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Modern Analytical Chemistry in Clinics

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Analytical chemistry is constantly present in the clinical environment, but how fast are novel methods being employed to routine practice? There is no doubt that multi-parameter diagnostic tools provide reliable and high throughput analysis of thousands of samples per day; however, modern medicine seems to currently have a need for diagnostic tools that allow for a personalized approach to the diagnosis and treatment of patients. Profiling of genome, metabolome or proteome gives us the opportunity to create the fingerprints of a given disease, find specific biomarkers, as well as predict patient response to a chosen course of therapy. While overall time of analysis is not a concern in the discovery of biomarkers for on-site monitoring a rapid method is crucial. Constantly, conventional and laborious techniques need to be replaced with modern methods, as it has already happened in the case of therapeutic drug monitoring (TDM), where the extraction of drugs with solvents followed by chromatographic separation was largely replaced by immunoassays, methods which are faster and more convenient for hospital laboratories. Unfortunately, as there is no perfect solution for all the challenges presented by the analysis of complex biological matrices, immunoassays also show some drawbacks such as cross-reactivity, which frequently causes overestimation of the drug concentration [1]. While this issue does not have a significant impact on the applicability of the method to TDM, it can yield false positive results leading to a misinterpretation of data when it comes to the determination of biomarkers. Therefore, for this purpose, mass spectrometers (MS) are favorable analytical instruments, providing very good selectivity and sensitivity. Regrettably, although the excellent performance of MS and its feasibility to identify and determine biomarkers for clinical applications have been proven a number of times, we cannot find these instruments in standard hospital labs. And indeed, the maintenance and operation of an MS instrument, as well as the preparation of samples for analysis are not trivial, and go beyond common clinical lab equipment use. This does not, however, close the door for MS-based assays; rather, it is a driving force for scientists to develop simpler, more efficient ways of sample preparation, or eliminate the need for it completely. At the same time, mass spectrometer manufacturers work on modifying their instruments so as to make them more robust requiring less maintenance.

Modern sample preparation approaches suitable for clinical settings should ensure good sensitivity using a small sample volume and low solvent consumption, while yielding a fast analysis and high throughput. Several years ago, dried blood spot (DBS) analysis appeared as a "big boom" bringing great promise to the pharmaceutical industry and medical labs. This very simple, inexpensive and eco-friendly method is easy to automate and requires only few microliters of sample. Additionally, it offers a very convenient way of storage and transportation. Unfortunately, they are some major issues related to DBS, such as the hematocrit effect, the non-uniform distribution of the blood spot on the sampling area, and subsequently the lack of assay reproducibility, and problems with ineffective calibration. Now, in the era of the 'OMICS' studies, DBS have become a candidate for a much needed simple and fast sample preparation method in clinical settings [2]. So far, a few studies on global metabolomics have been performed with the use of DBS. As reported, the analyte coverage in positive ESI mode, following LC separation was greater for DBS when compared with solvent precipitation in analysis of plasma. The reverse situation was observed when GC analysis was employed; it is possible that a lower number of extracted compounds were the result of losses during blood and plasma drying or/and strong interaction with the used filter paper [3]. An interesting finding was reported as well: DBS seems to be more suitable for high viscosity biofluids such as whole blood than for plasma or urine analysis, which analysis show lower precision of the assay [4]. One of the convenient features of DBS use is its easy storage and transportation. However, while it is easy to evaluate the effect of storage conditions on stability of a given target analyte, for an untargeted study, the issue becomes more complex. In this case the monitoring of losses has to be done in parallel to tracking newly appearing compounds, which are the products of degradation and can be falsely identified as biomarkers of the investigated biological processes.

As mentioned above, one of the main pitfalls of DBS is the presence of interferences originating from the biological matrix or filter paper. Recently, an alternative for DBS called Extracted Blood Spot (EBS) was proposed for analysis of drugs in blood [5] and urine [6]. This approach addresses the issue of poor sample clean-up by using a polymeric phase instead of filter paper, thus providing extraction of metabolites from the biofluid and removing other matrix components. As a result, a clean extract is either injected to the LC-MS system, or directly to MS using Direct Analysis in Real Time (DART) coupling. Currently, there are ongoing investigations on the applicability of the method for untargeted study. EBS is one of the existing formats of Solid Phase Microextraction (SPME) technology, which has been successfully used a number of times for target analysis when coupled to LC-MS, GC-MS or MS directly [7,8] as well as for global screening of plasma [9], saliva [10] and whole blood [11]. The main advantages of the method are its easy automation, efficient sample clean-up and its low invasiveness, permitting *in vivo* applications and repetitive sampling. SPME *in vivo* analysis is particularly appropriate for global studies because of the integration of a quenching step with sampling and extraction, which provides a true snapshot of the metabolome, improving reproducibility of the method [12,13]. A unique feature of SPME is its applicability to various matrices, which in the view of clinical analysis means both biofluids and tissues. Immersion of a microprobe in the examined tissue without any damage to the organ can be an excellent alternative to conventional protocols, which are laborious, time-consuming and invasive, and thus, not suitable for monitoring changes over time (e.g. TDM, biomarkers or metabolome profiling in real or close to real time on-site analysis). Recently, a direct *in vivo* and *ex vivo* extraction from liver and lung during organs transplantation was performed in pig models. The studies demonstrated the feasibility of the approach for tissue metabolic profiling, showcasing the advantages of using in vivo SPME sampling for on-site analysis especially for inter-surgical analysis

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of drugs and biomarkers (Bojko et al. Solid Phase Microextraction fills the gap in tissue sampling protocols; submitted).

To provide clinicians with rapid diagnostic tools, direct coupling of sample preparation tools with mass spectrometers is one of the main areas of current study. The Matrix Assisted Laser Desorption Ionization (MALDI) and Surface-Enhanced Laser Desorption/Ionization (SELDI), Desorption Electrospray Ionization (DESI) or DART are already well known approaches. During the past five years few others techniques like paper spray (PS) [14,15], Solid Probe Assisted nanoelectrospray ionization (SPA-nanoESI), [16], Rapid Evaporative Ionization Mass Spectrometry (REIMS) [17,18] or Needle Biopsy and Spray Ionization [19] were introduced. In all these cases, sample consumption and sample preparation is limited to an absolute minimum (PS, SPE-nanoESI, Needle Biopsy and Spray Ionization) or completely eliminated (REIMS). In PS, SPE-nanoESI and Needle Biopsy and Spray Ionization small biopsy is placed directly into the ionization source and extraction and ionization of analytes is aimed by addition of small volume of organic solvent. The REIMS is based on different principles; vapors created during electro surgery and laser surgery are directed to mass spectrometer for real time analysis.

Although the presented methods are in very early stages of development still requiring further studies in order to control or possibly eliminate matrix effects, improve reproducibility of the data and provide quantitative results, they clearly show that novel analytical approaches will soon be available to clinics, offering solutions for presently unreachable challenges, and, within the next few years will be permanently present in hospitals, aiming at a more personalized medicine approach.

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