Trends in Analytical Chemistry 83 (2016) 70–79

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

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

Saliva as an alternative specimen to plasma for drug bioanalysis. A review

Hatem Elmongy [a,b], Mohamed Abdel-Rehim [a,*]

[a] Department of environmental Science and Analytical Chemistry, Stockholm University, SE-10691 Stockholm, Sweden
[b] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Damanhour University, 22511 Damanhour, Egypt

ARTICLE INFO

Keywords:
Saliva
Plasma
Drug analysis
Extraction techniques
Therapeutic drug monitoring
Pharmacokinetics

ABSTRACT

Saliva provides a suitable medium for screening and determination of drugs. It is easy to collect and handle besides the non-invasive sampling. Extraction techniques such as micro-extraction by packed sorbent (MEPS) and dried saliva spot (DSS) provides fast and efficient recovery of the analytes. Moreover, MEPS could be fully automated to ascertain method reproducibility and DSS provides fast simultaneous collection and extraction of samples. Several studies were conducted to determine drugs in saliva in correlation to plasma aiming to establish rigid evidence on the suitability of saliva in monitoring of drug levels. Only free drug could be present in salivary fluid thus protein binding of drugs affect markedly on the salivary levels of drugs. Pharmacokinetic parameters could be determined for drugs in saliva with emphasis on diffusion parameters of drugs to salivary fluid such as pH and drug lipophilicity. Screening techniques are mainly based on mass spectrometry (MS) with an emphasis on Liquid Chromatography-Mass Spectrometry (LC-MS), due to limited sample volumes and the low detection limits. Saliva could make drug testing outside laboratory environments feasible with the appropriate techniques for analysis. This review focuses on the developments and challenges in testing of drugs in saliva in correlation to plasma and application to drug analysis in saliva regarding therapeutic drug monitoring and pharmacokinetics.
© 2016 Elsevier B.V. All rights reserved.

Contents

1. Introduction

Analysis of drugs in biological fluids is gaining a distinctive interest from clinical laboratories and drug manufacturers, particularly over the last two decades [1]. The use of alternative specimens to blood plasma or urine for evaluation of drug exposures became a significant trend in clinical chemistry and forensic toxicology [2]. Among these alternative specimens are hair [3], sweat [4] and oral fluid [5]. Oral fluid represent a quick and non-invasive alternative to blood but also as an alternative to urine due to suspected metabolic adulterations of the main analyte. Drawing blood requires the expertise of a professional while collecting oral fluid samples does not require the level of training needed for blood sampling. However, collection of saliva samples may be thwarted by lack of available fluid due to several physiological factors, including drug use itself [1]. Food and techniques designed to stimulate production of oral fluid can also affect the concentration of drugs. Besides, Monitoring drug concentration in oral fluid has been accepted clinically for only limited number of pharmacological agents due to not well

* Corresponding author. Tel.: +46707108122; fax: +46709569894.
E-mail address: mohamed.abdelrehim@aces.su.se, Mohamed.astra@gmail.com (M. Abdel-Rehim).

http://dx.doi.org/10.1016/j.trac.2016.07.010
0165-9936/© 2016 Elsevier B.V. All rights reserved.

established correlation between oral fluid and plasma concentrations for many substances [6]. On the other hand, many substances and their metabolites are present in different concentrations in plasma and urine. While plasma can reflect the actual circulating concentration of the investigated analyte, urine permits measurement of the accumulated concentration of analytes [7]. Unfortunately, the concentration of substances in urine is also dependent on fluid intake, which can vary substantially. Although more information could be obtained on drugs and their metabolites in plasma, urine tends to be more frequently used due to non-invasive sampling techniques. However, even the feasibility of collecting urine samples is being disputed in view of privacy intrusion in case of sampling supervision. Unlike urine samples, saliva can be collected under supervision without any privacy violation due to lack of direct observation of private functions [7].

Most of drugs are highly bound to blood proteins, but it came into consideration that only the free fraction is pharmacologically active [8]. Saliva contains only the free fraction of drugs that could infiltrate through the salivary tissues including the capillary wall, the basement membrane, and the membrane of the salivary gland epithelial cells [6]. Hence, better indication to the physiological activity and state of intoxication. Moreover, in clinical conditions in which protein binding varies, drug concentration in oral fluid is more closely related to the therapeutically active fraction of drug than in plasma [6,9]. Also, in circumstances where the concurrent use of two or more drugs may alter drug binding to plasma protein, the oral fluid concentration reflects the plasma free drug concentration. Therefore, saliva has been increasingly used for therapeutic monitoring of drugs as well as a diagnostic medium for the measurement endogenous markers [10–17].

Many analytical methods were developed for drug analysis in saliva mainly with high-performance liquid chromatography procedures that have been used in research laboratories [18,19]. Liquid chromatography combined with atmospheric pressure ionization (API) mass spectrometric detection (LC-MS/MS) represents a powerful and efficient tool in forensic analysis. It gained higher interest than classical methods utilizing ultraviolet, electrochemical, or fluorescence detection in the bioanalytical field. The most-used API sources are electrospray or ion spray (pneumatically assisted electrospray) and atmospheric pressure chemical ionization (APCI). The high sensitivity and selectivity of tandem MS has shortened the analysis time to be within the range of 1–2 min [20,21]. Unfortunately, good sample preparation procedures are required to prevent suppression of the analyte response during the ionization process, despite the high selectivity of the selected reaction monitoring mode (SRM). The bioanalytical procedure depends critically on data handling, sample preparation, and for some applications sample analysis [21].

The collected samples should be subjected to extraction procedure prior to the analytical step to remove interference due to sample matrix. Extraction procedures of biological samples mainly include solid phase extraction (SPE), solid phase microextraction (SPME), Liquid/liquid extraction (LLE). SPE provides superiority to the LLE technique due to lack of sample contamination with residual solvents, ease of operation, and more reproducible results. While SPME provides better performance than conventional SPE procedures due to lower samples and solvents consumption with better sensitivity and possibility of sample pre-concentration. Recently, microextraction by packed sorbent (MEPS) is a miniaturization of SPE technique that is used for sample purification and analyte preconcentration. It involves the extraction of analyte from biological samples on minimum amount of sorbent packed in a specialized syringe. The technique can be fully automated providingmaximum reproducibility and efficiency of extraction [22–26].

A number of reviews and major articles currently reported for drug testing in oral fluid. These include its use as a diagnostic tool [27], workplace applications [28], applications in drugs in driving [29], legal issues associated with drug testing in oral fluid [30], detection times and pharmacokinetics of selected drugs [31,32]. This review outlines the implementation of analytical assays, therapeutic monitoring, and pharmacokinetic studies of drugs in saliva samples in correlation to plasma as indication of efficiency or deficiency of the salivary fluid as a sampling medium to provide a clear clinical image of drug therapeutic and/or toxicological behavior in-vivo.

2. Physiology of saliva

Saliva is an exocrine fluid secretion. It is consisted of approximately 99% water, containing a variety of electrolytes (calcium, magnesium, sodium, potassium, chloride, bicarbonate, phosphate) and various proteins, represented by enzymes, immunoglobulins and other antimicrobial factors, mucosal glycoproteins, traces of albumin and some polypeptides and oligopeptides. It also contains glucose and some nitrogenous metabolic products, such as urea and ammonia [33,34]. These components interact and are responsible for the various functions attributed to saliva.2 Total or whole saliva refers to the complex mixture of fluids from the salivary glands, oral mucosa transudate, the gingival fold, besides the mucous secretion of the nasal cavity and pharynx, oral bacteria, food remainders, epithelial and blood cells, as well as traces of medications or chemical products [33].

At rest, without exogenous stimulus, there is a small and continuous salivary flow, denominated basal unstimulated secretion that covers, moisturizes, and lubricates the oral tissues. Whereas, stimulated saliva secretion is produced via mechanical, gustatory, olfactory, or pharmacological stimulus, which contributes to around 80% to 90% of the daily salivary production [33,34]. Mean daily saliva production in healthy subjects ranges from 1 to 1.5L [34].

Saliva preserves and maintains the health of oral tissues and has been used as a non-invasive source for investigation of metabolism and the elimination of many drugs. However, it receives little attention until its quantity diminishes or its quality becomes altered [34,35].

At present, saliva is increasingly useful mean of diagnosis for many diseases [36]. However, since salivary secretion and composition can be affected by several factors a standardized protocol for collection and handling must be made so the study would reflect the real functioning of the salivary glands and serve as an efficient means for monitoring health [37].

The salivary glands are made out of acini, in which the primary salivary fluid is created. The primary secretion is isotonic compared to plasma. The acini are associated by intercalated ducts and the discharged salivation flows to the oral cavity through striated and excretory channels. During this phase, the levels of a few electrolytes change because of dynamic ionic transport (Fig. 1), which renders the oral liquid its hypotonic character, when compared to plasma [39]. Saliva is kept in vesicles inside the acini of the salivary glands. These granules are filled with water, in which electrolytes and proteins are dissolved [40–42]. It is an energy demanding process for which adenosinetriphosphate (ATP) is needed, which is generated by metabolizing intracellular glycogen [43].

3. Advantages and disadvantages of saliva specimen

Saliva can act as a diagnostic medium which provides many advantages over plasma. Saliva is a non-invasive specimen that obviously advantageous for obtaining samples from those whom, for cultural reasons or age or because of physical or mental handicaps, it would be unethical to collect blood samples. The free, rather than the protein-bound drug molecules are considered to be the active component in blood. Thus, the drug levels in saliva are thought

Download English Version:

https://daneshyari.com/en/article/1247711

Download Persian Version:

https://daneshyari.com/article/1247711

Daneshyari.com