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Dried matrix spots and clinical elemental analysis. Current status, difficulties, and opportunities

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ABSTRACT

This article examines the increasing importance of dried matrix spots (DMS), such as dried blood spots, dried urine spots, etc., in biomedical research, the challenges associated with their analysis when quantitative elemental information is aimed at, as well as the benefits deriving from the further usage of these types of samples. The article briefly reviews the historical evolution of this sampling approach in elemental clinical analysis, stressing prospective areas of applications (e.g., newborns or prosthesis control), the methodologies most recently developed to produce DMS of known volume, as well as novel strategies proposed to analyze them, often related to direct solid sampling techniques or fast lixiviation methods. Finally, the article discusses the type of information that could be obtained after isotopic analysis of DMS when targeting non-traditional stable isotopes (e.g., Cu, Fe or Zn), which can significantly help in the early diagnosis of some medical conditions (e.g. Wilson's disease).

1. Introduction

In 1963, R. Guthrie and A. Susi published a seminal work describing the collection of capillary blood from the heel of newborns. Such method included the deposition of a few blood droplets on a filter paper (FP), a drying step, and, finally, the determination of phenylalanine for the screening of phenylketonuria [1].

This was actually not the first paper dealing with the microanalysis of blood collected on FP. Already in 1913, Bang described the determination of blood sugar levels by titration with a diluted iodine solution [2]. However, it can be argued that it was the work referred above by Guthrie and Susi [1] the one that laid the conceptual basis of an approach that has facilitated the diagnosis and early treatment of multiple congenital and hereditary abnormalities through newborn screening programs. Since then, analysis of the now called DBS (dried blood spots) has improved or saved many lives in both developed and developing countries [3].

The number of analytes investigated in DBS samples has been steadily increasing, with applications in metabolic-endocrine diagnosis, therapeutic drug monitoring, as well as toxicological, serological and molecular biology studies [4–7]. Moreover, in recent years (see Fig. 1a), there has been an exponential increase in the number of publications on this topic, which seemed to peak in 2014. The slow decrease in papers observed in the last couple of years does not necessarily mean that the interest in the field has decreased. Instead, it could mean that the field is reaching a state of maturity, as the pharmaceutical industry is using more and more this type of sample [8]. Also, some of the research is being transferred to the use of other biological fluids, such as urine (see Fig. 1b), giving rise to the so-called dried urine spots (DUS), and, to a much lesser extent, to other fluids such as cerebrospinal fluid [9,10], amniotic fluid [11] or saliva [12]. Biological samples deposited onto and dried on a FP receive the generic name of DMS (dried matrix spots).

The majority of this research has been focused on the monitoring of (bio) organic species *via* liquid chromatography–mass spectrometry (LC-MS). Several recent reviews covered these works [3,13–16] in detail. The current review will instead focus on the role that this field may also play in clinical elemental analysis. Obviously, some of the aspects discussed can be considered as general, regardless of the nature of the analyte, which will be noted. However, one of the key differences of clinical elemental analysis is that typically quantitative information is aimed at, as opposed to many other situations in clinical diagnosis where only qualitative or screening information is needed. This still represents an analytical challenge for DMS analysis.

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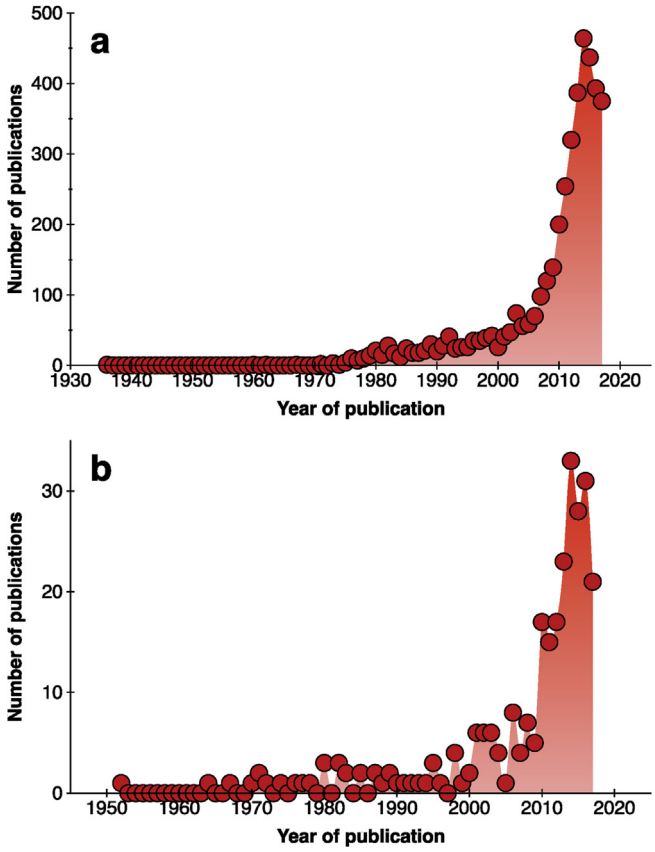

Fig. 1. a) Publications on DBS; b) Publications on DUS. Conference papers were excluded.
Source: Scopus, October 31, 2017.

2. Advantages of DMS for the analysis of biological fluids

From a purely analytical point of view, by producing DMS, liquid samples that are relatively simple to analyze after digestion or just dilution, are transformed into much more complex solid materials, which are typically not homogeneous. Therefore, from such point of view, this transformation is not so advantageous.

Moreover, deposition of other liquid materials on FP is also possible, and has been also explored in the literature [17,18], but such applications are rarely finally deployed in routine labs.

Therefore, what are the benefits of DMS to make this type of sample worthy of analytical research? There are a significant number of them, which will be discussed below.

2.1. Ease of sample collection

This advantage is particularly important in the case of blood. Development of the DBS methodology has been related to the expansion of neonatal screening programs in hospitals, because the method of collecting capillary blood on FP is very attractive for mass screening of children for the following reasons [19]: i) a minimal amount of blood is required; ii) pricking the heel (newborns) or finger (young children) with a lancet is easier and less traumatic than the conventional collection of venous blood; and iii) DBS collection can be performed by relatively untrained personnel, even by the parents or relatives at home (see Fig. 2).

DMS are becoming also popular for this reason in a pharmacological context (e.g., experimentation with new drugs or treatments). The traditional method of collection of blood from rodents is terminal, thus requiring a new animal for each measurement. Alternatively, DBS methodology enables serial sampling from a single animal, such that pharmaceutical companies can meet the "3R's doctrine" (reduction, refinement, and replacement) as regards animal experimentation [14].

Concerning other biological fluids, use of urine or saliva permits the development of truly non-invasive methods, although the amount of sample is typically not a problem for urine. In the case of other samples, such as cerebrospinal or amniotic fluids, the advantages are not so obvious, because sampling must be carried out by specialized medical staff following the hospitalization of the patient. Still, these venues are explored because of the increasing popularity of DMS.

2.2. Ease of transportation and storage

This is another key aspect for clinical labs. Requirements for transportation and storage of biological specimens collected on FP are much less stringent than those that have to be followed for the liquid samples. For example, many urinary metabolites show little stability. Thus, urine must be frozen (at −20°C or −80°C) until analysis, complicating the logistics of clinical laboratories, which often have to deal with hundreds of samples on a daily basis.

In contrast, several studies indicate that the conservation of the sample dried on a FP slows down the degradation processes that analytes may undergo [20], and therefore DMS are much more stable than the original wet samples. If the analysis is to be carried out one month after collection or before, it is generally possible to preserve DMS at room temperature; for longer periods, it is recommended to keep them refrigerated under controlled humidity [5].

2.3. Improvement of welfare conditions

For the reasons discussed before, DMS methodology enables the home collection of biological fluids and their submission to the lab by ordinary mail. This aspect can certainly improve the quality of life of people who must periodically undergo tests, such as chronic patients requiring frequent controls, or those with reduced mobility or, even, bedridden, and/or those living in isolated areas.

In addition, this strategy can lead to health care and business savings, decreasing the hours of staff dedicated to the collection of the samples, as well as to administrative aspects related with the frequent attention of patients in health centers.

2.4. Increased participation in epidemiological or population-based prevention programs

Both epidemiological and population-based preventive programs make use of the measurement of biomarkers and, in such studies, the collaboration of the population is essential. This collaboration involves certain discomforts to participating subjects: sample collection can be annoying (e.g., blood collection) and it often requires a visit to a health center for collection or delivery of the sample. When the study is epidemiological, in which the participants do not see a clear benefit for their participation (in contrast to a program of prevention or of early diagnosis of a disease), these inconveniences may outweigh their collaborative spirit.

In these situations, the development of protocols for the collection of these biospecimens at home and their easy shipment should lead to greater participation [21]. As stated by McDade et al.: "… the burden is on the researcher to bring methods to people in the community instead of relying on select individuals willing to