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DRIED BLOOD SPOT ANALYSIS IN CLINICAL CHEMISTRY AND MODERN ANALYTICAL METHODS

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ABSTRACT

Dried blood spot (DBS) technology has emerged as a useful instrument for qualitative and quantitative biological examination in recent years. Once the sample has dried, analysis can be done using contemporary analytical, immunological, or genomic techniques. DBS has been referred to as the best technique for biomaterial sampling because of certain inherent benefits, such as the low amounts of biomaterials needed, the lack of special storage and transportation conditions for samples, the enhanced stability of analytes, and the decreased risk of infection from contaminated samples. Since the 1960s, Blood that has been spotted and dried on a matrix has been examined in clinical chemistry. often known as "dried blood spot" or DBS, mostly for newborn screening. Numerous clinical analytes, such as lipids, small molecules, and nucleic acids, have since been effectively measured with DBS. Despite being an intriguing substitute for traditional venous blood collection, this pre analytical method is not widely used. Here, we examine how DBS technology is used in clinical chemistry.

Keywords: Dried blood spots (DBS); new born screening (NBS); polymerase chain reaction (PCR); enzyme-linked immunosorbent assay (ELISA)

INTRODUCTION

DBS sampling is a straightforward, easy sample technique that improves patient comfort. Capillary blood is drawn from a finger prick using an automated lancet in DBS sampling. After sufficient training and clear instructions, patients ought to be able to perform this finger prick on their own **[1].** Only a tiny amount of blood is needed, and the procedure is less intrusive. Additionally, DBS sampling can be done at home, allowing blood to be drawn at a pre-determined time and potentially reducing the number of hospital visits **[2]**. The DBS poses a minimal risk of infection since certain viruses, including hepatitis C virus (HCV), human T cell leukemia/lymphoma virus (HTLV)-I and-II, and HIV-1 and-2 **[3]**.

Ivar Christian Bang first used DBS in 1913 to track rabbit glucose levels. A DBS technique for phenylalanine as a biomarker for phenylketonuria was introduced by Robert Guthrie and Ada Susi in 1963. NBS's beginnings. Guthrie called DBS his "most important contribution" and underlined its significance for the creation of NBS, which is being used in many nations across the world to identify and start treating a variety of inborn illnesses. Mee *et al*.'s 1976 MS measurement of free fatty acids is another instance of the early application of DBS. Until the mid-2000s, DBS was primarily utilized for NBS and infection diagnoses **[4]**.

The discovery of cellulose paper cards for the collection of blood samples as a membrane carrier (MC) was made possible thanks in large part to the vision of Ivar Christian Bang (1869-1918). Bang first measured the amount of glucose in dried blood spot (DBS) components. Later, using same filter paper technique, Bang also used the Kjeldahl method to assess the amount of nitrogen. His method has now been applied by several researchers to examine serological samples **[5]**.

The application of mass spectrometric methods for dried blood spot testing has greatly increased due to the development of sophisticated analytical techniques and increased throughput. Researchers and clinicians are now very excited about the prospective uses of mass spectrometry based on dried blood spots. On the other hand, the sensitivity, repeatability, and general accuracy of dried blood spot quantification provide difficulties for analysts **[6].**

The two most common varieties of DBS are cotton paper filters with varying quality (Perkin Elmer 226 Spot Saver Card, Perkin; Whatmann 903 Protein Saver Cards, Springfield Mill, UK: Whatmann. Elmer,

Waltham, USA) and glass microfiber filter sheets (Agilent Bond Elut DMS, Santa Clara, CA, USA; Sartorius Glass Microfiber Filters, Goettingen, Germany). The primary distinction between the two supports is that non-specific analyte adsorption on the membrane is reduced Since the glass fibre does not absord reagents.DBS has advantages over traditional blood tests in terms of practicality, clinicality, and cost **[7]**.

General DBS procedure

First the collection region (heel, finger) needs to be cleaned. A sterile lancet is then used to penetrate the skin After dabbing the first drop of blood, the remaining drops are put on blotting paper. That has been circled to be filled (Figure 1) The blotting paper is placed on a nonabsorbent surface and allowed to dry for a few hours at room temperature once all the necessary circles have been filled. The drying period is crucial because remaining moisture encourages the growth of bacteria or mould and alters the extraction process **[8]**. After drying, the DBS cards—possibly with a desiccant and a humidity indicator—are placed in a waterproof plastic bag. In addition to completing the drying process, the desiccant reduces the possibility of infection during the sampling procedure. Depending on the biological component, storage times at ambient temperature range from Proteins take a week, but nucleic acids take a year or longer. When it comes to serology, after being received, the blotting papers are usually kept at -20°C. For long-term preservation (up to many years), the blotting papers are stored at either -20°C or -80°C. **[7]**.

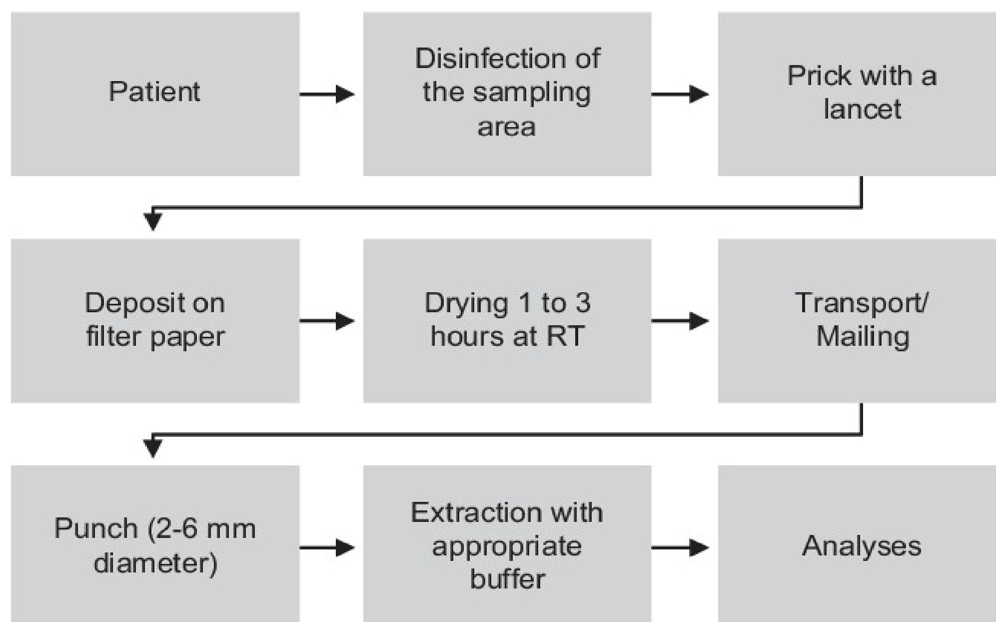

Figure 1: DBS collection process

The patient draws peripheral blood at home. Before blotting the blood onto premium filter paper, he cleans the region (finger) and punctures the skin with a sterile lancet. After drying for one to three hours at room temperature, the DBS is mailed in a traditional envelope. The DBS is kept at ambient temperature in the lab. Before analysis, the sample is punched (2–6 mm) and the analytes are extracted using the proper buffer.

Modern Analytical Methods for DBS Analysis

RNA\DNA Quantification: There is increasing interest in using DBS for virus screening and nucleic acid (RNA, DNA) detection using reverse transcription polymerase chain reaction (RT-PCR) or quantitative polymerase chain reaction (qPCR). These techniques need a tiny sample size (less than 20 µL) because of their extremely high sensitivity. It is crucial to remember that the quantity of material extracted from DBS samples is 1-2 logs less than that found in typical serum or plasma samples. On MC, nucleic acids remain stable for a long time **[9]**. if samples follow the guidelines for drying and keeping them out of the presence of moisture. The primary purpose of PCR detection of the nucleic acids eluted from the DBS surface is for viral illness screening, including CMV and herpes simplex virus· hepatitis B, hepatitis C and HIV **[5].**

Protein\peptide detection: Numerous biological processes are carried out by proteins, and measurements of these proteins can reveal both normal and disease-causing protein malfunctions. As a result, protein biomarker quantitative analysis has become a crucial clinical tool for illness diagnosis, risk assessment, disease progression tracking, and treatment efficacy evaluation. Cost-effective assays with accurate, high-throughput capabilities have been made possible by significant technological advancements in proteomic research in recent years, particularly in quantitative immunoassay techniques. Only a small number of these assays have been validated for DBSs, despite the fact that the majority were created for use in serum or plasma. In a large-scale multi-center experiment, Martin *et al*. confirmed the use of an enzyme-linked immunosorbent test (ELISA) to quantify adiponectin. In the business world **[10]**. Our investigation of dried and wet samples up to 30 years old shows that most proteins are still identifiable throughout this time, indicating that the samples are suitable for long-term storage for protein analysis in the dried condition. A distinct tendency towards declining levels was noted for a number of proteins, with half-lives of

some protein levels as low as 10 years. However, for some proteins, no declines were recorded even after 30 years of storage. The proteins in 91 of the 92 examined samples that were dried and kept at 4°Corat 24°C for 30 years, respectively, were considerably reduced. Out of 92 proteins, 5 were the corresponding number for wet samples that were kept at 70 °C for 45 years. The fact that the several people studied most likely have varying protein levels complicates the results **[11].**

Metabolite detection: samples were examined utilizing a broad-spectrum targeted metabolomics approach on a Shimadzu LC-20AD high-performance liquid chromatography (HPLC) system connected to a SCIEX Qtrap 5500 mass spectrometer (LC-ESI-MS/MS). In short, the metabolites were separated using hydrophilic interaction liquid chromatography (HILIC) mode on a polymer-based NH2 column (250 × 2 mm, 4 µm, Asahipak NH2 P-40 2E, Showa Denko America, Inc., New York, NY, USA). In a single injection, 78 stable isotope internal standards and 622 endogenous metabolites were targeted. Multiquant 3.0 (Sciex) was used to manually verify the peaks, and the peak area was exported for additional examination. The metabolite extraction and MS detection were observed using the spiking stable isotope internal standards. **[12].** DBS technology is also applicable for dissociation-enhanced lanthanide fluorescent immunoassay. Zimmermann *et al*. used this technique to identify thyroglobulin in dried spots of whole blood for the analysis of thyroid function in children **[13]**.

Comparison of Dried Blood Spots and Venous Blood

An effective substitute for venous blood analysis is blood spot. • A fresh opportunity for TDM is the blood spot approach **[14]**. in a sample of venous blood as soon as the blood is extracted, mix all of the tubes. Any delay could have an impact on the sample's quality **[15]**. For venous blood collection Medical, nursing, and ancillary healthcare personnel can undertake testing with little training at a number of rotating collection sites on the body, including the heel, fingertip, and earlobe **[16]**. In case of DBS Particularly when bleeding neonates, capillary blood collection on filter paper offers several benefits over venepuncture, including ease of use, low training requirements, and elimination of the hazards related to syringe and needle use and disposal. Since certain viruses that are known to be present in serum or plasma, such as HIV-1 and-2, human T cell leukemia/lymphoma virus (HTLV)-I and-II, and hepatitis C virus (HCV), lose their

infectious potential when their envelopes are disrupted during drying, the DBS is considered to provide a low infectious danger **[3]**.

Venous blood samples were analyzed for the presence of SARS-CoV-2 IgG antibodies using the Abbott chemiluminescent microparticle immunoassay (CMIA). DBS samples were analyzed by the EUROIMMUN enzyme-linked immunosorbent assay (ELISA) for SARS-CoV-2 IgG antibodies. DBSs are a useful substitute for venipuncture in large-scale SARS-CoV-2 serosurveillance investigations, particularly for senior participants for whom drawing venous blood can be difficult. Higher sensitivity and specificity as well as the ability to (semi-)quantitatively evaluate the antibody response are provided by DBS testing in contrast to quick serological tests, which can also be used in extensive SARS-CoV-2 seroepidemiological investigations. Additionally, DBS examinations offer the benefit of sample collection and preservation for numerous studies. As a result, the same sample can be used for many experiments, including antibody assays that target distinct antigens. However, because DBS testing do not require medical personnel for collection or complicated shipping and storage, they offer benefits that are comparable to those of fast tests **[17]**.

Use of DBS in clinical chemistry

Systematic newborn screening is the main application of DBS in France. Since it is challenging to get blood from babies, DBS technology is a good substitute. DBS testing was created in 1978 by the French Association for Screening and Preventing Disabilities in Children (http://http://www.afdphe.org/).Newborn samples can be used to identify sickle cell disease, hypothyroidism, phenylketonuria, adrenal hyperplasia, and cystic fibrosis (in some regions). There is ongoing discussion of expanding the scope of these tests to include more disorders, much like in the USA. Additional specific tests will always be performed to confirm or rule out a positive result. DBS can be used to evaluate a variety of clinical analytes in addition to newborn screening. **[7]**. Numerous innovative approaches will enhance the application of DBS in clinical and screening labs. When DBS's benefits greatly exceed its alleged drawbacks, this improvement could be seen. This is obviously true for metabolic diagnostic labs and neonatal screening. The proof for its increase may come from clinical chemistry domains like clinical trials or disease and medication monitoring. Any analytical worries may be outweighed in these two areas by the requirement for remote, small volume

collection with stable storage and biosafety **[18]**.

Natural nucleic acids: Measurement of nucleic acids is typically required in the field of virology. Nucleic acid detection (RNA, DNA) for viral screening is becoming more and more common. using DBS, as contemporary molecular biology technologies [quantitative polymerase chain reaction (Q-PCR) and reverse transcription polymerase chain reaction (RT-PCR)] require only a small sample size (<20 μL) and are extremely sensitive. It is important to keep in mind, though, that the material obtained from a DBS sample is one to two logs lower than that of a normal serum or plasma sample. Blotting paper can preserve nucleic acids for extended periods of time as long as it is properly dried and kept out of the presence of moisture in a plastic bag with a desiccant. The primary purpose of DBS nucleic acid detection **[7]**.

Proteins-peptides: Proteome analysis of volumetric self-sampled DBS adds clinical blood collections to earlier COVID-19 findings by enabling accurate investigation of clinically important proteins, such as those secreted into the circulation or detected on blood cells. Our population surveys confirm the value of DBS and highlight how sample collection should be timed to support clinical and precision health monitoring programs **[19]**. Although direct comparison to plasma samples is challenging, the measurement of cellular proteins in DBS may provide diagnostically valuable investigations of the cellular composition in blood samples. Before blood drops are dried on paper, a number of methods have been developed to separate the cells and plasma, which could further boost the value of dried blood sample biobanks. The uniformity of protein distribution across a DBS is crucial if numerous small parts need to be examined **[11]**.

Xenobiotic: Monitoring opioid exposure is necessary because opioid overdoses pose a serious public health risk in the United States. Twelve fentanyl analogs, four metabolites (e.g., fentanyl), and an LC-MS/MS technique for fentanyl are used to evaluate human exposure to fentanyl and fentanyl analogs. Seymour *et al*. developed and verified 3-methylfentanyl and ocfentanil. The authors illustrated the value of chromatography using an Agilent Pursuit pentafluorophenyl column and a Sciex 6500 triple quadrupole mass spectrometer. They showed that 3-methylfentanyl and α-methyl fentanyl share the same MRM transition, and that the concentration of each individual compound could not have been ascertained without chromatographic separation. Serum steroid levels are measured for anti-doping tests and

the diagnosis of various endocrine disorders. DBS sampling may be less intrusive than venous blood sampling and easier than urine sampling in these situations. A DBS LC-MS/MS was described by Salamin *et al*. technique for measuring eight conjugated and eleven free steroids that has been approved in accordance with World Anti-Doping Agency guidelines **[50].** DBS (HemaXis DB10 kits) and serum from healthy women were examined using a Phenomenex Kinetex C18 column equipped with a Waters Xevo-TQ S triple quadrupole; the findings were found to be in good agreement. Additionally, the investigators showed that the examined steroids were stable for one to three weeks at room temperature, four, and -20°C. This suggests that DBS is a good sample material for anti-doping purposes because the samples can be carried at room temperature, which facilitates field sampling **[4]**.

Genomics: With an average temperature of 28ºC and 73% relative humidity—the typical meteorological conditions at the Department of Medical Science, Ministry of Public Health, Nonthaburi, Thailand—genomic DNA in dried blood preserved on filter paper remains stable for at least ten years. The capacity to identify a brief DNA fragment of the PAX8 gene in extracts from dried blood specimens that have been maintained for longer than ten years suggests that dried blood specimens can be used for genetic and epidemiologic research, including the detection of disease-associated polymorphisms **[20]**. Important relationships between human diseases, the environment, and genotypes may be revealed more affordably by using DBS rather than obtaining new samples **[21]**. For genome-wide SNV, InDel, and copy number analysis, DBS offers high-quality WGS data. Heteroplasmy estimations and haplotype analysis were comparable to those performed on venous blood samples. DBS is a reliable sample type for genetic research in large population-based investigations because of how simple it is to collect, transport, and store samples **[22]**.

Applications of DBS

Dried blood spot (DBS) sampling is one technique used in clinical research and routine patient care as part of therapeutic drug monitoring (TDM). A skin prick is used to transfer capillary blood to a sampling card, which is subsequently allowed to dry. These DBSs can be used to measure blood drug concentrations and clinical chemical parameters such as creatinine or antiviral antibody titers **[23]**. The limits of the small sample sizes in DBS cards may be solved by combining the high sensitivity of new diagnostic techniques for the measurement

and analysis of proteins, small molecules, and nucleic acids with the benefits of sample stability during storage and transportation. The literature on the use of DBS cards for the diagnosis, surveillance, and epidemiological research of virus infections other than HIV, such as CMV, HBV, HCV, HAV, HEV, HTLV, EBV, HSV, measles, rubella, and dengue viruses, is the focus of this survey. It is anticipated that extra possibilities to measure and analyze viral illness indicators in situations with limited resources or when obtaining a little sample of blood will be made possible by the minimally intrusive nature of sampling and the relative simplicity of handling and storing DBS cards. In order to screen for congenital infections, extensive retrospective studies of viral infections in neonates utilizing saved DBS cards have already been conducted. Furthermore, in places with limited resources, DBS cards have been utilized prospectively for prevalence studies, outbreak surveillance, mass viral infection screening, chronic illness follow-up, and therapy **[24]**. Using DBS in conjunction with point-of-care testing, assessed a panel of biomarkers pertinent to the main public health issues facing this community. This is a totally distinct example that looks into excess male mortality, health inequities, and their relationship to health behaviors in US men **[25]** The sensitivity of DBS samples for both polar and non-polar analytes has increased due to advancements in ion source technology **[6]**.The use of DBS with preclinical studies makes a significant contribution towards the principles of the 3Rs in that the number of rodents used for each study can be reduced and there is a significant refinement in blood sample collection procedures from rodents and non-rodents **[26]**. Disease diagnosis, sero-surveillance, and genetic research are the primary uses of DBS technology in biology and veterinary medicine. DMS specimens from many animal species offer quick sample throughput appropriate for extensive epidemiological studies, which are bolstered by PCR and serological screening techniques. DBS technology holds promise for diagnosing infectious illnesses, genotyping, and sero-surveillance in poultry and livestock, as well as for serum antibody control after vaccination. Foot-and-mouth disease, enzootic leucosis, bluetongue disease, trypanosomosis, brucellosis in cattle, toxoplasmosis, and Peste des petits ruminants virus disease in small cattle, Aujeszky disease, porcine reproductive and respiratory syndrome, African swine fever in pigs, avian influenza, Newcastle disease, infectious bronchitis, infectious bursal disease in chickens, and numerous other conditions were

monitored and diagnosed using livestock and poultry air-dried bio samples on filter paper **[27]**.

DBS are highly use full in forensic **[28]**. When compared to conventional whole blood collection methods, the DBS has a number of advantages. A modest sample volume is collected using this straightforward, minimally intrusive method, which is both portable and storable. Additionally, it makes pre-analytical sample processing—including its automation—less necessary. Additionally, because DBS is a dry matrix, it reduces the risk of infection from handling samples, which helps to inactivate pathogens like the hepatitis virus and HIV/AIDS **[29]**. Nilotinib plasma concentrations could be calculated on the basis of DBS **[30]**. DBS provides a way to avoid medication degradation since the enzymes that cause it denatures as they dry on filter paper. DBS is also useful for labile prodrugs, glucuronides, metabolites, and photosensitive medications **[31]**. From a historical and contemporary standpoint, the most important use of dried blood spots is the collection and transportation of blood sample on filter paper by newborn screening programs. The special qualities of the dried blood spot and its medical benefits are allowing their application in various scientific fields including pharmacology and toxicology, in addition to the advantages of identifying pre symptomatic patients with congenital metabolic problems **[32]**.

CONCLUSION

The DBS sample technique is without a doubt the most economical and moral way to gather, transport, and preserve the biomaterial. Clinical and pharmaceutical laboratories frequently employ this novel method of blood collection, which has several benefits: It is a straightforward, minimally invasive sampling procedure; (2) it offers a practical way to store and transfer biomaterial because deep freeze chambers are not necessary; (3) the patient can easily collect the biomaterial on their own; (4) it offers the possibility of long-distance transportation at low cost; (5) it lowers the risk of blood borne transmission; and (6) in contrast to conventional methods for collecting blood samples, It significantly streamlines the process by requiring a smaller volume of sample (less than 100 μL). The possibility of "self/home blood sampling," which is simplified, is one interesting aspect of DBS. The patient will be able to take blood on their own, safely. After that, the DBS will be mailed to the lab. Numerous clinical analytes are already accessible on DBS, as this review explains.

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