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Review

Electrophoretic separations on paper: Past, present, and future-A review

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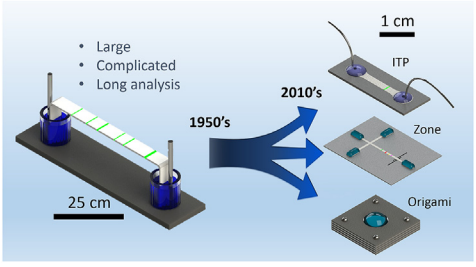
HIGHLIGHTS

- Trends of paper-based electrophoresis from 1930's to 2010's was deliberated.
- Critical developments focused towards rapid, cheap, and portable diagnostic devices.
- Paper-based electrophoresis shows recurring popularity after introduction of μPAD.
- Growing number on zone electrophoresis and isotachophoresis on μPAD was reported.
- Electrophoresis on μPAD shows potential as sample preparation and concentration device.

GRAPHICAL ABSTRACT



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ABSTRACT

Point-of-collection (POC) devices aim for a fast, on-site detection for medical and environmental purposes. In this area, microfluidic Paper-based Analytical Devices (μPADs) have recently gained popularity because these are potentially cheap and environmentally friendly to produce, and easy to use. From an analytical perspective, paper is well known for its use as a substrate for chromatography, but less known for its use in electrophoretic separations. With the recent interest in μPADs, most applications are based on rather simple assays with relatively few applications incorporating an analytical separation. The focus of this review is on paper-based electrophoresis, originating with the key developments in the 1940s and 1950s as well as the recent developments of electrophoretic μPADs, and concluding with a critical discussion of the opportunities and challenges for electrophoretic μPADS in the future.

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Contents

1. Introduction

Separation science plays an important role in analytical chemistry since it may lead to the identification of one or more individual components within unknown mixtures by separating them from one another. Chromatography and electrophoresis are the most commonly used separation techniques. While a variety of substrates have been utilised to perform a separation, paper represents one of the oldest and cheapest substrates [1–3].

The origins of paper chromatography date back to the 1850s and it is still popular and well-known today [2,4]. It started off with the German physicist, Friedlieb Ferdinand Runge, who observed circular colour-forming patterns on filter paper impregnated with metal solutions resulting from the difference in complexation of different dyes with the immobilised metals. Even though this initial observation was not used the way we know chromatography today, his work inspired many scientists to understand and subsequently exploit this behaviour and can be considered fundamental to paper chromatography. The inventor of paper chromatography as we know it, was Mikhail Semonovich Tswett who introduced fundamentals and principles of the technique through his experiments on plant pigments using filter paper as the replica to plant tissue in early 1900's [4–8].

Technically, paper chromatography can be considered as a variant of thin layer chromatography (TLC), and it was initially introduced in order to overcome the limitations of conventional substrates used at the time (i.e. silica gels). It suffered from complicated preparation of the support and difficulties in detection. By using filter paper, the preparation steps associated with silica gel were simply eliminated [9]. Paper chromatography is performed by placing a small sample spot near one end of the paper, followed by placing this end into a suitable solvent. The solvent, drawn through the paper by means of capillary action, carries the analytes across the paper, allowing for a separation based on the differences in retention between the components. Colorimetric detection is the most widely used method for visualisation, but fluorescence and UV imaging are also popular options. In early work, filter paper was attractive because it allowed visualisation of the analytes directly on the substrate using a colorimetric spray, in contrast to silica gels where they needed to be transferred onto pre-treated paper [10]. The position of the spot – a measurement of the distance travelled – is indicative of the analytes' distribution between the mobile and the stationary phases and can be used for identification [2]. In the late 1940s, some researchers started to estimate the concentration of each component based on the intensity of the colour using optical scanners such as the transmission densitometer, the photoelectric densitometer and the X-ray viewer [2,11–14]. Paper chromatography was initially developed for the separation of natural products, and later also applied to synthetic and inorganic compounds [2,13,15]. Because the separation of similar compounds was difficult to achieve using paper chromatography (selectivity could only be adjusted by varying the mobile phase), paper electrophoresis was proposed as an alternative, adding resolving power based on the differences in electrophoretic mobility.

Electrophoresis was initially thought to be superior to chromatography and to provide a micro-scale diagnosis capability, faster analysis time, and better resolved peaks. Because, electrophoresis requires an electric field to be imposed across the paper, more instrumentation is required than in the case of paper chromatography [2]. The popularity of paper as a substrate for electrophoresis started to decline after the 1950s with rapid developments in more sophisticated separation methods and principles (i.e. agarose and polyacrylamide gel-electrophoresis, isotachophoresis, 2-dimensional electrophoresis, and then capillary/microchip electrophoresis), outperforming paper electrophoresis in terms of resolution and sensitivity [16–19].

It was not until approximately 50 years later that paper was reintroduced in analytical research with the development of the microfluidic Paper-based Analytical Devices (μPADs) for Point-of-Collection (POC) analysis (Fig. 1). The rationale for this regained popularity has been the low cost of paper as microfluidic substrate and the ability to move fluids by capillarity without the need for pumps. With the popularity of μPADS, the interest in paper electrophoresis also revived, and this review aims to link the past and the present efforts in this field. Firstly, in this review, historic perspectives on paper electrophoresis considering the hardware, conditions, potential uses in analysis, and the limitations leading to its dip in popularity are provided. Then, the review focuses on how this knowledge was used with the development of portable electrophoretic μPADs and how further improvements could lead towards easy to use, portable paper-based separation platforms.

2. History of electrophoresis on paper

Electrophoresis on paper was first reported in the late 1930s with the implementation of Tiselius' classical moving boundary method to separate amino acids [20]. Despite being over-shadowed in number by paper chromatography, comparisons between paper chromatography and paper electrophoresis all agreed on the higher resolution that could be obtained with paper electrophoresis [2,17,21–23].

It was the realisation that combining complementarity separations could achieve a higher resolution that led to the first two-