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EDITORIAL

ABC Spotlight on paper-based strips analytics

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An increasing number of articles dealing with paper-based analytics are being published. The proposed dips, strips, and chips use dry chemistry (e.g., a reagent is immobilized on a support material that is kept on the shelf in a dry state). Either the dip is dipped in the sample solution and a reaction with the reagent (a color change) occurs or the sample solution flows across the immobilized reagent and the amount of interaction is monitored by various detection methods. This paper-based analytics is applied in point-of-care testing and in environmental analytics—basically whenever results are required quickly. The present hype in publications and the widening range of applications make it advisable to review the history of dry chemistry in analytics.

Around the year AD 1300, litmus was first used by the Spanish alchemist Arnaldus de Villa Nova [1]. From the sixteenth century on, litmus was extracted from lichens; it was used to identify substances and later especially to test whether a solution was acidic or basic, the beginning of so-called dry chemistry.

Around 1950, strips containing a reagent pad for glucose that had been dipped in urine were used for the first time to determine protein and glucose—this was the beginning of diagnostic reagents strips, commonly used in simple clinical analysis especially of urine [2]. These were usually sticks with up to ten reagent spots per stick that changed color. They are still used today by general practitioners for simple urine prescreening. Examples include the Roche Combur-Test product line (https://www.roche.de/diagnostics/tests-parameter/point-of-care-diagnostik/combur-test-produktlinie.html#Merkmale) and Siemens Multistix (https://www.healthcare.siemens.de/point-of-care/urinalysis/multistix-10-sg-reagent-strips). Even nowadays, such strips are used in clinical diagnostics. After 1980, the development of spectrometric instrumentation and of dry reagent strip technology opened the market for the Reflotron®—it was the first analytical system, produced by Boehringer Mannheim and used in many practitioners' surgeries [3]; this system monitored diagnostic reagent strips using diffuse reflection and an Ulbricht sphere. On dry reagent strips, chromatographic effects and enzymatic and immunologic reactions with a biomarker are visualized by the change in color of a dye. With the Reflotron®, quantification of the biomarker-induced reaction became possible. The miniaturized and optimized Reflotron® (Reflotron® Plus system, Roche Diagnostics) is used nowadays in point-of-care diagnostics to quantitatively determine parameters in clinical chemistry.

During the 1980s, the development of a technique first called "sol particle immunoassay" began. This used prefabricated strips of a carrier material containing a dry reagent that were activated by the fluidic sample. They differ from normal "dip sticks", which are based on immunoplotting, and do not rely on lateral fluid flow through a membrane. This was the beginning of lateral flow (immuno)assays together with the immunochromatographic technique, coming to the market more and more after 2000 (see Fig. 1). This combination is nowadays called "lateral flow assay" (LFA). Its strengths, weaknesses, opportunities, and threats were reviewed by way of survey of the literature till 2008 [4]. This was the next step in the development of fast paper-based devices. Their history was reviewed in 2013 [5]. In that review, the properties of paper with regard to its optimum use in fast diagnostics are discussed. The advantages and disadvantages of different fabrication techniques

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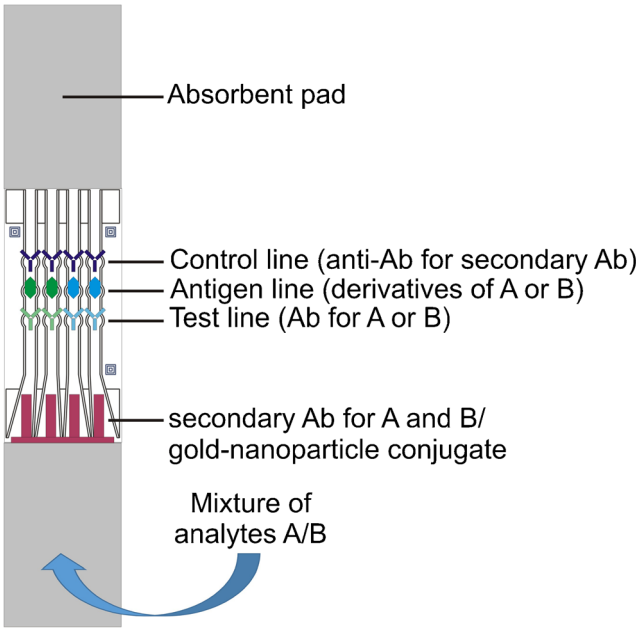

Fig. 1 A lateral flow strip with structured channels with a sample pad for inlet of the sample, the reservoir for the secondary detection antibodies conjugated with nanoparticles or fluorophores, and the three detection lines (sandwich test, nonsandwiched antibodies, and superfluous secondary antibodies). It can be used for multiparameter detection or reproducibility on-chip tests. Ab antibody

are compared. As readout techniques, not only colorimetry but also surface-enhanced Raman scattering techniques can be used, and fluorescence measurements are also discussed. Optical methods are compared with electrochemical methods, and perspectives and trends are listed.

The increasing number of publications discussing applications of paper-based sensors, especially in point-of-care diagnostics, proved the growing interest in this technique as an addition to classical instrumentation. Accordingly, many reviews compare such LFAs with sandwich and competitive formats; they demonstrate the achievements obtained with gold nanoparticles or carbon tubes and carbon nanoparticles, introduce luminescent particles as quantum dots and rare earth elements, and even consider upconversion techniques [6]. In many literature citations and tables, the results for a large number of analytes are listed for the LFA type (assay format, detection principle), and the linear range and detection limit are provided. Meanwhile, multiplexed lateral-flow biosensors are being developed, allowing multiparameter detection and even a 2D-paper-network approach [7]. Their use in detecting bacteria, viruses, parasites, drugs, and proteins is reported.

The consequence of improved strips is an extended development of more advanced readout instruments versions of readout techniques, thus allowing lateral flow strips to become part of the "internet of things" as an attractive and cost-effective analytical platform for applications in the areas of clinical diagnostics and food and even water safety [8]. Such systems are sometimes called "microfluidic paper-based analytical devices." Reviews have been published in the fields of measuring pharmaceuticals, point-of-care diagnostics, and bioterrorism detection. Of main interest is the short test time and negligible sample preparation. The quality of this type of lab-on-a-chip device depends on the dependencies on the support materials, problems with assays, and selected readout being overcome. Thus, many attempts to overcome these dependencies by chemometrics have been published to find strategies to optimize the conditions of such devices with use of factorial design strategies [9]. Most of these devices use photometers or spectrometers for the readout. However, smartphones in combination with multichannel paper microfluidic devices and simple setups with LEDs can be used for the readout. Such paper-based assays are nowadays even used in the genotyping of single nucleotide polymorphism, where the digital camera can be replaced with a smartphone as a detector [10]. New approaches have a structure that allows multichannel devices that make possible multianalyte detection or internal referencing [11]. The nitrocellulose strips are structured into a fluidic network by short laser pulses. In addition to the usual two test positions in the four channels, a third test line was introduced to take into account the Hook effect. The strips allowed calibration curves for *Salmonella* serovars to be obtained.

Paper-based sensing is an upcoming field in clinical diagnostics and environmental control of food and water. The simple measurement technique and the advanced biochemistry and readout techniques make such strips interesting for analytics, where results have to be obtained within very short times. Since quantification beyond yes/no decisions and parallel multianalyte measurements is becoming possible, the field of application is expanding as an interesting supplement to conventional instrumental analytics. *Analytical and Bioanalytical Chemistry* has been following the development from the beginning, starting with articles in *Fresenius' Journal of Analytical Chemistry*, and will be happy to report assay, readout, and quantification improvements in the future.

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