biosensors

MDPI

Supplementary Materials

Application of Paper-Based Microfluidic Analytical Devices (μPAD) in Forensic and Clinical Toxicology: A Review

Table S1. Paper-based devices proposed for clinical and forensic toxicology issues.

Category	Analyte	Matrix	Detection [sensing molecule]	Explanation of the approach	Equipment [detection system]	Limit of detection	Linearity	Comparison with a different method	Ref.
Detection of toxic compounds in biofluids	Arsenic	Urine	Colorimetric [AgNPr]	The authors developed and tested an arsenic sensor for detecting As (III) using silver nanoprisms (AgNPr). In particular, it has been observed that As (III) promotes the modification of AgNPr to spherical shape associated to a color change.	Qualitative determination with naked eye	0.5 µg/L (6.7 nmol/L)	0.5 - 1000 µg/L (6.7 - 13000 nmol/L)	Spectrophotometric method (UV-Vis)	[125]
	Cyanide	Liquid samples	Colorimetry [Pd dimethylglioximate]	An homemade device has been designed to detect HCN at the gas phase. The liquid sample is gently insuffled with air, and added with phosphoric acid (30%). The detection was carried out using palladium-dimethylglioximate.	Homemade device integrating air flow module, addition of acid and LED-based detector [LED detector and laptop for signal elaboration]	10 µg/L (0.4 µmol/L)	n/a	GC-MS	[129]
	Cyanide	Blood (plasma)	Colorimetry [Pt complex ([Pt(p-MeC6H4)2(phen)])]	An origami paper-based device constituted by 5 layers is used for i. deposit the sample, ii. separating cyanide from methemoglobin by acidification, iii. collecting the analyte in HCN form, iv. basify HCN to form cyanide, and v. detect the analyte by a	Centrifuge [smartphone and laptop for signal elaboration]	10 µg/L (0.4 µmol/L)	26 - 2600 µg/L (1.0 - 100 µmol/L)	GC-MS	[130]

			color changing from orange to colorless.				
Thiocyanate (metabolite of cyanide)	Urine	Colorimetric [cobalt porphyrin derivative]	The identification of urinary thiocyanate was carried out using a cobalt porphyrin derivative reagent which produced a color changing from pink to yellow	[smartphone and laptop for signal elaboration]	73 µg/L (1.26 µmol/L) [smartphone]; 2.9 mg/L (50 µmol/L) [naked eye]	1 – 100 µmol/L	Ion Chromatography	[131]
Ethanol	Blood (mice blood, sheep blood)	Colorimetric [ABTS]	An enzyme-based reaction is integrated in a gas diffusive device. Ethanol is converted in H2O2 by means of alcohol oxidase. Horseradish peroxidase catalyzes the oxidation of color forming reagent, i.e. 2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) through H2O2	[camera and laptop for signal elaboration]	0.12 g/L (2.6 mmol/L)	0.12 - 1.2 g/L (2.6 - 26 mmol/L)	HS-GC-MS	[132]
	Breath	Colorimetric [Cerium Nanoparticles]	The colorimetric reaction is catalyzed by Cerium nanoparticles (Ce-NPs) which act both as reducing agent and colorimetric reagent. Ce-NPs promotes the conversion of H2O2 to O2 and water. The conversion from CeO2 to Ce2O3 produces a yellow color.	[smartphone and laptop for signal elaboration]	0.01 g/L (0.2 mmol/L)	0.2 - 1.2 g/L (4 - 26 mmol/L)	Electronic Breathalyzer	[162]
Nitrite	Saliva	Colorimetric [Griess reagent]	The authors proposed an electrokinetic stacking process for increasing the	Centrifuge, circuit for generating	75 µg/L (1.6 µmol/L)	75 - 1000 µg/L (1.6 - 21 µmol/L)	n/a	[134]

		sensitivity of the test. After, the concentration of a glass fiber support by means of voltage application, nitrite is then revealed using Griess reagent.	voltage [smartphone]				
Artificial Urine	Colorimetric [Griess reagent]	Griess reagent used colorimetric reagent for nitrite determination is applied on a paper-based device in which the hydrophobic barriers have been obtained by dissolving adhesive tape using toluene.	[smartphone and laptop for signal elaboration]	2.3 mg/L (50 μmol/L)	N/A	n/a	[135]
Saliva	Colorimetric [modified Griess reagent -Phosphoric acid]	In order to maximise the color development acetic acid of the Griess' reagent was replaced by 5% H3PO4. Also, the authors separated the two components of the Griess' Reagent, suggesting to use nitrogen to store the device.	Nitrogen to store the device [scanner and laptop for signal elaboration]	0.46 mg/L (10 μmol/L)	0.46 - 46 mg/L (10 - 1000 μmol/L)	Spectrophotometric method (UV-Vis)	[139]
Saliva	Colorimetric [modified Griess reagent - Phosphoric acid]	The authors tested two different composition of the Griess reagent: i. 116 mM of sulfanilamide; 500 mM of ortho-phosphoric acid; 8 mM of N1NED; ii. 50 mM of sulfanilamide; 330 mM of citric acid; 10 mM of N1NED, and demonstrated the higher sensitivity of reagent i. in detecting nitrite. Authors	[scanner and laptop for signal elaboration]	7.8 μg/L (0.17 μmol/L) [nitrite]; 16.7 mg/L (0.27 mmol/L) [nitrate]	0.23 – 11.5 mg/L (5 - 250 μmol/L) [nitrite]; 9.2 – 55.2 mg/L (0.2 - 1.2 mmol/L) [nitrate]	n/a	[140]

		developed the device also for detecting the main metabolite of nitrite, i.e. nitrate					
Saliva	Colorimetric [Griess reagent - Citric acid]	For the first time the spraying technique has been used for fabricating a single-layered 3D-μPAD, creating three dimensional channels in a single piece of paper	[smartphone, photo box equipped with 84LED and laptop for signal elaboration]	0.46 mg/L (9.6 μmol/L); 3.4 mg/L (74 μmol/L)	0.92 mg/L (0.02 - 5 mmol/L)	n/a	[136]
Saliva	Colorimetric [modified Griess reagent – hydrochloric acid]	A preconcentration step is proposed for detecting nitrite in saliva specimens using stamped μPADs, multiple deposition of the sample (n=10) allows to increase the sensitivity of the detection.	[scanner and laptop for signal elaboration]	0.26 mg/L (5.6 μmol/L) (it is not specified if the LOD is calculated using standard solution or saliva specimens)	0.26 – 1.15 mg/L (5.6 - 25 mmol/L)	Spectrophotometric method	[141]
Saliva (artificial)	Colorimetric [modified Griess reagent – hydrochloric acid]	A computer simulation has been carried out for designing a paper-based micromixer device: as a result of the geometry device, sample and sulfanilamide were mixed before the interaction with NED (spotted on opposite end of the device).	[smartphone and laptop for signal elaboration]	0.26 mg/L (5.7 μmol/L)	0.26 - 46 mg/L (5.7 – 1000 μmol/L)	HPLC-UV	[142]
Urine / Serum	Colorimetric [Griess reagent] citric acid	The determination of nitrite ion was carried out Griess reagent integrated in a	[smartphone and laptop for	0.2 mg/L	0.23 - 27.6 mg/L	n/a	[137]

			bidimensional device (2D-μPAD) for detecting the analyte in urine, and in a three-dimensional device (3D-μPAD) for identifying nitrite ion in serum.	signal elaboration]	(4.3 μmol/L) [serum]; 0.1 mg/L (2.3 μmol/L) [urine]	(5 - 600 μmol/L) [serum]; 0.23 - 4.6 mg/L (5 - 100 μmol/L) [urine]		
		Saliva	Colorimetric [Griess reagent] citric acid	The quantification of saliva nitrite was carried out by means of Griess reagent integrated in a deepstick-like paper-based device	[smartphone and laptop for signal elaboration]	1.15 mg/L (25 μmol/L)	1.15 - 11.5 mg/L (25 - 250 μmol/L)	n/a	[138]
		Saliva	Colorimetric [Griess reagent - Citric acid]	A custom-made extruder allows to fabricate a device in single step consisting only in the deposition of the wax on the paper. In fact, the rapid solidification of the printed wax pattern does not require to melt wax	[scanner and laptop for signal elaboration]	0.69 mg/L (0.015 μmol/L)	0.04 - 1 mM (1.8 - 46 mg/L)	n/a	[36]
		Whole Blood	Chemiluminescence [Cu-MOF]	The authors proposed the use of a Cu-MOF system for catalyzing nitrite-peroxide hydrogen reaction	Ring-oven approach for MOF synthesis	0.09 μg/L (2 nmol/L)	0.09 – 4.6 μg/L (2 – 100 nmol/L)	n/a	[143]
Detection of drugs and illicit drugs in biofluids	Alprazolam	Blood; Vitreous Humor	Colorimetry [Silver nanoparticles]	The detection of alprazolam was performed by evaluating the color changing due to the aggregation of silver nanoparticles (AgNPs). The aggregation is promoted by the formation of H-bonding between alprazolam aminogroup and NP	Plastic cassette cabinet [smartphone and laptop for signal elaboration]	smartphone: 10 μg/L (32 nmol/L)	1 – 10 μg/L (3.2 – 32 nmol/L)	UV-Vis	[144]

			stabilizing (citrate) carboxylic groups.					
	Urine	Cyclic Voltammetry and amperometry	Working (WE) and counter electrode (CE) were firstly assembled on the paper using commercially available conducting carbon ink. Then, methylene blue doped silver core palladium (Ag@ Pd) shell nano-hybrids were drop casted on the carbon-based WE followed by room temperature air drying. Alprazolam was reduced to corresponding dihydro derivative on the methylene blue Ag@Pd modified surface.	Potentiostat, two electrode configuration	0.025 μg/L (0.08 nmol/L)	1 – 300 μg/L (3.2 - 980 nmol/L)	n/a	[82]
Diazepam	Urine	Cyclic Voltammetry	Silica coated gold nanorods (Si@GNRs) were synthesized and physically deposited by drop casting on the working electrode previously fabricated on paper using carbon ink. A reduction peak was observed due to the reduction of azomethine functional group at the position four of the benzodiazepine ring.	Potentiostat, two electrode configuration.	0.42 μg/L (1.5 nmol/L)	1 μg/L - 1 g/L; (3.5 nmol/L - 3.5 mmol/L)	n/a	[83]
Cathinone. Mephedrone	Urine	Colorimetry [TMB]	The device was based on a competitive immunoassay using an anti-cathinone	[smartphone and laptop for	4.34 ng/mL (0.03 μmol/L)	n/a	n/a	[90]

			antibody and cathinone-HRP . The sample adsorbed on the paper is washed twice with water, if the sample contained the analyte, the color development promoted by 3,3',5,5′-tetramethylbenzidine (TMB) is proportionally reduced.	signal elaboration]				
Cocaine	Urine	Colorimetry [iodine]	The detection of the analyte was carried out by using an aptamer-crosslinked glucoamylase-trapped hydrogel integrated in a paper-based device. In particular, the structure of hydrogel is broken as result of the interaction between the target compound, i.e., and aptamers which stabilize the hydrogel, and it releases glucoamylase. The enzyme then catalyzes glucose production, which fluids on paper where reacts with glucose oxidase producing hydrogen peroxide. The reaction product is then reduced by horseradish peroxidase, while iodide (colorless) is oxidated to iodine (brown).	[smartphone and Laptop for elaborating pictures]	2.3 ng/mL (4.5 μmol/L)	3 - 15 ng/mL (10 - 500 μmol/L)	n/a	[64]

Urine	Colorimetry	The authors proposed a device based on the formation of a hydrogel. In particular, the presence of the analyte does not permit the formation of the hydrogel, because of the primary interaction with aptamers, which act as structure stabilizers. The formation of the hydrogel does not allow the solution to fluid towards the colorimetric reagent area. The principle was demonstrated by proposing a distance-based approach and a device based on the formation of the color.	Qualitative determination with naked eye	15 ng/L (50 μmol/L)	n/a	n/a	[145]
Saliva; Blood (rats)	Luminescence [ACA-UCNPs]	Up-conversion nanoparticles (UCNPs) functionalized with anticocaine aptamers. In the presence of cocaine, the UCNPs luminescence is quenched. The luminescence change can be observed by naked eye for qualification or recorded by a smartphone camera.	[smartphone]	15.15 μg/L (50 nmol/L) [saliva]	n/a	n/a	[147]
oral fluid (spiked)	Surface Enhanced Raman Scattering Spectroscopy	A paper-based SERS substrate is produced by depositing nano gold (from an HAuCl4 precursor solution) on paper using the	Raman microscope with 785 nm laser and 1200 line/mm grating	1 ng/mL (3.29 nmol/L)	n/a	n/a	[163]

			plasma-assisted chemical vapor deposition.					
Fentanyl	artificial urine; serum (rat)	Surface Enhanced Raman Scattering Spectroscopy	A liquid/liquid self-assembled film of gold nanospheres was deposited on filter paper. The substrate was immersed in NaCl (0.5 M) solution to improve its sensitivity.	Portable Raman spectrometer with a 785 nm excitation laser	0.59 μg/mL (1.75 μmol/L) [urine]; 2.78 μg/mL (8.26 μmol/L) [serum]	4–20 μg/mL (12 - 60 nmol/L)	n/a	[150]
Ketamine	Saliva	Colorimetry [3,3′,5′,5 - tetramethylbenzidine (TMB)]	A competitive ELISA test was integrated in a μPAD. Detection of ketamine utilizes ketamine antibody (K-Ab) and ketamine conjugated horseradish peroxidase, with 3,3′,5′,5-tetramethylbenzidine (TMB) which is used as chromogenic substrate.	[scanner, smartphone and laptop for signal elaboration]	0.03 ng/mL (0.1 pmol/L)	1 - 1000 ng/mL (4.2 - 4200 pM)	GC-MS	[153]
MDMA*	Urine, sweat	Differential Pulse Voltammetry	A two electrode circuit consisting of a counter electrode (CE) and a working electrode (WE) was created on paper using carbon ink. The working electrode was then coated with zinc oxide nanorods (ZnONRs) by drop casting to promote electro-oxidation of MDMA at the electrode surface.	Potentiostat, two electrode configuration	19 ng/mL (0.1 μmol/L)	0.19 – 190 mg/L (1 - 1000 μmol/L)	n/a	[100]
Morphine	Saliva	Colorimetry [gold-conjugated anti-immunocomplex Fab]	A paper-based later-flow assay for detecting morphine in saliva specimens was	piezo-electric inkjet printer [scanner and	20 ng/mL (0.07 μmol/L)	20 - 2000 ng/mL (0.07 – 7 μmol/L)	n/a	[155]

				developed. The two reagents, anti-morphine Fab M1 and anti-human F(ab′)2, were printed on the paper to form test and control lines.	laptop for signal elaboration]				
	Synthetic Cannabinoid. JWH-073	Saliva	Colorimetry [rhodamine B–loaded polymersomes] - Fluorescence	A paper-based later-flow assay system was developed for detecting a synthetic cannabinoid (JWH-073) in saliva specimens. The authors proposed both competitive and sandwich strategies. The system used a rhodamine B– loaded polymersome functionalized with anti-K2 antibodies.	[smartphone and laptop for signal elaboration] - also fluorescence	0.53 ng/mL (1.6 nmol/L) [sandwich]; 0.31 ng/mL (0.9 nmol/L) [competitive]; 0.16 ng/mL (0.5 nmol/L) [fluorescence]	5 - 1000 ng/mL (15 - 3058 nmol/L)	n/a	[157]
	Tetrahydrocabinol	Saliva	Differential Pulse Voltammetry	The device enables the detection of Δ^9-THC as effective biomarkers in saliva. It consists of a circular PAD for sample loading and pre-treatment attached to a PVC layer containing the three electrodes circuit assembled by screen printing. A graphene ink containing 3% of copper-phthalocyanine was used to create the WE while Ag/AgCl ink was used for the reference electrode.	Potentiostat, three electrode configuration	1.4 µg/L (4.5 nmol/L)	0.01 - 1.5 mg/L (32 - 4700 nmol/L)	HPLC-UV/vis	[86]
Detection of compoun	Flunitrazepam	Carbonated and non-	Potentiometry	All solid-state miniaturized ion-sensing devices with reference and indicator	Digital Ion Analyzer	0.17 mg/L (0.55 µmol/L)	0.31 mg/L – 3.1 g/L (1 µmol/L - 0.01 mol/L)	Titrimetric method	[96]

ds added to beverages for drug-facilitated crimes(DFC)		carbonated soft drinks		electrodes were screen-printed on a paper substrate using silver and carbon inks, respectively. PEDT nanoparticle dispersion was applied on carbon surface and the sensor was used for determination of flunitrazepam				
	GHB*	Beverages	Colorimetric [pentacosadiynoic acid-gabazine]	The proposed device was based on the interaction between the analyte and pentacosadiynoic acid-gabazine reagent which turns from blu to red	[smartphone and laptop for signal elaboration]	9.6 mg/L	n/a	n/a	[158]
	Ketamine	Cola, Rum, Whiskey	Colorimetric [bromocresol]	A distance-based device using bromocresol has been designed for detecting ketamine in different kind of beverages	[smartphone and dedicated smartphone app]	2.4 g/L (0.01 mmol/L)	n/a	n/a	[63]
		Beverages	Colorimetric [cobalt thiocyanate]; Fluorescence [Carbon dots-gold nanoparticles]; Potentiometry	A Paper-based device was designed to combine potentiometric, fluorimetric and colorimetric detection. It consists of a first paper layer where two electrodes are printed using MWCNTs ink for further application of a PANI dispersion and PVC indicator and reference membranes. A second PAD with three zones corresponding to detection	Digital ion analyzer Smartphone and ultraviolet-LED torch with 395 nm light for the fluorimetric and colorimetric detection	10 g/L (42 mmol/L) [colorimetry]; 0.048 g/L (0.2 mmol/L) [potentiometry]; 0.0008 g/L (0.003 mmol/L) [fluorimetric]	0.04 - 0.4 mmol/L [colorimetry]; 3.2 μmol/L 0.01 mol/L [potentiometry]; 0.2 - 1 mmol/L [fluorimetric]	n/a	[159]

			mechanism was aligned. Carbon dots-gold nanoparticles and cobalt thiocyanate were used in the fluorescence and color detection zones, respectively.					
	Alcoholic (whiskeys) and non-alcoholic drinks (real juices)	Cyclic Voltammetry	Graphene-oxide nanocrystals (Zeo–GO) were deposited on the surface of the working electrode previously fabricated on paper using carbon ink and then kept at room temperature for drying. The redox transition of the methylene blue (MB) was exploited for the determination of ketamine drug.	Potentiostat, two electrode configuration.	0.24 μg/L (1 nmol/L)	0.24 - 1.2 μg/L (1 nmol/L – 5 μmol/L)	n/a	[85]
Metamizole	Whiskey	Square Wave Voltammetry	A three electrodes circuit was hand drawn on vegetal paper with a graphite pencil and then the reference electrode (RE) was painted with silver ink.	Potentiostat, three electrode configuration	20 mg/L (0.064 mmol/L)	50 – 250 mg/L (0.16 - 0.8 mmol/L)	n/a	[77]
Midazolam					4.8 mg/L (0.015 mmol/L)	25 – 1000 mg/L (0.077 - 3.1 mmol/L)	4.8 mg/L (0.015 mmol/L)	
Scopolamine	Alcohol beverages	Colorimetric [ZnTPP, Methyl orange, Bromocresol green, Iodoplatinate, Dragendorff's, Chen's	A multiplex device based on six different colorimetric reagents was used for identifying eight psychoactive substances (scopolamine, atropine, cocaine, morphine, ephedrine, caffeine, dipyrone,	[scanner and laptop for signal elaboration]	0.6 g/L (2 mmol/L)	n/a	Spectrophotometric method	[161]

			and alprazolam). A chemometric approach was implemented and used for detecting scopolamine in four alcoholic beverages					
Xylazine	Beverage	Electrochemical	A three-electrode system consisting of a WE, a (RE) and a CE was deposited on paper using a graphene ink. Ag/AgCl ink was applied with a paintbrush to the RE. Polyaniline modification of WE provide an electron transfer medium with a larger effective surface area that promoted charge transfer.	Lab-built portable device	0.06 mg/L (0.27 μmol/L)	0.2 mg/L-0.1 g/L (0.9 μmol/L – 0.45 mol/L)	n/a	[84]

*MDMA (Methylenedioxymethamphetamine); GHB (gamma-hydroxybutyric acid).

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