical applications regarding therapeutic intervention or as diagnostic or prognostic biomarkers [8,9].

Researchers in the clinical and pharmaceutical field have concentrated efforts on developing of faster, more sensitive, and more selective analytical methods. Considering the physicochemical properties of drugs, high performance liquid chromatography (HPLC) has emerged as the reference analytical technique to analyze drugs and metabolites in biological samples.

Biological matrices contain endogenous compounds (acids, bases, salts, and protein) and other organic compounds with properties similar to those of the analytes (drugs) [10]. Unfortunately, these nonvolatile endogenous compounds can co-elute with the target drugs during chromatographic separation and irreversibly adsorb onto the analytical column stationary phase, which modifies retention mechanism of the drug and/or suppresses ions formation in electrospray ionization mass spectrometry (ESI-MS). Hence, direct injection of biological samples into conventional HPLC systems is not convenient. A sample preparation step is usually necessary to eliminate the majority of endogenous compounds and to concentrate the drugs that often exist at low concentrations in these complex matrices. This should help increase the selectivity and sensitivity of analytical methods.

Recent trends in biological sample preparation have focused on miniaturized analytical systems-these systems simplify automation and allow for high-throughput performance and online coupling with analytical instruments. In turn, online analytical systems require small biological samples and consume extremely low amounts of organic solvent or even no solvent at all. Minimizing the steps on biological sample preparation not only diminishes the sources of error but also reduces analysis time and cost [11–16].

In this context, online solid-phase microextraction (in-tube SPME) coupled with HPLC or liquid chromatography coupled to mass spectrometry (LC-MS) is worthy of mention. This technique uses a capillary column as the extraction device and enables continuous extraction, concentration, desorption, and injection by means of an LC autosampler [17].

Drugs present in biological samples can be extracted and preconcentrated into the stationary phase of the capillary column by repeated draw/eject cycles of the sample solution. Then, it is possible to directly transfer the extracted drugs to the analytical LC column. The in-tube SPME-LC system is fast to operate, easy to automate, solvent-free, and inexpensive [17]. Books [10,18] and other well-documented reviews [13,17,19,20] contain more detailed information on the use of microextraction techniques to prepare samples, including in-tube SPME.

This review focuses on the development and application of selective tailored capillary coating materials, especially polypyrrole, restricted-access materials, immunosorbents, molecular imprinting polymers, and monolithic phases, in the analysis of drugs and biomarkers in biological samples by in-tube SPME-LC.

2. Analysis of biological samples by in-tube SPME-LC

In-tube SPME involves a traditional LC system equipped with an autosampler. It is easy to combine in-tube SPME with HPLC or