Journal of Pharmaceutical and Biomedical Analysis xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

SPME as a promising tool in translational medicine and drug discovery: From bench to bedside

Krzysztof Goryński[a], Paulina Goryńska[a], Agnieszka Górska[a], Tomasz Harężlak[a,b], Alina Jaroch[c,d], Karol Jaroch[a], Sofia Lendor[a], Cezary Skobowiat[a], Barbara Bojko[a,*]

[a] Department of Pharmacodynamics and Molecular Pharmacology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Toruń, Poland
[b] Hospital Pharmacy, 10th Military Research Hospital and Polyclinic Independent Public Healthcare Center in Bydgoszcz, Bydgoszcz, Poland
[c] Department and Institute of Nutrition and Dietetics, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Toruń, Poland
[d] Department and Clinic of Geriatrics, Faculty of Health Science, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Toruń, Poland

ARTICLE INFO

Article history:
Received 28 February 2016
Received in revised form 3 May 2016
Accepted 4 May 2016
Available online xxx

Keywords:
Solid phase microextraction
SPME
Translational medicine
Drug discovery
Cell culturing
Animal studies
In vivo analysis
Drug
Analysis

ABSTRACT

Solid phase microextraction (SPME) is a technology where a small amount of an extracting phase dispersed on a solid support is exposed to the sample for a well-defined period of time. The open-bed geometry and biocompatibility of the materials used for manufacturing of the devices makes it very convenient tool for direct extraction from complex biological matrices. The flexibility of the formats permits tailoring the method according the needs of the particular application. Number of studies concerning monitoring of drugs and their metabolites, analysis of metabolome of volatile as well as non-volatile compounds, determination of ligand-protein binding, permeability and compound toxicity was already reported. All these applications were performed in different matrices including biological fluids and tissues, cell cultures, and in living animals. The low invasiveness of *in vivo* SPME, ability of using very small sample volumes and analysis of cell cultures permits to address the rule of 3R, which is currently acknowledged ethical standard in R&D labs. In the current review systematic evaluation of the applicability of SPME to studies required to be conduct at different stages of drug discovery and development and translational medicine is presented. The advantages and challenges are discussed based on the examples directly showing given experimental design or on the studies, which could be translated to the models routinely used in drug development process.

1. Introduction

Today, the introduction of new drugs into the market is extremely costly and burdened with a high risk of failure. Only one in ten substances passes all testing requirements to become a new medical product. The average time of drug development, from issuing a new chemical molecule a unique code, to its introduction into to the market, is about 8–12 years. Prior to registration, chemical substances must undergo clinical trials consisting of several phases. Basic research starts with the determination of a specific medical need and identification of a molecular target, followed by an entire process of design and synthesis of the molecule, as well as evaluation of its biological activity. The next stage, preclinical research, evaluates the pharmacological, pharmacokinetic, and pharmacodynamic properties of a given drug. This is followed by the first stages of drug discovery, where *in vitro* assays are generally used. Having passed the first stages, new tests are then carried out on experimental animals; these can include toxicological tests, as well as assessments of the influence of the new substance on given pathological processes (*e.g.*, carcinogenesis) and on the reproductive system of living organisms [1]. If the drug is proven suitable, human trails can then begin, generally involving both healthy volunteers and patients. This phase is a multi-step process, and can widely vary in the number of participants (from 20 to 100 to several thousands), as well as in the timeframe needed to obtain comprehensive information related to drug administration [2]. As illustrated in Fig. 1, there are many parameters involved in the assessment of the suitability of a drug candidate to enter the market. Within these parameters, absorption, distribution, metabolism, and excretion (ADME) are considered to be of critical importance in such

* Corresponding author at: Nicolaus Copernicus University, Faculty of Pharmacy, Department of Pharmacodynamics and Molecular Pharmacology, Dr Jurasza 2, PL-85-089 Bydgoszcz, Poland.
E-mail address: bbojko@cm.umk.pl (B. Bojko).

http://dx.doi.org/10.1016/j.jpba.2016.05.012
0731-7085/

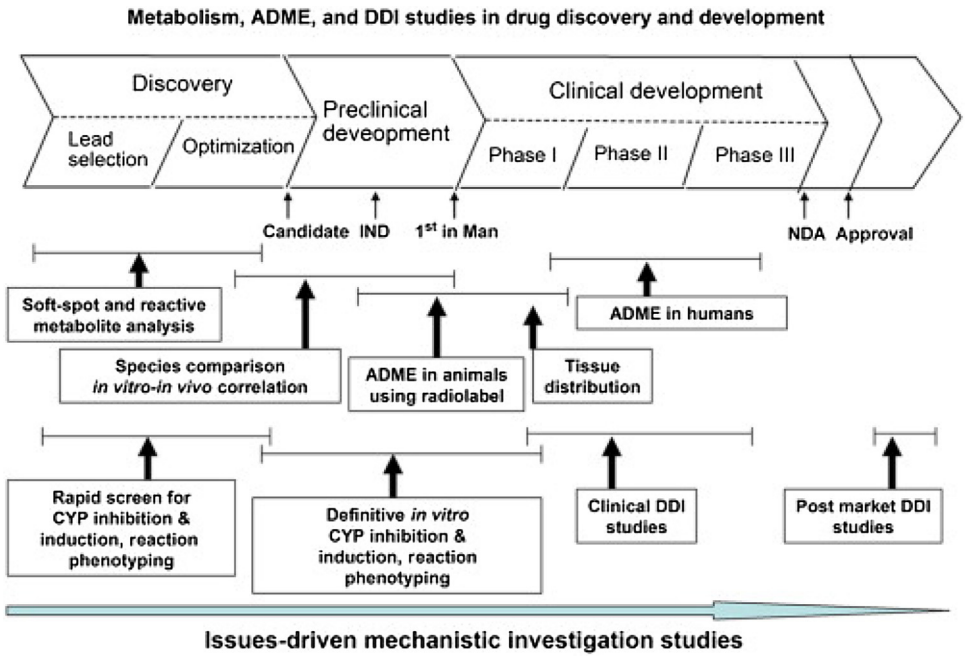

Fig. 1. Diagram showing the typical pathway for drug selection. Figure reprinted from Ref. [4] with permission.

determinations, as they are used to predict drug behavior in the human body. As such, the reliable collection of ADME information from *in vitro* and *in vivo* models (permeability, metabolic stability, protein binding, drug–drug interaction possibilities), together with rigorous data analysis, can greatly aid the process of drug development and selection, minimizing errors that can lead to drug development failure, and potential human harm [3,4].

Once a drug is on the market, it requires determining an initial dosage regimen appropriate for the various clinical situations depends on many factors particularly for drugs characterized by high inter-individual variability or dangerous toxic effects. The process individualize therapeutic regimens for optimal patient benefit, called therapeutic drug monitoring (TDM), comprises determining drug concentrations in different biological fluids and is used mostly for monitoring drugs with narrow therapeutic ranges, drugs with noticeable pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and drugs known to affect therapeutic and adverse effects. Thereby, this research provides information about the most appropriate dosage regimen to achieve the optimal response with minimal toxicity [3]. Considering the harmful, and sometimes possibly lethal side effects of certain drugs, each study within the drug discovery and development process has to be performed with the highest precision and reliability [5]. This requires employment of effective sample preparation, which can be a challenge undertaking the own of the complexity of biological matrices Currently, the majority of drug tests accomplish in the clinical setting are some variant of commercially available test kits [6]. Method applicable for clinical trials and experiments performed on preclinical studies should be: simple and easy to handling, fast and feasible to automation, especially when hundreds sample analysis is needed. Generally, the pharmaceutical industry has grown a global effort to harmonize the concepts used in validation, and most drug testing laboratories developed their assay procedures based on highly sensitive and selective instruments such as LC or GC–MS(/MS) and incredible progress in development of sample preparations methods provide the high level reliability and accuracy of measurements and meet strict criteria for bioanalytical methods. All analytical process can be unused if an unsuitable sample preparation method has been employed before the sample gets the chromatograph and the analyzer. Solid Phase Microextraction (SPME) is a relatively new sample preparation method for bioanalysis, although its applicability has already been shown towards various types of analyses of different biological matrices, including towards the extraction of a wide range of analytes with various physicochemical properties, and for analytical protocols tailored to specific applications [7].

Sample preparation is usually a time-consuming procedure. Whenever large numbers of samples need to be analyzed within a short period of time, as is generally the case in bioanalysis and drug discovery, automation becomes an essential part of the procedure [8]. Since SPME's inception, the technique has been adapted for automation with the use of the multi well-plate for a variety of applications [9]. Although the most commonly used SPME format employed in high throughput mode is thin film, the format compatible with multi-well plates can also be adapted for other geometries like fibers (Fig. 2), which might be more suitable for given application for instance because of limited sample volume. For further information, a thorough review of high throughput SPME in multi-well plate format is available in the literature [10].

In addition to its innumerous applications towards analysis of collected samples, SPME has been shown to be applicable for *in vivo* analysis in live animals. SPME enables solventless extraction by means of a solid support (metal of fused silica fiber) coated with a thin layer of sorbent/extraction phase. This open-bed geometry allows for SPME to be applied directly to sample blood or tissue of animals *in vivo* (Fig. 3), without the need for samples to be withdrawn or biopsied (*e.g.*, blood collection, tissue biopsy). As pharmacological and toxicological studies, especially those performed in rodents and dogs (beagles), are an essential link between the preclinical and clinical development phases of a given drug molecule [11], the suitability of SPME for *in vivo* applications can present a large advantage in the drug development process. Likewise, pharmacokinetic investigations are an important part of preclinical studies, and require analyses at several time points over an appropriate time period [12,13]. Owing to advances in genomic manipulation, the creation and use of genetically engineered mice has greatly increased the popularity of mice as models for such applications [14,15]. However, their relatively small size, and thus

Please cite this article in press as: K. Goryński, et al., SPME as a promising tool in translational medicine and drug discovery: From bench to bedside, J. Pharm. Biomed. Anal. (2016), http://dx.doi.org/10.1016/j.jpba.2016.05.012