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Review

Advances in paper-analytical methods for pharmaceutical analysis

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ABSTRACT

Paper devices have many advantages over other microfluidic devices. The paper substrate, from cellulose to glass fiber, is an inexpensive substrate that can be readily modified to suit a variety of applications. Milli- to micro-scale patterns can be designed to create a fast, cost-effective device that uses small amounts of reagents and samples. Finally, well-established chemical and biological methods can be adapted to paper to yield a portable device that can be used in resource-limited areas (e.g., field work). Altogether, the paper devices have grown into reliable analytical devices for screening low quality pharmaceuticals. This review article presents fabrication processes, detection techniques, and applications of paper microfluidic devices toward pharmaceutical screening.

1. Introduction

Microfluidic systems (Whitesides, 2006) have been well studied and used in clinical diagnostics (Suveen et al., 2013), biological, biomedical (Sackmann et al., 2014) and environmental (Jokerst et al., 2012) fields for over the last two decades. Such miniaturized systems offer several advantages such as low consumption of chemicals/reagents/samples, rapid and high throughput analysis, low cost, and automation compared to their traditional counterparts (Nguyen and Wereley, 2002; Sackmann et al., 2014; Whitesides, 2006).

Different substrates are used for fabricating microfluidic devices on the basis of their applications (Lei, 2014; Nge et al., 2013). During early development, silicon and glass were used as substrate for fabrication of microfluidic device. The high thermal conductivity and resistance as well as relatively high operating temperature makes silicon useful in Polymerase chain and bio-reactions; however due to relatively high cost and optical opacity properties of silicon, this conventional substrate has been replaced by other substrates (Lei, 2014). Glass is commonly used substrate because of its beneficial optical properties, surface stability, solvent compatibility and well-understood fabrication process; whereas, the non-biodegradable and high processing cost of glass may limit its use as disposable devices (Nge et al., 2013). Silicon and glass microfluidic devices have been used in chromatographic separation techniques, such as gas chromatography and liquid chromatography (Iliescu et al., 2012). Recently, polymers (Becker and Locascio, 2002), such as polymethylmethacrylate (Brown et al., 2006), polystyrene (Anderson et al., 2000; Becker and Locascio, 2002), polycarbonate (Liu et al., 2001), and polydimethylsiloxane (Friend and Yeo, 2010) have been widely used as material for microfluidic devices. The polymer substrates offer additional advantages over conventional substrates, namely low cost, ease of fabrication, and efficient design patterning.

The past decade has seen cellulosic paper as an alternative substrate material for the fabrication of microfluidic devices due to its advantages, including low manufacturing cost, analyte/reagent low volume requirements, good wicking properties, and biocompatibility. Milli or microfluidic paper analytical devices (*m*PADs or *μ*PADs, respectively) are analytical devices with milli or micro-fluidicially-patterned paper as their main component. In general, the *μ*PADs can be considered as either a paper variant of conventional microfluidics or an advanced version of classical dipsticks. (Chen et al., 2015; Costa et al., 2014; Li et al., 2012).

Work of translating cellulose paper to chemical testing device can be traced back to Karl Dieterich from Germany. He insulated different strips of paper through saturation with substances like paraffin, ceresin, wax, and varnish with the aim of separating different chemical solutions (Dietrich, 1902). Foundation for the realization of fluidic devices made from paper was laid down in middle of twentieth century (Müller and Clegg, 1949). However, Whitesides and his co-workers first introduced the term *μ*PAD in 2007 (Martinez et al., 2007). The same group demonstrated two- and three-dimensional paper-device

Abbreviations: AgNPs, silver nanoparticles; APTES, 3-triethoxysilylpropylamine; CCD, charge coupled device; CL, chemiluminescence; ECL, electrochemiluminescence; *e*PADs, electrochemical paper-based analytical devices; LOD, limit of detection; OFLX, ofloxacin; OXY, oxytetracycline; WMRS, wavelength modulated Raman spectroscopy; *μ*PADs, microfluidic paper analytical devices

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Table 1
Commonly used paper substrate in μPAD and their selected properties.

Substrate name	Material	Filtration speed* (sec/100 mL)	Pore diameter** (μm)	Porosity (%)	pH	Thickness (mm)	Weight (g/m^2)	Source/remarks
Advantec 1	Alpha cotton cellulose	45	N/A	65	N/A	0.20	90	http://www.advantecmfs.com
Advantec 2	Alpha cotton cellulose	80	N/A	80	N/A	0.26	125	http://www.advantecmfs.com
Ahlstrom 319	Cellulose	72	N/A	N/A	5.99	0.48	180	http://ahlstrom.episerverhosting.com
Whatman GF/B	Borosilicate glass	195	1.0	N/A	NA	0.68	143	www3.gehealthcare.in
Sartorius 292	Cellulose	450	5–8	N/A	6.39	0.18	87	https://www.sartorius.com/sartorius/en
ITW TechniCloth	Cellulose & polyester	N/A	N/A	N/A	N/A	N/A	67	https://www.texwipe.com
VWR 413	Cellulose	N/A	5–13	Medium	N/A	0.20	98	https://us.vwr.com
VWR 600	Cellulose	N/A	13	N/A	N/A	0.15	64	https://us.vwr.com
Whatman 2	Cellulose	240	8	Medium	N/A	0.19	97	www3.gehealthcare.in
Whatman 3 mm	Cellulose	N/A	6	N/A	6.26	0.34	189	www3.gehealthcare.in
Whatman 41	Cellulose	54	20–25	Coarse	N/A	0.22	85	www3.gehealthcare.in
Whatman 5	Cellulose	1420	2.5	Fine	N/A	0.20	98	www3.gehealthcare.in
Whatman BA85	Nitrocellulose	N/A	0.45	N/A	N/A	N/A	N/A	www3.gehealthcare.in
Whatman P81	Cellulose	N/A	N/A	N/A	NA	0.23	230	Ion- exchange capacity = 18.0 μEq cm^2 www3.gehealthcare.in
Whatman 1	Cellulose	150	11	Medium	6.31	0.18	87	www3.gehealthcare.in
Whatman 113	Cellulose	28	30	N/A	6.24	0.42	125	www3.gehealthcare.in
Whatman 114	Cellulose	38	25	N/A	N/A	0.19	77	www3.gehealthcare.in
Whatman 3	Cellulose	325	6	N/A	NA	0.39	185	www3.gehealthcare.in
Whatman 4	Cellulose	37	20–25	42, course	6.22	0.20	92	www3.gehealthcare.in
Whatman 54	Cellulose	39	22	N/A	4.00	0.18	90	www3.gehealthcare.in
Whatman SG81	Cellulose	N/A	N/A	N/A	6.45	0.27	105	www3.gehealthcare.in

* Herzberg, ** or Particle retention, N/A = data not available.

(Martinez et al., 2008) that have opened up a new and thriving research area in analytical chemistry, bioanalytics, and diagnostic medicine. The μPADs have been envisioned as low-cost, disposable, simple-to-use analytical devices applicable in low-resource settings (developing countries, in field analysis or in private homes) where technical infrastructure is limited and trained experts are minimal. Ideal μPADs are considered to be self-standing analytical systems that integrate all the components of analytical assay such as sample transport, sample pretreatment, assay reagents, and signaling system (Cate et al., 2015a).

Like other microfluidic devices fabricated on glass and polymers, paper-based devices consume small amount of reagent and samples and are suitable for multiplexed analysis (Nge et al., 2013). The channels in paper-devices unlike the hollow and closed channels in glass/polymer devices are open and porous. In a simplest form, a conventional microfluidic device can be treated as a “single capillary” system, where the channel dimension defines the amount of sample. In contrast, the μPADs can be simply considered as a device consisting of multiple capillaries having different radii. The most important aspect of μPADs is that the fluid flow in μPADs depends on capillary action and therefore does not require external force for pumping liquids (Alava and Niskanen, 2006).

Paper as a substrate for microfluidics has some inherent properties (Alava and Niskanen, 2006). The physical-chemical properties of cellulosic paper make it an extremely versatile material suited for microfluidics. Paper is composed of thin and lightweight cellulose fibers. These fibers may provide different pore size based on varying length of fibers and the pressure by which the fibers are put together (Alava and Niskanen, 2006). Paper can be easily stored and transported; making the fabrication of μPADs simple and low in cost. The chemical composition of paper allows for surface modification and immobilization of both biomolecular and dry chemical reagents. The high surface-to-volume ratio of paper is also beneficial. Paper can be easily decomposed, making the μPADs eco-friendly. Most paper is white in color, thus making it suitable as a substrate for the simple and rapid colorimetric analyses of μPADs. (Klemm et al., 2005).

Although still relatively young, the topic of microfluidic paper-based analytical devices has been reviewed (Cate et al., 2015a) multiple times for various applications (Lavis and Raines, 2008), fabrication procedures (Xia et al., 2016), detection techniques (Nery and Kubota, 2013). A very few articles have covered pharmaceutical sector application. This review aims to provide general overview of paper microfluidics and focuses on pharmaceutical sector of μPADs research and its future prospective.

2. Fabrication of paper microfluidic device

The paper device consists of hydrophilic macro- or micro-channel and/or assay regions separated by hydrophobic boundaries. Various methods have been utilized to create such combination of hydrophilic and hydrophobic areas on paper substrate.

2.1. Selection of paper type

Before choosing which fabrication method is to be employed to make the paper device, one has to decide the appropriate type of paper for the given application.

Filter, blotting, and chromatography paper are the most widely used substrates for μPADs. These papers are composed of pure cellulose; most do not have any additives such as brighteners that may cause high background emission in fluorescence-based detection. However, some applications require the use of treated or colored cellulose paper, nitrocellulose paper, or glass microfiber as substrate. The cellulosic paper fiber contains abundant hydroxyl groups (-OH) and few carboxylic acid groups (-COOH) (Credou and Berthelot, 2014). These functional groups can easily serve as chemical scaffolds for the immobilization of substances required in a μPAD.

There are many types of papers with different physical-chemical characteristic, selection of appropriate paper type is challenging. The paper selection for a μPADs substrate depends on the fabrication or designing process, the intended purpose of the test device, and the method of detection (Evans et al., 2014; Yetisen et al., 2013). Some of the most commonly used papers are (Sherma and Zweig, 2013) Whatman No. 1, 114 and P81 chromatographic papers and Ahlstrom 319 blotting paper and are listed in Table 1. In most common applications, the paper device requires the mixing of reagents and samples, storage of reagents in dry form, and the chromatographic separation of products (Sherma and Zweig, 2013). For example, μPADs that require reagent mixing and storing may use borosilicate glass microfiber paper as they can retain very fine particles down to submicron range rather than cellulose filter papers. μPADs used for separation process may use