A review on advances in methods for modification of paper supports for use in point-of-care testing

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Abstract

Paper is a widely used support for use in devices for point-of-care testing (POCT) in clinical diagnosis, food safety monitoring and environmental pollution. Paper is inexpensive, biocompatible, biodegradable and allows a sample fluid to flow by capillary force. Numerous method have been developed recently for chemical modification of papers in order to introduce different functionalities. This review (with 148 refs.) summarizes the recent progress in paper-based POCT devices. The introduction summarizes the state of the art of paper-based POCT devices and the physicochemical properties of existing unmodified materials (including cellulose, cellulose-based composites, cotton fibers, glass fibers, nitrocellulose, thread). Methods for paper modification for sample pretreatment are summarized next, with subsections on sample storage and collection, sample separation, nucleic acid extraction and sample preconcentration. Another main section covers approaches for paper modification for improving POCTs, with subsections on assays for proteins, nucleic acids, drugs, ion and organic molecules. The advantages and disadvantages of these approaches are compared. Several tables are presented that summarize the various modification techniques. A concluding section summarizes the current status, addresses challenges and gives an outlook on future perspectives of POCTs.

Keywords Paper-based POCT device · Nanomaterials · Lateral flow assays · Sample pretreatment · Nanolabels

Introduction

Point-of-care testing (POCT), an affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable (ASSURED) technology [1], has utilized outside of clinical laboratory near the patient or bedside [2] and further found widespread applications in biomedical fields, including disease diagnosis, food safety monitoring

and environmental pollution detection [3–5]. Paper, as a ubiquitous substance in daily life, has attracted increasing attention as a powerful microfluidic platform for POCT due to its low cost, biocompatibility, portability, biodegradability and capability to drive fluid flow by capillary force [6–9]. For detection of various targets using the paper-based POCT devices, development of different types of papers is needed.

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Normally, samples contain multiple components and need pretreatment procedure to purify target before detection. Different types of papers have been directly used to fabricate paper-based devices for sample pretreatment and detection [10–16]. For instance, blood separation membranes with highly asymmetric pore structures was used to separate plasma from whole blood [17]. Fusion 5 membranes from Whatman® was used for nucleic acid extraction [18] based on the high affinity between the positively charged glass fibers of the Fusion 5 and negatively charged DNA. Nitrocellulose (NC) membranes, adsorption paper and glass fibers as the main materials were used to fabricate lateral flow assays (LFAs) test strips based on their physicochemical features (*e.g.*, noncovalent interactions/electrostatic adsorption between the paper and chemical molecules) for detections of proteins [19], nucleic acids [15] and ions/chemical molecules [20]. However, these papers have limitations which restrict their further POCT applications [21]. For example, the limited range of sample volumes on one layer of blood separation membrane (10 μL [22]–100 μL [23]) cannot meet the requirements of the relatively low detection sensitivity of several assays [17]. The efficiency of Fusion 5 in extracting nucleic acid is low because of the nonspecific absorbance of cell debris and interferents (*e.g.*, hemoglobin), which affects the extraction purity and thus the analytical result [21]. In addition, the detection sensitivity and specificity of LFAs are still poor because the biological molecules (*e.g.*, DNA, antibodies and antigens) are immobilized on NC membranes based on the simple physical adsorption of chemical reagents, which causes the nonspecific adsorption issue [24, 25]. To improve the performance of the paper-based devices and overcome these challenges, modification approaches to prepare papers with more functions for POCT applications are needed.

With the recent advances in paper materials, micro/nanotechnologies and nanomaterials, various modification approaches have been developed and used to improve the performance of paper-based POCT devices (Fig. 1). For example, a chitosan-based modification technology was utilized to modify Fusion 5 paper to improve the adsorption performance of DNA on the paper [12]. Paper functionalized with zinc oxide nanorods was used to preconcentrate myoglobin with enhanced performance compared to that of the unmodified paper [13]. A chemoenzymatic modification technology was developed to prepare paper-based fluorogenic esterase biosensors [26]. A wax-based technology was applied to modify hydrophobic patterns and hydrophobic barriers on paper using a wax printer [27] and a pen-writing approach [28]. Different nanomaterials, such as quantum dots (QDs) [29–33], gold nanoparticles (AuNPs) [24, 34–46], AuNFs^{MBA}@Ag [47] Cu-Pd/rGO nanoparticles [48], upconverting fluorescent nanocrystals [49], metal-organic framework [50], fluorescent nanoparticles [51], gold nanocage [52], gold nanorods [53], multi-walled carbon nanotubes and graphene oxide [54] and

polymer nanoparticles [55], have also been used as reading signal in paper-based POCT devices. The functional papers prepared by these advanced modification approaches significantly extend the application potential of paper as the substrate of POCT devices.

Thus, considering the paper modification approaches are critical for improving the performance of paper-based POCT devices, it is urgently needed for a review to summarize and compare the existing modification approaches of paper. Previous reviews mainly focus on the working principles [56], fluid flow theory [57], inkjet-printed fabrication technology [58] and fabrication materials and methods [59] of paper-based POCT devices. So in this review, we first summarize the existing papers and their physicochemical properties. Then we introduce the paper modification approaches for sample pretreatment and sample detection, which are the two major steps of paper-based POCT, and then highlight modification processes for fabricating paper-based devices. The advantages and disadvantages of paper modification approaches are also compared. Finally, we discuss the challenges and future perspectives of paper modification technology for POCT.

Existing unmodified papers for paper-based POCT and their physicochemical properties

Sample analysis process normally includes two steps: sample pretreatment (*e.g.*, sample collection and storage, sample separation, nucleic acid extraction and sample pre-concentration) and sample detection (*e.g.*, nucleic acid detection, protein detection and ion/chemical molecule detection). Conventional methods for sample pretreatment and sample detection, such as centrifuge, thermocycling instrument, filter device, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), usually require large, expensive, nonportable and complex equipment. And professional and skilled workers are needed to purify samples and retain targets before downstream analysis. Hence, portable, cheap and easy-to-use devices are urgently needed, especially for the resource-limited situations. Since Whiteside's group first used paper to fabricate paper-based microfluidic devices [60], various types of papers with biomolecule adsorption capability and porous structure have been invented and used to prepare low-cost, simple and portable paper-based microfluidic devices, especially for sample pretreatment and sample detection in the POCT field.

Physicochemical properties of existing unmodified papers

The physicochemical properties of paper are the key factors affecting the performance of paper-based devices [61, 62]. For example, the pore size, specific surface area and

Fig. 1 Existing paper modification approaches for paper-based POCT. Different paper materials, including Fusion 5, filter paper, chromatography paper, cellulose paper, Whatman® No.1 filter paper and NC

membrane, have been modified with various reagents for paper-based sample pretreatment and paper-based detection

hydrophobicity/hydrophilicity of paper affect the capillary forces [63], adsorption ability and flow rate of the paper [64, 65]. Chemical groups on paper surface (e.g., hydroxyl and carboxyl groups) can help immobilize chemical reagents on paper to achieve chemical reactions [66]. Thus, to provide a reference and guidance for choosing proper materials for preparation of paper-based devices, various types of the papers (including cellulose, cotton fiber, glass fiber, nitrocellulose membrane, thread) and their physicochemical properties are first introduced. A material selection diagram according to the equilibrium time and adsorption capacity of the paper material is shown in Fig. 2.

Cellulose Cellulose usually with diameter of 30–40 nm (up to ~100 nm) and specific surface area of $1.4 \text{ m}^2 \cdot \text{g}^{-1}$ is produced by plants or bacteria. Cellulose contains hydroxyl groups on its surface and has the properties of hydrophilicity, easy usability, high porosity, high mechanical strength and degradability [86, 87]. Cellulose can be made into cellophane films and has a porous structure to provide abundant binding sites for adsorption of biomolecules through functionalization [88]. Bacterial cellulose (BC), which is produced by bacteria and has natural biosorbent, renewable, biodegradable and biocompatible properties has emerged as a new type of cellulose paper for preparing paper-based POCT devices [89]. And the BC fiber has a size of 100 nm and high porosity of 92% [90–92]. The amino groups on the BC surfaces can be used to remove residues and adsorb biomolecules, including proteins

(e.g., bovine serum albumen, BSA) and heavy metals (e.g., Pb^{2+} , Cd^{2+} and Ni^{2+}) [67]. The porous structure of BC can adsorb biomolecules based on chemical bonds or physical adsorption. BC can be used as a substrate in paper-based POCT devices for sample pretreatment and sample detection.

Cellulose-based composite materials Cellulose-based composite papers are composed of hybrids of cellulose with various materials, such as Eichhornia crassipes/chitosan, graphene oxide, maleic and phthalic anhydride [68–70, 93, 94]. The physicochemical properties of these composite materials such as surface functional groups, specific surface area and hydrophilicity, are better than those of the pure cellulose. For example, *E. crassipes*/chitosan composite materials have hydroxyl groups and $-\text{CH}$ groups on their surface and with specific surface areas ranging from $132.95 \text{ m}^2 \cdot \text{g}^{-1}$ to $172.49 \text{ m}^2 \cdot \text{g}^{-1}$ and adsorption abilities of up to $0.606 \text{ mg} \cdot \text{g}^{-1}$ at an equilibrium time of 180 min [93]. Graphene oxide/sawdust composites have both the advantages of graphene (e.g., abundant oxygen-containing groups) and cellulose (e.g., nontoxic, biodegradable, renewable and modifiable) and contain mainly C–C groups on their surface. Graphene oxide/sawdust composites have a specific surface area ranging from $124.92 \text{ m}^2 \cdot \text{g}^{-1}$ to $78.13 \text{ m}^2 \cdot \text{g}^{-1}$ and an adsorption capacity up to $158.98 \text{ mg} \cdot \text{g}^{-1}$ at 30 min [68]. Graphene oxide/microcrystalline cellulose aerogels, with the advantages of low density, high specific surface area and hydroxyl groups on their surface, show a high adsorption ability (up to $2630 \text{ mg} \cdot \text{g}^{-1}$) for organic pollutants (e.g., methylene blue) [69]. Graphene oxide/carboxymethyl

Fig. 2 Material selection diagram: adsorption ability plotted against equilibrium time. It is helpful to provide guidelines for paper-based biosensor fabrication [67–85]

cellulose monoliths with a unidirectional porous structure have a compressive strength of 70 kPa, surfaces with abundant hydroxyl and carboxyl groups, a highest porosity of 96% and an adsorption capacity ranging from 46.13 to 82.93 mg.g⁻¹ [71]. Cellulose modified with maleic and phthalic anhydride displays better adsorption capacity than cellulose, with maximum adsorption capacities up to 370 mg.g⁻¹ and 111 mg.g⁻¹, respectively, by introducing carboxyl groups [70].

Cotton fiber Cotton fiber, a natural material, has a specific surface area of 37 m².g⁻¹ and contains hydroxyl groups on its surface, which can be modified with nitric acid, amino or collagen to change its structure or surface chemical groups to improve the adsorption capacity for molecules (e.g., 2, 4-dichlorophenoxyacetic acid [72], active brilliant red X-3B dye [73] and proteins) on its surface [74, 75]. Additionally, the high hydrophilicity and high porosity of cotton fiber can provide a porous network architecture, which contributes to the high fluid flow driven by capillary force in cotton fiber.

Glass fiber Glass fiber is a kind of synthetic fiber and is formed of silica-based thin strands. Glass fiber has a diameter ranging from 15.2 to 18.4 μm, a tensile strength ranging from 0.24 N to 0.4 N [95], a density ranging from 2.5 g.cm⁻³ to 2.7 g.cm⁻³ [95], and a high modulus of elasticity of 60 GPa [96]. Glass fiber has been widely utilized as a support matrix in paper-based devices for adsorption of biomolecules (e.g., proteins, nucleic acids and nanoparticles) [76]. This material has the advantages of good chemical resistance, good tensile strength, excellent dimensional stability and high insulation ability [97].

Nitrocellulose membranes NC membranes are created by the reaction of cellulose and nitric acid [98]. The surfaces of NC membranes, containing the strong dipoles of nitrate groups, can interact with the dipoles of peptide bonds on a protein surface and then immobilize the protein on the NC membrane. Furthermore, NC membranes have a negative charge and can adsorb biomolecules with a positive charge (e.g., antibodies, antigens or other proteins) through electrostatic adsorption. HF-90, HF-135 and HF-180 are the three main types of NC membranes used in POCT. The porosities and pore sizes of HF-90, HF-135 and HF-180 are 80.65%, 79.54% and 78.67% and 10–55 μm, 10–30 μm and 9–14 μm, respectively. The adsorption capacities of NC membranes for proteins are affected by its pore size [77], and the maximum adsorption capacities of HF-180, HF-135 and HF-90 are 2038 mg.g⁻¹, 1810 mg.g⁻¹ and 1135 mg.g⁻¹, respectively.

Thread Threads (e.g., spun thread, cotton yarn and cotton thread) are composed of a tremendous number of fibers tightly bonded with one another to form a twisted structure [99]. Because of the high tensile strength and flexibility, easy operation and modification, good wicking capacity, absorption capacity and fluid capillary flow of thread, it with excellent potential to form hydrophilic or hydrophobic transport channels has been used as the support material of POCT devices [99, 100]. Moreover, the pores of flow channels in threads show a wide variety of interfiber gap sizes and woven/twisted interstitial porosities and spaces. Thus, the properties of threads are affected by many factors such as porosity and pore size. Additionally, the specific surface area of thread is limited, and these patterning and printing

Table 1 Existing unmodified papers for POCT and their physicochemical properties

Type	Material	Physicochemical properties	Application	Refs.
Fusion 5	Glass fiber	Adsorption ability: 40 mg. cm ⁻² Surface charge: positively charge;	DNA extraction	[12, 15, 21]
LF1	Polyvinyl alcohol-bound glass fiber	Adsorption water ratio: 25.3 mg cm ⁻²	Whole blood separation, it mainly used for lateral flow testing or percolation detection	[22]
MF1	Polyvinyl alcohol-bound glass fiber	Adsorption water ratio: 39.4 mg cm ⁻²	Lateral flow assay, paper-based device	[77, 101–104]
VF1	Binder-free glass fiber	None	Lateral flow assay, paper-based device	[77, 101–104]
VF2	Polyvinyl alcohol-bound glass fiber	Adsorption water ratio: 86.2 mg cm ⁻²	Lateral flow assay, paper-based device	[77, 101–104]
NC membrane	Nitrocellulose	Pore size: 0.45 µm Functional group: nitrate groups, Adsorption ability: 1135 mg.g ⁻¹ to 2038 mg.g ⁻¹	Lateral flow assay, paper-based device	[77, 101–104]
Absorbent pad	Cellulose	Functional group: hydroxyl groups Adsorption ability of water: 660 g.m ⁻² to 1600 g.m ⁻²	Lateral flow assay, paper-based device	[77, 101–104]
Conjugate pad/ Sample pad	Glass fiber	Adsorption ability: 19 µL.cm ⁻² to 54 µL.cm ⁻²	Lateral flow assay, paper-based device	[77, 101–104]
Back pad	Plastic	It mainly be used to paste different paper materials and not to adsorb biomolecules	Lateral flow assay, paper-based device	[77, 101–104]
Filter paper	Cotton pulp	Porosity: 16.2% to 40.2% Pore Size: ≤ 50 µm: Functional group: hydroxyl groups	Paper-based channel of DNA extraction, Esterase detection, Myoglobin preconcentration, protein separation	[11, 13, 21, 26]

technologies are difficult to use for the fabrication of POCT devices [100].

Existing unmodified papers used in paper-based POCT

To satisfy the development of POCT technologies, different types of papers and nanomaterials have been used to fabricate paper-based devices, as illustrated in Table 1.

LFA strips, the most commonly used paper-based microfluidic devices for sample detection in POCT, mainly include adsorption pads, NC membranes, conjugate pads, sample pads and back pads [101, 105, 106]. In LFAs, NC membranes, based on a versatile porous material with nitrate groups on its surface, can immobilize nucleic acids, proteins and other biomolecules through hydrophobic, noncovalent or electrostatic interactions [98]. Adsorption pads can adsorb water based on their good hydrophilicity. Conjugate pads and sample pads can store colloidal gold particles and samples because of their good hydrophilic and release properties. The adsorption pad, NC membrane, conjugate pad and sample pad are pasted on the back pad. For example, for nucleic acid detection, NC membranes have been used as a reaction substrate of LFAs to immobilize nucleic acid sequences by streptavidin-biotin reactions because streptavidin can be directly adsorbed on NC membranes by physical adsorption [64, 102, 107] or UV-light cross-linking between two oligonucleotide sequences and the NC membrane [108]. For protein detection, NC membranes have been used to directly immobilize antibodies through physical adsorption [101]. Thus, the performance of LFAs is affected by several factors, including the properties of sample pad, conjugate pad, absorbent pad and signaling molecules.

In addition, filter paper has also been directly utilized to prepare paper-based channels to drive liquid flow through filter paper and reach the reaction area based on capillary force [21]. Additionally, Whatman® filter paper No. 1 has been used to fabricate paper-based devices to detect esterase [26]. Moreover, filter paper with chemical groups on its surface can immobilize chemical molecules through chemical reactions [109].

Besides the above mentioned paper materials, various types of nanomaterials, such as carbon dots (CD) [110, 111], silver nanoparticles (AgNP) [41], AuNPs [38, 39, 43, 112, 113] and AuNPs@SiO₂ NPs [25] and other nanomaterials [48, 50, 55], have also been used as detection probes to generate colorimetric signals on the test strips of LFAs (Table 2). The nanoparticles on LFAs are modified with different biomolecules (e.g., antibody), which can immobilize on conjugation pad and interact with target and then bind the biomolecules on test line for detection.

Paper modification approaches for sample pretreatment

Biological samples generally contain complex components, which makes direct detection challenging. Thus, sample pretreatment procedure before detection, including sample storage and collection, sample separation, nucleic acid extraction and sample pre-concentration, is necessary. For the POCT applications, different types of papers modified with various reagents to change their physicochemical properties (e.g., chemical groups and surface charge) and to enhance their performances for sample pretreatment have been used to prepare the paper-based microfluidic devices, as summarized in

Table 2 An overview on commonly used nanomaterials for modification of papers for use in LFAs

Material type	Paper type	Application	Refs.
AuNP	FP membrane, NC membrane, filter paper	Nucleic acid, C-reactive protein, photometric, listeria monocytogene serotypes and digoxigenin detection, etc.	[34–38]
Carbon dots and AgNP	NC membrane	Zearalenone detection	[41]
Polymer nanoparticles	NC membrane	Nucleic acids detection	[55]
Quantum dots	Whatman filter paper, NC membrane	Mercury, fumonisins, tetracycline antibiotics and enrofloxacin detection	[29–32]
Gold nanorods	NC membrane	<i>E.coli</i> O157:H7 detection	[53]
Gold nanocage	NC membrane	Immunoglobulin G detection	[52]
Red fluorescent nanoparticles	NC membrane	Multi β -agonist residues detection	[51]
Metal-organic framework	Filter paper	Peroxidase mimetic detection	[50]
Cu-Pd nanoparticles	Filter paper	Glucose detection	[48]

AuNP gold nanoparticle, *AgNP* Silver nanoparticles

Table 3 Existing papers with modification approaches for paper-based sample pretreatment

Application types	Type of paper	Modification reagent	Advantage	Disadvantage	Refs.
Sample storage and collection	FTA card	Chemical reagent (Proprietary)	Storage of blood sample up to 22 years; buccal samples up to 12 years	Complex operations of extraction nucleic acid	[21, 114]
	Whatman® 903 protein saver card	Chemical reagent (Proprietary)	Storage up to 13 weeks at room temperature	Complex operations of extraction nucleic acid	[115]
	Nobuto filter paper	Chemical reagent (Proprietary)	Up to 3 months at room temperature	Less storage period	[116]
	Whatman® filter paper	Chemical reagent (Proprietary)	Up to 92 days (transport simulation, room temperature and freezer)	Complex operations of extraction nucleic acid	[117]
	Whatman® Chromatography paper	Butylated hydroxytoluene ^(a)	Up to 180 days at 4 °C, or room temperature	Less storage period Components (e.g., Eicosapentaenoic Acid, docosahexaenoic acid) in fingertip prick blood sample are possible to be degraded	[118]
Sample separation	Thread	EDTA ^(a)	One step processing	Temperature and storage time can affect the performance of modification	[119]
Nucleic acid extraction	Whatman® Chromatography paper	Wax ^(b)	The modification reagent is low cost	Fabrication method (e.g., printer) is high cost and requires high skills	[17]
	Whatman® grade 1 paper	Wax ^(b)	The modification reagent is low cost	Fabrication method (e.g., printer) is high cost and requires high skills	[11]
	Fusion 5	Chitosan ^(a)	This modification technology can increase the efficiency of nucleic acid extraction based on the physical entanglement of long-chain DNA molecules and the fiber matrix and electrostatic adsorption between DNA and the chitosan-modified filter fibers	The extraction efficiency of nucleic acid can be affected by pH	[12]
	Whatman® No.1 filter paper	Spermine, PVP 40 and the cationic polymers (e.g., PEI and chitosan) ^(a)	This modification technology can increase the efficiency of nucleic acid extraction by a positive charge and can bind negatively charged DNA by electrostatic adsorption	Not all cellulose papers can purify nucleic acid	[109]
	Whatman® filter paper	Zinc oxide nanorods ^(b)	This modification technology can increase the binding sites of antibody to capture target protein to achieve protein pre-concentration	This modification process is complex	[13]

(a) Butylated hydroxytoluene, EDTA, Chitosan, Spermine, PVP 40 and the cationic polymers can be widely used for other modification approaches, because there are low cost and easy to fabricate

(b) Wax and Zinc oxide nanorods are not suitable for widely application, because wax fabrication method (e.g., printer) is high cost and requires high skills

Fig. 3 Paper modification approaches for sample storage and collection and sample separation. **a.** Commercial papers for sample collection and storage [21, 114–117]. **b.** EDTA-treated modified technology for one step whole blood plasma separation [119]

Table 3. In the following section, we will introduce the main paper modification approaches for sample pretreatment.

Sample storage and collection

In most cases, biological samples (*e.g.*, whole blood, tissue, saliva and urine) need be stored and transported at low temperature before analysis. Tubes, bottles and refrigerators are normally utilized to collect and store samples. Compared to these conventional methods, paper has the advantages of low cost, porous structure, portability and ease of use. Thus, the paper-based sample storage and collection methods have been developed and used for pretreatment of biological samples.

For storage of different biological samples (*e.g.*, blood, tissues, cells and bacteria) on paper, various chemical reagents have been used to modify different kinds of papers to change the chemical groups on their surfaces. For example, commercial papers, such as FTA cards, Whatman® 903 protein saver cards, Whatman® 3MM filter paper and Nobuto filter paper, were modified with chemical reagents to protect nucleic acids or proteins from being destroyed by bacteria or ultraviolet light (Fig. 3a) [115–117, 120]. Chromatography paper modified with butylated hydroxytoluene was used to collect and store blood sample [118]. These modified papers allow storage and collection of various samples at room temperature and are compatible with several downstream extraction methods, *e.g.*, RNeasy Mini Blood kit [115], making them suitable for POCT applications. The sample storage periods of these papers are different and depend on the chemical reagents used for modification. For instance, Whatman® 3MM filter paper and Whatman® 903 protein saver cards can store blood samples for up to 13 weeks at low temperatures (*e.g.*, -80°C , -20°C and 4°C) and at 35°C [115]. Chromatography paper can store blood samples for up to 92 days at 4°C or room temperature [117]. Nobuto filter paper can store samples for up to

three months at room temperature [116]. FTA cards can store blood samples for up to 22 years and buccal samples for up to 12 years at room temperature. However, these commercial papers have not been fully used for the sample in-result out bedside diagnosis, because they still need combine with the downstream analysis technologies (*e.g.*, PCR [12], RT-PCR [121]) to accomplish the testing step.

Sample separation

Variability of debris components (*e.g.*, red blood cells, inorganic salts and metabolites) in samples (*e.g.*, whole blood, urine and sweat) can affect the accuracy of analytical results. Thus, sample separation is a necessary step to obtain targets from complex samples. But the most used lab method for sample separation, *i.e.*, centrifugation, is expensive and not widely accessible for out-of-lab circumstance.

To realize the inexpensive and fast sample separation process, paper modification approaches have been developed for sample separation. For instance, in a thread-based device composed of cotton thread, holder and glass, ethylenediaminetetraacetic acid (EDTA) was modified on cotton thread to wick whole blood samples and separate plasma (Fig. 3b) [119]. The working principle of this device is that the scouring pretreatment using Na_2CO_3 solution is used to remove the natural wax of cotton thread and increase the wicking properties of material and the absorbability of the reagent into the thread. After this process, the surfaces of the cotton thread and polymer have positive charges and hydroxyl groups, respectively, which can induce blood clotting on their surfaces. After modification of EDTA, the cotton thread can inhibit blood clotting process by activating platelet activity. The EDTA-treated cotton thread device has lower detection limit (114 mg.L^{-1}) than that of the conventional blood analysis (133 mg.L^{-1}). It is a low-cost, accurate and fast analytical platform for POCT in

Fig. 4 Paper modification approaches for sample separation. a, b. Wax-based modification technology is used for sample separation [11, 17]

resource-limited settings. However, the performance of this device is influenced by temperature and storage time. In addition, chromatography paper modified with wax was used to prepare paper-based blood plasma separation device (Fig. 4a) [17]. This paper-based device is consisted of wax and chromatography paper, including the plasma separation zone in the center and the test area in the periphery. In the modification process, wax patterns designed by illustration software (e.g., CAD software) were printed on paper using a solid-ink printer. Then, the wax-printed paper was placed on a hotplate to melt the wax and create hydrophobic barriers which spans the device [17]. After patterning, the paper was modified with agglutinating antibodies and colorimetric chemical reagents by physical adsorption. The as-prepared device is capable of separating blood plasma based on the agglutination technique of red blood cell in the plasma separation area integrated into the device and detecting glucose for medical applications at

home. However, for the application of this device, the expensive wax printer is still needed and the antibodies can easily denature, which affects the accuracy of detection result.

In another example, a paper origami-based electrophoretic device (oPAD-Eps) was fabricated by patterning wax on a slip layer and origami paper (Whatman® grade 1 paper) using CorelDraw software and a wax printer (Fig. 4b) [11]. Since the molecules can move through the paper-based substrate of oPAD-Eps device based on electrophoresis under an external electric field, the oPAD-Eps can separate fluorescent molecules, e.g., Ru(bpy)₃Cl₆, 4,4-difluoro-1,3,5,7,8-pentamethyl-4-bora-3a, 4a-diaza-s-indacene, 8-methoxypyrene-1,3,6-trisulfonic acid trisodium salt, 1,3,6,8-pyrenetetrasulfonic acid tetrasodium salt, rhodamine 6G, methylene blue and rhodamine B [11]. Thus, this sample pretreatment device can be further integrated with other paper-based detection devices for fluorescent detection. However, it is difficult to be used

Fig. 5 Paper modification approaches for nucleic acid extraction. a. Chitosan-modified filter paper for nucleic acid extraction [12]. **b.** Whatman® No.1 filter paper modified with spermine, PVP 40 and the cationic polymers for nucleic acid extraction [109]

for bedside diagnosis because its needs of complex fabrication process and extra electric field. Additionally, the modification technology has a high cost because of the use of an inkjet printer.

Nucleic acid extraction

For detection of nucleic acids, nucleic acid extraction is a key step in isolating targets (e.g., DNA, RNA) from complex samples before analysis. However, the conventional extraction methods always include lysis, washing and elution procedures, which are complex, time consuming and not suitable for POCT applications.

To achieve rapid and simple extraction of nucleic acid, several papers (e.g., Fusion 5, glass fiber) have been used. However, the extraction efficiencies of these papers are still poor due to the nonspecific absorbance of cell debris and interferents (e.g., hemoglobin) on paper, which affects the extraction purity and sensitivity of downstream analysis. To enhance the extraction efficiency, several modification approaches have been utilized to change the surface charges of paper for nucleic acid extraction. For example, chitosan was used to modify Fusion 5 for paper-based DNA extraction (Fig. 5a) [12]. The device is composed of Fusion 5, PDMS membrane and PMMA. Fusion 5 was inserted into PDMS membrane and then sandwiched by two PMMA layers. In the

modification process, Fusion 5 was modified sequentially by oxygen plasma activation, chitosan treatment, deionized water washing and vacuum drying. The capture principle of DNA in the modification process is based on the physical entanglement of long-chain DNA molecules and the fiber matrix and electrostatic adsorption between DNA and the chitosan-modified filter fibers. With this modification, the capture efficiencies of K562 human genomic DNA (up to 98%) and bacteriophage λ -DNA (up to 95%) are significantly improved. Fusion 5 can also preconcentrate λ -DNA from a diluted sample by more than 30-fold. But on the other hand, the extraction efficiency of nucleic acids of this device is affected by pH. The device requires syringe pump and valve to achieve automated extraction of DNA from a small volume of sample, indicating that it still needs improve its portability for bedside diagnosis. In addition, Whatman® No. 1 filter paper was modified with spermine, polyvinylpyrrolidone (PVP) 40 and cationic polymers (e.g., polyethylenimine (PEI), dopamine, 3-aminopropyl trimethoxysilane (APTMS) and chitosan) to bind DNA/RNA from animal, plant and microbe samples (Fig. 5b) [109]. In the binding process, the surface of the modified filter paper has a positive charge and can bind negatively charged DNA by electrostatic adsorption. The binding ability of nucleic acids on the chitosan- and PEI-modified filter paper is better than that of other compounds. The cellulose dipstick is composed of a wax impregnated handle and nucleic acid binding region.

Fig. 6 Paper modification approaches for preconcentration. Paper modified with zinc oxide nanorods for Myoglobin preconcentration [13]

Table 4 Existing papers with modification approaches for paper-based sample detection

Application types	Type of paper	Modification reagent	Limit of Detection and detection range	Advantage	Disadvantage	Refs.
Protein detection	Whatman® chromatography paper	CMC ^(a)	LOD: 0.03 ng.mL ⁻¹ Detection range: 0.03 ng.mL ⁻¹ to 2 ng.mL ⁻¹	This modified technology can improve the stability of the platform	The higher density of antibody attachment can increase the background noise	[122]
	Whatman® chromatography paper	PAMAM dendrimer ^(b)	LOD: 10 cells Detection range: 10 cells to 1000 cells	This modified technology shows excellent selectivity for the detection of telomerase activity	This modification is expensive	[123]
	Whatman® chromatography paper	FF ^(a)	LOD: 1 ng.mL ⁻¹ in PBS and 10 ng.mL ⁻¹ in plasma Detection range: 1 ng.mL ⁻¹ to 10 ⁴ ng.mL ⁻¹	Improve the detection performance and the stability of immobilized Antibodies	It still requires small amounts of reagents as compared to other methods	[124]
	Whatman® chromatography paper	Chitosan and glutaraldehyde ^(a)	LOD: 0.5 nM Detection range: 0.5 nM to 15 nM	Such modified technology can improve the binding-stability and wet-strength of the covalent coupling of antibody	The modification process can be influenced by pH	[125–127]
	Filter paper	SBA-15 ^(b)	LOD: 0.025 mg. Kg ⁻¹ Detection range: 0 µg. Kg ⁻¹ to 160 µg. Kg ⁻¹	This modified technology shows acceptable stability and good reproducibility	The synthesis and functionalization of SBA-15 is time-consuming and complex	[128]
Nucleic acid detection	Thread	Polysiloxanes ^(b)	LOD: 500 CFU. mL ⁻¹ in PBS, 1000 CFU. mL ⁻¹ in milk, 1000 CFU. mL ⁻¹ in juice and 5000 CFU. mL ⁻¹ in lettuce Detection range: 1 CFU. mL ⁻¹ to 10 ⁵ CFU. mL ⁻¹	The sensitivity is enhanced by this modified technology	The preparation of this modified reagent is complex	[129]
	NC membrane	Dipropylene glycol methyl ether acetate containing 20% acrylic polymer ^(b)	LOD: 1 ng. mL ⁻¹ Detection range: 0.1 ng. mL ⁻¹ to 100 ng. mL ⁻¹	The modified reagent is low cost	Fabrication method (e.g., printer) is high cost	[130]
	Whatman® No.1 filter paper	Xyloglucan, amine-functionalized ayloglucan, 1,4-phenylene--disothiocyanate ^(a)	LOD: 0.2 pmol Detection range: 0 pmol to 5 pmol	It is able to activate cellulosic fibers for coupling with aminated DNA without changing the morphology of the fiber	Need two steps to finish the modification process	[108]
	Cellulose paper	Wax ^(b)	LOD: 2×10 ⁻¹⁶ mmol.L ⁻¹ Detection range: 8×10 ⁻¹⁶ mmol. L ⁻¹ to 5×10 ⁻¹⁰ mmol. L ⁻¹	The modification reagent is low cost	Fabrication method (e.g., printer) is high cost	[131]
	NC membrane	Polydimethylsiloxane ^(b)	LOD: 10 ² IU.mL ⁻¹ Detection range: 10 ² IU.mL ⁻¹ to 10 ⁴ IU.mL ⁻¹	Fabrication method (e.g., dropping by pipette) is simple	The cost of modification reagent is higher than that of wax	[14]
Drug detection	Cellulose paper	APTES ^(a)	LOD: 30 ng.mL ⁻¹ Detection range: 30.3 ng.mL ⁻¹ to 6.06×10 ⁴ ng.mL ⁻¹	This modification is time-saving (less than 1h) and can achieve a mass-scale production	This modification process was influenced by the reaction time of APTES	[132]
	Whatman® chromatography paper	MWCNTs/THI/AuNPs ^(b)	LOD: 10 pg.mL ⁻¹ Detection range: 10 pg.mL ⁻¹ to 100 ng.mL ⁻¹	This modified technology is low cost (\$0.3) and makes electrode show excellent electrical conductivities	The synthesis and functionalization of MWCNTs/THI/AuNPs is time-consuming and complex	[133]
Ion detection	Whatman® chromatography paper	APTMS/TEPSA/MPTMS ^(a)	LOD: 0.24 ppm for Ni(II), 0.18 ppm for Cr(VI), 0.19 ppm for Hg(II) Detection range: 0 to 20 ppm of Ni(II), Cr(VI) and Hg(II)	This modified technology shows high repeatability	The uniformity of this modified technology should be further improved	[134]
	Filter paper	Chitosan ^(a)	LOD: 124 µM Detection range: 124 µM to 800 µM	Such modification can enhanced the stability of CdS Ag QDs immobilization and		[29]

Table 4 (continued)

Application types	Type of paper	Modification reagent	Limit of Detection and detection range	Advantage	Disadvantage	Refs.
	Whatman® chromatography paper	BSA ^(a)	LOD: 1 ppm Detection range: 0 to 20 ppm	accelerated the process of colored adduct formation This modified technology shows good wettability-controlled feature	This modification process is influenced by chitosan concentration The modified process is affected by reaction temperature	[135]
	Filter paper	CoPe/IL/G ^(b)	LOD: 0.67 μ M Detection range: low concentration of 0.01 μ M to 1.5 μ M and high concentration of 1.0 μ M to 5.0 μ M	This modified technology makes the electrode show excellent electrocatalytic activity	This modified technology needs multi-steps modification	[136]

(a) CMC, FF, Chitosan and glutaraldehyde, APTES, APTMS/TESPSA/MPTMS and BSA can be further utilized for modification approaches in other paper-based devices, because there are low cost and easy to fabricate

(b) PAMAM dendrimer, SBA-15, Polysiloxanes, MWCNTs/THI/AuNPs and CoPe/IL/G cannot be suitable for further application, because these modification processes are expensive, complex and time-consuming

The cellulose-based dipstick can extract nucleic acid within 30 second without any pipette or electrical equipment and can combine with simple portable amplification device for POCT applications. In short, these modification approaches for filter paper can improve the extraction efficiency of DNA and can be integrated into paper-based devices for the rapid testing of nucleic acids in POCT.

Sample preconcentration

At the early stage of diseases, biomarkers with low concentrations are present in samples. The rapid detection of targets with low concentrations still meets challenges. Sample preconcentration process before detection is thus needed. Conventional preconcentration methods (e.g., centrifugation and filtration) are complex, expensive and time-consuming, making them difficult to be integrated into the POCT devices.

To address this issue, various fast, portable and inexpensive technologies for sample preconcentration have been developed. For instance, Whatman® No. 1 filter paper modified with zinc oxide nanorods using a hydrothermal method was developed to fabricate paper-based ELISA device for preconcentration of myoglobin (Fig. 6) [13]. The ZnO nanostructured-paper composite can form the oriented micro- or nanostructures on paper to provide the high surface area of binding sites, which contribute to the immobilization of biomolecules. And the modified paper treated with 3-APTES through salinization can increase the antibody binding sites (amides) on the paper surface to capture the target protein (myoglobin) for protein preconcentration. This device can detect myoglobin based on the antigen-antibody interaction. And the ELISA testing result of this device indicates that the preconcentration efficiency of biomarkers from a diluted solution (myoglobin < 50 nM) was enhanced 3-fold compared to that of the unmodified paper. However, the ZnO nanostructure-paper composite cannot independently use for POCT because it needs to combined with other biosensors.

The above examples show that various papers have been modified with different chemical reagents for sample pretreatment. These modification approaches have potential for fabricating functional devices with hydrophobic patterns and enhancing the performance of paper-based devices.

Paper modification approaches for sample detection

For the rapid detection of different targets (e.g., proteins, nucleic acids and ions/chemical molecules), various paper modification approaches have been used to improve the detection efficiency by changing the physicochemical properties of papers (e.g., chemical groups, hydrophobicity/hydrophobicity, wet strength and surface charge) (Table 4).

Protein detection

Proteins in whole blood, urine, saliva and sweat have been widely used as biomarkers for detection of various diseases [137]. Paper-based devices have been developed and utilized to detect different proteins [27, 35, 138]. However, the low detection efficiency of the paper-based devices limits their further applications in POCT.

To address this, different modification approaches have been developed to change the features of papers, including the surface functional groups, wet strength and specific surface area. For example, Whatman® chromatography paper was modified with carboxymethyl cellulose (CMC) to form a linker for immobilizing biomolecules in a hydrophilic barrier made of wax as reaction region to promote the functionality and stability of paper-based ELISA devices (Fig. 7a) [122]. The device was used to detect tuberculin based on the antigen-antibody interaction, and its hydrophilicity increased by CMC can reduce non-specific binding of random proteins to improve its detection sensitivity. In the modification process, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride/N-hydroxy-succinimide (EDC/NHS) was crosslinked with the CMC-modified cellulose surface to produce NHS ester groups, which can enhance the specific binding between the paper substrate and the ligands or proteins by covalent conjugation. This modification technology can achieve a detection limit of 0.03 ng.mL^{-1} for tuberculin protein. The CMC-modified paper shows potential as an equipment-free diagnostic platform. However, the higher density of antibody

attachment on paper substrate can increase the background noise and wax printer is expensive. Additionally, Whatman® chromatography paper was modified with polyamidoamine starburst dendrimer (PAMAM dendrimer) to fabricate a paper-based device for the detection of telomerase activity (Fig. 7b) [123]. The modification approach functionalized the paper surface with amino groups, which can improve the efficiency of biomolecules immobilization. The paper-based device was fabricated by hand drawing with using a template and was used to detect telomerase activity based on the hybridization of Cy5 modified single strand DNA probes with telomerase extension products. The PAMAM-based device is a simple and amplification-free fluorescence assay, making it suitable for disease diagnosis at bedside. However, this modification is expensive. Additionally, a novel peptide of diphenylalanine (FF) was used to modify Whatman® chromatography paper to prepare nanocomposite electrodes for detection of alpha-fetoprotein (AFP) (Fig. 7c) [124]. The device is composed of a lower sheet of plastic and an upper layer of cellulose paper modified with silver-graphene printed electrodes and uses antibody captured target protein to generate electrical response relevant to the concentrations of target protein. In the modification process, FF not only enhances the stability of immobilized antibodies via amine-aldehyde reactions, but also increases the wet strength of paper by forming paper-plastic integrated chips. The paper-based device can screen AFP with a range from 1 ng.mL^{-1} to 10^4 ng.mL^{-1} and achieve a detection limit of 10 ng.mL^{-1} . It can be integrated into a miniaturized portable

Fig. 7 Paper modification approaches for protein detection. a. Cellulose paper modified with CMC through EDC/NHS crosslinked for tuberculin-purified protein detection [122]. b. Paper modified with PAMAM dendrimer for telomerase activity detection [123]. c. Cellulose modified with FF for Alpha-fetoprotein detection [124]

Fig. 8 Paper modification approaches for protein detection. **a.** Paper modified with chitosan for protein detection [125]. **b.** Paper modified with SBA-15 technology for gliadin detection [128]. **c.** Thread modified with polysiloxanes technology for *Salmonella enterica* Serotype Enteritidis detection [129]. **d.** Dipropylene glycol methyl ether acetate containing 20% acrylic polymer is printed on the surface of the NC membrane to form barrier to achieve multi-step operations [130]

device as a paper-based biosensor for POCT. However, it still requires small amounts of reagents (*e.g.*, hexafluoroisopropanol) compared to other methods.

Similarly, chromatography paper was modified with chitosan and glutaraldehyde to enhance the immobilization efficiency of antibody (*e.g.*, ubiquitin or enhanced green fluorescent protein, cherry protein) on paper in the paper-based ELISA device (Fig. 8a) [125]. The device was fabricated by attaching paper disk to a plastic strip using double-sided tape and then building the straw region on the paper surface. And the modification process changes the hydrophobicity of the paper surface with varying the amounts of chitosan-glutaraldehyde. Based on the antigen-antibody interaction on the paper substrate, the target antibodies can be captured by protein, which leads to a color change on the paper. The testing results showed that the linear range of the targeted antibodies was 0.5 nM to 15 nM. Such modification technology is easy to perform without need of any special reagent or instrumentation and can also be used for paper-based enzyme and DNA assays based on the covalent coupling of enzymes and DNA molecules, making the paper-based device suitable for more POCT applications. However, the reactivity of glutaraldehyde and the zeta potential of chitosan are influenced by pH, which can affect the immobilization efficiency of protein on the paper surface. In another example, filter paper was modified with the amino-functionalized mesoporous material Santa Barbara Amorphous (SBA-15) to achieve the fluorescent detection of gliadin (Fig. 8b) [128]. The paper-based device used wax to prepare hydrophobic barriers to form microzone for reaction and mesoporous material to modify paper to provide more aldehyde groups on paper to enhance its immobilization

efficiency of biomolecules. The modification process can improve the immobilization capacity of anti-gliadin antibodies on the paper surface by increasing the specific surface area of nanoporous structures and achieving the amino functionalization of SBA-15. The device achieves a detection limit of 0.025 mg.kg^{-1} , good reproducibility and detection stability. Whereas, the synthesis and functionalization processes of SBA-15 are time consuming and complex. And the paper-based device is not suitable for fast detection of gliadin at resource-limited settings because it need to use extra equipment for analysis of fluorescent signal.

Moreover, paper and cotton thread were modified with hydrophobic reagents to enhance the detection efficiency of protein by delaying sample fluid flow rate. For example, polysiloxanes was modified on the surface of cotton thread and the fabricated cotton thread-based device was used to detect *Salmonella enterica* Serotype Enteritidis based on the antigen-antibody reaction (Fig. 8c) [129]. Similar with the fabrication of LFA, the thread-based device is composed of thread, adsorption pad, conjugation pad, sample pad and back pad. It uses antigen-antibody reaction to finish detection and incorporates polysiloxanes to change the hydrophobic of paper-based channel. The modification process used polysiloxanes to reduce the pore size and porosity of the cotton thread by forming hydrophobic barriers on the cotton thread. The detection limit is enhanced approximately 10-fold compared to that of the unmodified thread-based device. However, the preparation of this modified reagent is complex. Additionally, dipropylene glycol methyl ether acetate containing 20% acrylic polymer was modified on a NC membrane surface to create hydrophobic patterns, which can decrease the

sample fluid flow and automate the multistep analysis on the paper-based ELISA device (Fig. 8d) [130]. The device was fabricated by printing dipropylene glycol methyl ether acetate containing 20% acrylic polymer on NC membrane to prepare hydrophobic barrier to form different regions, including non-delayed channel, a wax-delayed channel a test zone and a control zone. As an automated, one-step and portable paper-based ELISA device, it can be used for bedside diagnosis. However, this modification process needs extra equipment (e.g., wax printer). In a word, the performances of these modification approaches can be further enhanced by optimization of the modification processes with simpler procedures and equipment.

Nucleic acid detection

Nucleic acids, as one of the most fundamental biological substances in all organisms, have been used as typical biomarkers [34]. Detection of nucleic acids plays an important role in disease diagnosis. Unmodified paper cannot achieve high performance in nucleic acid detection due to its limited physicochemical properties. For example, unmodified Fusion 5 has low extraction efficiency of nucleic acid due to the higher adsorption ability of nonspecific biomolecules on its surface

[18, 21]. The modification approaches of papers are thus needed for developing the paper-based nucleic acid detection devices.

For example, Whatman® No. 1 filter paper was modified with 1,4-phenylenediisothiocyanate and the fabricated paper device was used to detect nucleic acid based on the DNA hybridization reaction (Fig. 9a) [108]. In the modification process, the surface of Whatman® No. 1 filter paper was activated with aminated xyloglucan and xyloglucan to change the chemical groups on the fibers to react with aminated DNA without changing the morphology of fibers. The functionalized filter paper can accurately differentiate sequence-tagged amplicons of canine and human DNA in mock forensic samples. Moreover, such paper as a rapid and specific diagnostics can be used in real-life situations. In addition, papers modified with hydrophobic reagents were used to improve their detection efficiencies for nucleic acid detection. For instance, cellulose paper was modified with wax to form hydrophobic and insulating patterns on paper sheet and the unprinted wax area on paper with good hydrophilicity and porous structure was used as reaction area for the target in samples. Then the Ag/AgCl ink was screen-printed on the paper surface as electrodes to form paper-based electrochemical DNA assay (Fig. 9b) [131]. The prepared paper-based DNA assay was

Fig. 9 Paper modification approaches for nucleic acid detection. **a.** 1,4-phenylenediisothiocyanate-based modification technology for nucleic acid extraction [108]. **b.** Wax-based modification technology is used to form hydrophobic and insulating patterned paper sheet for screen-printing electrodes in paper-based electrochemical DNA assay [131]. **c.** PDMS-based modification technology is used to fabricate the hydrophobic barrier on the NC membrane for improving the sensitivity of strip [14]

successfully used to electrochemically detect the concentrations of DNA in samples. It shows not only good detection sensitivity but also the capability for integration into emerging electronic devices for the development of high-throughput POCT devices in resource-limited settings. However, this process still needs extra wax printer. Besides wax, polydimethylsiloxane (PDMS) was also added on the NC membrane surface of LFA test strip to create hydrophobic barrier to delay fluid flow (Fig. 9c) [14]. The detection sensitivity of the prepared LFA for nucleic acids based on the nucleic acid hybridization reaction was improved 2-fold over that of the unmodified LFAs. Furthermore, the combination of a shunt and PDMS barrier in the LFAs yielded a 10-fold improvement in detection sensitivity over that of the unmodified LFAs. It can be utilized for bedside diagnosis or resource-limited settings.

Drug detection

Drugs have been extensively utilized to treat, control and prevent diseases in human or animals. At present, various paper-based devices have been developed to detect drug concentrations in samples. But the low detection sensitivity of the paper-based devices is still a problem during their applications.

To handle this problem, several modification approaches by changing the surface groups on papers have been developed and utilized to improve the performance of the paper-

based devices. For example, cellulose paper was modified with 3-triethoxysilylpropylamine (APTES) and the prepared paper-based test strip was used to detect oxitetracycline (OXY) through observing color change (Fig. 10a) [132]. The modification method can amine the paper surface using APTES based on the self-assembly approach, because the amine group can bind metal ions (Fe(III) and Cu(II)) to form color. The detection concentration of OXY using this device is as low as 30 ng.mL^{-1} . This device is inexpensive, equipment-free and environmental-friendly, making it suitable for resource-limited setting. However, this modification process needs complex approach and is influenced by the reaction time of APTES. Furthermore, Whatman® chromatography paper was modified with multiwalled carbon nanotubes (MWCNTs)/thionine (THI)/gold nanoparticles (AuNPs) nanocomposites, which function as the screen-printed working electrodes on paper for the detection of 17β -estradiol (Fig. 10b) [133]. The prepared paper-based device was used to detect 17β -estradiol based on electronic signal response. The modification process increases the specific surface area, which can improve the immobilization capacity of 17β -estradiol antibodies, allowing a higher density load of electroactive materials on paper surface to enhance the electrochemical current. The fabricated paper device has a wide linear detection range of 10 pg.mL^{-1} to 100 ng.mL^{-1} and a detection limit of 10 pg.mL^{-1} . To achieve the really POCT, it still needs to develop a wireless portable electrochemical

Fig. 10 Paper modification approaches for drug detection.

a. Cellulose paper modified with APTES to prepare paper-based color test strip for oxitetracycline (OXY) detection [132]. **b.** Whatman® chromatography paper modified with MWCNTs/THI/ AuNPs Nano composites to prepare the screen-printed working electrodes for 17β -estradiol detection [133]

detector to combine with this device. However, the synthesis and functionalization of MWCNTs/THI/AuNPs is time consuming and complex.

Ion/other chemical molecule detection

Heavy metals and toxic chemical molecules in drinking water threaten human health worldwide. Various novel paper-based devices have been fabricated and used for ion/chemical molecule detection. However, the low detection sensitivity of these devices is still a challenge for their further applications.

To handle this problem, various modification approaches have been utilized to change the surface chemical groups and hydrophilic/hydrophobic features of paper for ion/chemical molecule detection. For instance, APTMS, 3-triethoxysilylpropyl succinic anhydride (TESPSA) and mercaptopropyl trimethoxysilane (MPTMS) were modified on Whatman® chromatography paper by depositing vaporization for achieving multiplex detection of heavy metals (Fig. 11) [134]. The modification process immobilized amine groups, carboxyl groups and thiol groups on the surface of chromatography paper by condensation reactions. Three chromogenic reagents that reacted strongly with Ni(II), Cr(VI) and Hg(II) were covalently coupled to these functional groups, leading to color change of paper based on metal complexation reaction. The detection limits of the prepared devices are

0.24 ppm for Ni(II), 0.18 ppm for Cr(VI) and 0.19 ppm for Hg(II), respectively. It provides a simple and reliable analytical tool for POCT in low-resource settings. However, the uniformity of the modification approach need be further improved. In addition, filter paper modified with chitosan was also used to fabricate a colorimetric test strip for detection of mercury (Hg(II)) (Fig. 12) [29]. The paper test strip was fabricated by incorporating silver-doped CdS dots capped with mercaptoacetic into chitosan-coated filter paper, which can make a visualized color change from yellow to deep brown when Hg(II) ions were captured by the mercaptoacetic acid on CdSAg. The modification process enhanced the stability of CdSAg QDs immobilization and accelerated the process of colored adduct formation. The detection limit of the paper test strip for Hg(II) was 124 μ M. It is a rapid and portable diagnostic, making it in real-time detection. However, this modification process is influenced by the chitosan concentration. Moreover, BSA was utilized to tune the wettability of Whatman® chromatography paper and the BSA-modified chromatography paper was used as a substrate of patterned paper assay by simple writing and stamping patterns on its surface (Fig. 13) [135]. This modification technology achieved the position control and spatial confinement of assay regions via the low solubility of the colored product. And the fabricated paper assay was successfully used to perform multi-target detections of Cu^{2+} and Ni^{2+} based on the precipitation

Fig. 11 Paper modification approaches for ion/other chemical molecule detection.

Whatman® chromatography paper modified with APTMS, TESPSA and MPTMS for Ni(II), Cr(II) and Hg(II), respectively [134]

Fig. 12 Paper modification approaches for ion/other chemical molecule detection. Filter paper modified with chitosan has been used to fabricate a colorimetric test strip for the detection of mercury (Hg(II)) [29]

reaction. It provides a portable diagnosis tool for POCT. However, this modification process is affected by the reaction temperature.

In addition, the wax patterned filter paper modified with cobalt(II) phthalocyanine/ionic liquid/graphene composite (CoPc/IL/G) was used to fabricate an electrochemical paper-based assay for glucose detection (Fig. 14) [136]. The paper-based assay was fabricated by printing wax, CoPc/IL/G composite solution onto filter paper to prepare reaction regions and electrodes and depended on electronic signal to achieve detection. The modification process conferred the paper-based electrode excellent conductivity and fast electron transfer kinetics compared to those of the unmodified paper-based electrodes by enhancing the specific surface area of the paper-based material. The detection limit of glucose of this assay is $0.67 \mu\text{M}$, and the linear dynamic ranges are $0.01 \mu\text{M}$ - $1.3 \mu\text{M}$ and $1.3 \mu\text{M}$ - $5.0 \mu\text{M}$ for low and high concentrations of glucose. To achieve the reality of POCT, the portable electrochemical

detection device will be further developed. However, this modification technology requires multistep modification.

Based on the above summary, various chemical reagents, including CMC, PAMAM dendrimers, FF, chitosan, SBA-15, polysiloxanes, acrylic polymers, 1,4-phenylenediisothiocyanate, wax, PDMS, APTMS/TEPSA/MPTMS, APTES, CoPc/IL/G, MWCNTs/THI/AuNPs and BSA, have all been used to modify different types of papers to improve their detection efficiencies of nucleic acids, proteins, drugs and ions/other chemical molecules, respectively. Among these reagents, CMC, PAMAM dendrimers, 1,4-phenylenediisothiocyanate and APTMS/TEPSA/MPTMS can change the chemical groups on the paper surface. Polysiloxanes can change the hydrophilic/hydrophobic nature of thread. Chitosan, FF and BSA can change the wet strength of paper. Wax, PDMS and acrylic polymers can penetrate into paper to form hydrophobic barriers. CoPc/IL/G and MWCNTs/THI/AuNPs can improve the specific surface area

Fig. 13 Paper modification approaches for ion/other chemical molecule detection.

Whatman® chromatography paper modified with BSA for multi-targets detection of Cu^{2+} and Ni^{2+} [135]

Fig. 14 Paper modification approaches for ion/other chemical molecule detection. Filter paper after wax patterned modified with CoPc/IL/G for the glucose detection [136]

of paper. SBA-15 was used to modify paper by changing the specific surface area and altering the surface chemical groups on the paper. However, to alter other features of paper (e.g., porosity and pore size), the types of chemical reagents for modification are still limited.

Conclusion and future perspectives

Papers with different physicochemical properties have been utilized to fabricate various paper-based devices and used for sample pretreatment and sample detection in the POCT field. Considering that the performance of the paper-based devices with using the unmodified papers is still not satisfactory, many modification approaches have been utilized to tune the physicochemical features of paper materials, such as chemical groups, surface charge, hydrophilicity/hydrophobicity, wet strength and hydrophobic patterns/barriers. However, even the most common modification approaches are also associated with some limitations and cannot be widely used for batch preparation of paper-based devices. For example, experimental results often lack theoretical verification, such as the theory of fluid flow and the mass transfer/bioreactions inside the paper. Thus the mathematical models should be developed to analyze the convection-diffusion-reaction process in paper before and after modification [14, 21, 139, 140]. And the model results should be compared with the experimental results. In addition, to further understand the regulatory mechanism of modification reagents on paper, the physicochemical properties of paper before and after modification need be measured [141]. Furthermore, most chemical modification

approaches are carried out on the commercial papers, resulting in the poor uniformity of structure due to artificial operation [29]. To improve the poor uniformity of structure, new paper modification approaches based on the papermaking process, such as addition of chemical reagents during the pulping process [142], can be used to produce special functional papers. Finally, hydrophobic patterning and barrier modification approaches will be further developed for integration with paper-based electronic chips [143].

Further effort will focus on developing the novel cellulose-based composite materials with programmable and tunable physicochemical properties for the fabrication of paper-based devices. To realize the practical use of paper-based devices and LFAs in POCT, the existing mature modification approaches (e.g., wax-based modification approach [144, 145] and chitosan-based modification approach [12, 109]) will step into the market. Furthermore, to fabricate paper-based integrated electronic chips, single paper material with multifunctional areas will be developed using different modification approaches. To integrate the extra criterion of R (real-time connectivity) and E (ease of specimen collection and environmental friendliness) into the ASSURED of POCT device and then create a new standard of REASSURED additionally, POCT devices should incorporate environmental-friendly modification reagents (e.g., chitosan [146]) to change the physiochemical feature of paper materials. Finally, paper-based modification approaches will play a greater role in POCT. For example, novel properties paper will be used for POCT detection (e.g., polydiacetylene-based paper assay shows chromatic properties and then it can be used for naked-eye detection of pandemic influenza a virus [147]).

Composites materials can be utilized to increase the features of papers (e.g., graphene oxide/thionine/gold nanoparticles nanocomposites have been used for increase the adsorption ability of biomolecules on paper for cancer antigen 125 detection [148]).

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