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Review Paper

Electrochemical Paper-Based Analytical Devices for Pharmaceutical Analysis: Materials, Detection Strategies, Applications, And Translational Outlook

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ABSTRACT

Electrochemical paper-based analytical devices (ePADs) have emerged as a promising bridge between conventional laboratory-centered pharmaceutical analysis and the growing demand for rapid, low-cost, portable, and decentralized testing. By combining capillary-driven paper microfluidics with electrochemical transduction, ePADs can integrate sample handling, reagent localization, analyte recognition, and quantitative signal generation within a disposable format. This review critically examines the evolution of paper-based analytical devices toward electrochemical systems relevant to pharmaceutical analysis. Emphasis is placed on structural materials, fabrication routes, electrochemical detection principles, signal- enhancement strategies, active pharmaceutical ingredient (API) analysis, drug screening in biological and environmental matrices, counterfeit and substandard medicine detection, multiplex sensing, analytical validation, and translational barriers. Recent advances in laser-directed electrode formation, conductive polymer–paper interfaces, molecularly imprinted and tamer-based recognition, wearable paper microfluidics, portable potentiostats, and regulatory-style analytical validation are highlighted. The literature shows that ePADs have progressed from proof-of-concept patterned paper strips to increasingly sophisticated analytical platforms capable of supporting dosage-form analysis, biomarker measurement, residue monitoring, and field-oriented drug testing. However, reproducibility, long-term stability, calibration robustness, matrix tolerance, manufacturing standardization, and reference-method benchmarking remain central challenges for routine pharmaceutical deployment. Overall, ePADs represent a rapidly advancing analytical technology with substantial potential for decentralized pharmaceutical quality control, therapeutic and exposure monitoring, and next-generation sustainable sensing.

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INTRODUCTION

Conventional pharmaceutical analysis remains dominated by chromatographic, spectrometric, and bench-top electrochemical techniques, including HPLC, GC, LC–MS, UV–vies spectrophotometry, and laboratory voltammetry systems. These approaches are indispensable for regulatory-quality quantification because they provide high sensitivity, selectivity, method traceability, and compatibility with established analytical validation frameworks. Nevertheless, they also depend on centralized infrastructure, trained personnel, sample preparation, reagent consumption, and relatively longer analytical workflows, which can limit their utility for rapid field screening, decentralized quality control, emergency response, and near-patient measurement1-5.

Paper-based analytical devices were developed to reduce this accessibility gap. Paper is inexpensive, lightweight, widely available, disposable, porous, and able to transport liquids through capillary action without external pumps. These intrinsic properties make paper attractive for point-of-need analytical systems, especially where low cost, reduced sample volume, rapid visual or instrumental readout, and simple fabrication are priorities6-10. The addition of electrochemical transduction further increases the analytical value of paper platforms by allowing quantitative, sensitive, and portable measurements that are less dependent on ambient lighting or subjective color interpretation5,11-14.

Electrochemical paper-based analytical devices, commonly referred to as ePADs or electrochemical pads, are especially relevant to pharmaceutical analysis because many

Drugs, degradation products, metabolites, and residue analyses are electro active or can be detected through catalytic, affinity, potentiometric, or impedance-based mechanisms. Recent reviews identify pharmaceutical quality control, drug-residue monitoring, forensic screening, environmental surveillance, and point-of-care biomarker analysis as major growth areas for paper electro analysis1, 2,4,15. At the same time, adjacent electrochemical sensor literature is rapidly advancing through Nano carbon electrodes, conductive polymer interfaces, miniaturized potentiometric formats, additive manufacturing, and smart wearable systems, all of which are influencing the design of next-generation paper devices16-19.

The present review synthesizes the state of ePADs for pharmaceutical analysis and related drug-monitoring applications. Rather than treating paper sensors simply as low-cost substitutes for conventional assays, this review examines how paper-based electrochemical systems integrate materials science, microfluidic design, electro analytical methodology, and application-specific validation. Particular attention is given to the transition from demonstrative sensing to translational readiness, including real-matrix testing, reference- method comparison, stability studies, device reproducibility, and alignment with modern analytical development and validation principles20, 21.

MATERIALS AND METHODS

Evolution of Paper-Based Analytical Devices in Pharmaceutical Analysis

The modern era of paper-based microfluidics began with the demonstration of patterned paper as a low-cost platform for bioassays. Martinez and coworkers showed that hydrophilic channels bounded by hydrophobic barriers could guide microliter-scale liquid transport and support portable analytical testing6. Subsequent work extended the concept to three- dimensional paper-and-tape devices, enabling vertical flow, multi-zone routing, and parallel reactions in a compact

disposable format22. The field matured further as paper microfluidics became associated with decentralized diagnostics and low-resource analysis7-9.

Early fabrication research established the practical basis for PAD manufacturing. Inkjet printing, wax printing, and thermal processing enabled rapid patterning of fluidic pathways in cellulose or nitrocellulose substrates23-26. Krasner and colleagues demonstrated that paper devices could quantify clinically relevant analyses in urine and saliva, illustrating their potential beyond purely illustrative microfluidic demonstrations27. These advances created an analytical foundation that later supported pharmaceutical and drug-related applications.

A decisive turning point was the integration of electrochemical detection. Dung chai et al. demonstrated aerometric detection of glucose, lactate, and uric acid in paper microfluidic devices, establishing that paper could serve not only as a fluidic support but also as part of a quantitative electro analytical platform11. Nia et al. then introduced paper-based electrochemical sensing layouts and demonstrated compatibility with commercial electrochemical readers, which moved the technology closer to practical field operation12, 13. These studies defined the pad concept and opened the door for drug, biomarker, and environmental residue analysis.

From 2012 onward, device engineering became more sophisticated. Origami-inspired paper platforms enabled controlled assembly of three-dimensional electrochemical architectures, while high-throughput 3D prototyping simplified multilayer PAD fabrication28, 29. Subsequent studies investigated microware electrodes, quasi-steady flow, inkjet-printed Nano carbon traces, zinc oxide nanowire integration, carbon-black electrode modification, and laser- structured paper platforms, each improving some combination of conductivity, current density, signal-to-noise ratio, device manufacturability, or application scope30-37.

The pharmaceutical relevance of this evolution has become increasingly explicit. Reviews now describe ePADs as tools for API analysis, quality screening, and counterfeit medicine

Detection, residue monitoring, and drug-related bio analysis1, 2, 4. In parallel, point-of-need PAD reviews and sustainable sensor perspectives emphasize the importance of low-resource deployment, reduced waste, and integrated portable instrumentation10,15,19,38. Thus, the field has progressed from patterned paper strips to electrochemical systems with genuine pharmaceutical and translational ambition.

Structural Components and Materials Used In ePADs

The performance of a pad reflects the combined behavior of its paper substrate, hydrophobic barriers, electrode system, modifiers, recognition layer, and readout interface. Unlike inert plastic or glass substrates, paper simultaneously serves as structural scaffold, capillary pump, reagent reservoir, porous reaction matrix, and, in some designs, a direct electrochemical support. This multifunctionality is central to the strengths and weaknesses of ePADs3, 5, and 15.

Paper Substrates

Cellulose filter paper remains the most widely used substrate because it combines capillary transport, low cost, flexibility, and ease of fabrication. Whitman-type papers are popular in proof-of-concept and applied studies because of their relatively reproducible wicking properties, whereas chromatography paper and nitrocellulose are selected when fluid routing, biomolecule retention, or immunoassay-type functionality are required5, 23, 26. Office paper, waxed paper, paper towel, and alternative commercial cellulose substrates have also been explored to reduce cost

or tailor surface texture, conductivity, and wetting behavior35, 38.

Hydrophobic Barriers and Fluidic Architecture

Hydrophobic barriers determine the geometry of paper microfluidics. Wax printing remains one of the most practical approaches because it is low-cost and readily scalable, producing complete barriers after heating and wax penetration through the paper thickness24, 25. Inkjet printing and photolithographic methods offer finer control but may require more specialized equipment9, 23. Newer laser-based methods and Paradigm–wax melting strategies aim to improve barrier control, prototyping speed, and fabrication precision36, 39.

Electrode Materials

Carbon and graphite inks dominate pad electrode design because they are inexpensive, printable, electrochemically versatile, and compatible with disposable formats. Screen- printed carbon electrodes can incorporate working, counter, and reference components on the same device, while pencil-drawn or microware formats offer alternative routes for low-cost prototyping and high current density5, 30, 40. Noble metals such as gold and silver remain important for reference electrodes, conductive traces, affinity immobilization, and high- performance electrochemical interfaces41, 42.

Nanostructures and Conductive Polymers

Nanomaterial's are frequently used to increase electro active surface area, accelerate electron transfer, improve adsorption of target analyses, or enable affinity chemistry. Carbon nanotubes, grapheme, reduced grapheme Nano ribbons, carbon black, gold nanostructures, silica-coated gold Nano rods, metal oxides, and laser-induced grapheme are among the most widely reported materials in the broader paper-electrochemical literature32,33,35,37,43-45. Conductive polymers are increasingly valuable for creating flexible paper electrodes. PEDOT: PSS-based paper interfaces have been used in cancer biomarker detection, grapheme–PEDOT: PSS autosensing, and more recent immunosensor architectures, showing that polymeric conductivity and biocompatibility can be combined with paper substrates46-49. Enzyme-immobilized chromatography-paper architectures further show that the paper matrix

Can support bio catalytic recognition while retaining compatibility with electrochemical signal generation50.

Recognition Layers

Selectivity in ePADs can be achieved through enzymes, antibodies, a tamers, molecularly imprinted polymers (MIPs), gonophores, and hybrid recognition schemes. A tamer-based paper electrochemistry has been demonstrated in origami sensing and microfluidic electrochemical platforms, while molecularly imprinted layers have enabled simultaneous detection of oxidative stress biomarkers and selective drug-related sensing28, 51-54. Potentiometric paper devices for phenobarbital show the value of ionosphere-based recognition in charged pharmaceutical analyses55. These developments are essential because simple electro oxidation alone is often insufficient for robust selectivity in complex biological, pharmaceutical, or environmental matrices.

Electrochemical Detection Principles in Drug Analysis

The analytical behavior of ePADs depends on the choice of electrochemical transduction mode. Voltammetry, aerometry, potentiometric, and electrochemical impedance spectroscopy each address different sensing problems and have distinct advantages for pharmaceutical analysis.

Voltammetry Techniques

Voltammetry methods are the most common electrochemical tools in drug analysis because

many APIs and related analyses undergo oxidation or reduction within accessible potential windows. Cyclic voltammetry is often used for mechanistic characterization, whereas differential pulse voltammetry and square-wave voltammetry are preferred for quantitative determination because they reduce no faradaic background and improve sensitivity2, 16, and 42. Nearing et al. reported a Si@GNR-modified electrochemical paper platform for diazepam with Nano molar sensitivity in formulations and urine, while Camargo et al. used waterproof paper for voltammetry determination of paracetamol and melatonin43, 56. Pharmaceutical electro analysis outside the pad niche also illustrates how nanostructured electrodes can improve the detection of acetaminophen, paracetamol, p-aminophenol/paracetamol mixtures, and dexamethasone in complex samples, providing design principles that are increasingly transferable to paper substrates57-61.

Aerometric and Chronoamperometric Techniques

Aerometric sensing is valuable when analyte recognition generates a steady current at a fixed potential. This is especially effective for enzyme-mediated reactions, mediator systems, and rapid screening applications. The foundational pad study by Dung chai et al. used chronoamperometry for serum analyses with Prussian Blue-mediated hydrogen peroxide detection11. Gautama et al. later integrated paper-based plasma separation with non-enzymatic electrochemical detection of ascorbic acid, demonstrating a complete sample-handling and readout workflow in a disposable device62. A 3D-printed batch injection cell coupled to pencil-drawn ePADs enabled rapid aerometric determination of 5-hydroxytryptophan in commercial food/pharmaceutical products, emphasizing the compatibility of ePADs with high-throughput flow-inspired formats40.

Potentiometric Techniques

Potentiometric sensing is attractive for low-power devices and analyses that can be measured using ion-selective or molecular-recognition membranes. Historically, potentiometric paper devices have been less visible in drug-specific pad literature than voltammetry and aerometric formats, but this is changing. Fully inkjet-printed potentiometric paper ion

Sensors demonstrated the feasibility of paper-integrated potential-based measurement41. More directly relevant to pharmaceutical analysis, Almehizia et al. developed a paper-based potentiometric device for phenobarbital determination using solid-contact ion-selective electrodes, thereby showing that therapeutic drug analysis can be addressed through paper potentiometric rather than oxidation-current readout alone55. Recent review work further indicates that planar potentiometric devices are gaining momentum for point-of-care applications but continue to face challenges in potential reproducibility, calibration stability, and long-term drift17.

Electrochemical Impedance Spectroscopy

Impedimetric detection is particularly useful for affinity sensing, molecular binding events, interface characterization, and label-free approaches. It is often employed where analyte binding alters charge-transfer resistance, capacitance, or interfacial transport rather than generating a strong direct redox signal. In pad-related bio analysis, grapheme–PEDOT: PSS paper apt sensors and dual-imprinted paper platforms show how interface-sensitive sensing can improve recognition of biomarkers and structurally similar analyses47, 53. Impedance also plays an important secondary role in characterizing Nano modified paper sensors, conductive polymer interfaces, and paper electrode optimization34, 46, 48.

Signal Enhancement Strategies

Signal enhancement in ePADs is achieved through materials, geometry, and chemistry. Nanomaterial's can increase electro active area and promote electron transfer; imprinted or affinity layers can raise selectivity; and fluidic architecture can improve analyte delivery and stabilize transport. Diazepam sensing with silica-coated gold Nano rods, oxidative biomarker detection using imprinted silver–silica structures, and dual-analyte origami 3D ePADs illustrate these strategies43, 53, 54. Carbon nanomaterial's, laser-induced grapheme, PEDOT: PSS composites, and additive-manufactured carbon black/PLA architectures represent broader electrochemical design developments that can be adapted to paper-based formats18, 37, 45, and 46.

Analytical Parameters Influencing Drug Detection

Analytical performance is influenced by pH, supporting electrolyte, applied potential, scan frequency, pulse amplitude, wetting rate, paper porosity, device geometry, modifier loading, and matrix composition. These variables affect peak position, signal intensity, transport kinetics, current stability, and background noise2, 5, 31. In pharmaceutical applications, optimization becomes even more important because dosage forms may contain excipients, biological samples may contain proteins and salts, and environmental matrices may include organic matter and competing electro active species. The most convincing studies therefore evaluate interference, real-sample recovery, repeatability, and comparison against a reference method rather than reporting only low limits of detection20, 53, 62, and 63.

Fabrication Strategies and Device Designs

Fabrication strategy determines not only device cost but also analytical reproducibility, channel geometry, electrode consistency, and suitability for scale-up. Wax printing remains a foundational technique because it is inexpensive, rapid, and effective for creating hydrophobic channels in cellulose paper24, 25. Wax methods have also been adapted to nitrocellulose membranes, where barrier formation must be compatible with biomolecule retention and surface chemistry26.

Electrode fabrication introduces a second design axis. Screen printing supports standardized three-electrode architectures and integration of carbon, silver/silver chloride, and modified inks. Alternative methods, including pencil drawing, microwares, inkjet printing, and laser-

Derived electrodes, can lower cost or improve conductivity depending on the application30, 32, 36, 40. Laser-directed fabrication is especially promising because it can reduce multistep assembly and produce conductive patterns directly in or on paper-like substrates36, 37, and 45.

Multilayer and foldable devices expand the functional capacity of paper systems. Three-dimensional stacked PADs allow sample splitting, vertical routing, and multiplex zones, while origami devices enable fluidic activation upon folding and compact integration of recognition, incubation, and detection steps22, 28, 29. In drug and biomarker sensing, these layouts are valuable when the assay requires pretreatment, plasma separation, dual-analyte recognition, or sequential reagent contact53, 54, 62.

The emergence of 3D printing and additive manufacturing provides a complementary route for holders, injection cells, alignment modules, and electrochemical device housings. The pad/3D-BIA system for 5-hydroxytryptophan demonstrated that paper electrodes can be incorporated into reusable analytical fixtures without losing their disposable advantages40. More broadly, additive-manufactured electrochemical sensors for pharmaceuticals show how low-cost fabrication and rapid prototyping may support customized decentralized assays18.

Applications Of ePADs In Drug Analysis

Analysis of Active Pharmaceutical Ingredients in Formulations

The direct determination of APIs in dosage forms is among the most important pharmaceutical applications of ePADs. A strong example is the diazepam paper-chip sensor developed by Nearing et al., which was applied to tablets, injections, and urine. Camargo et al. demonstrated waterproof-paper electrodes for paracetamol and melatonin determination, confirming that paper can function as a viable disposable substrate for small-molecule drug analysis43, 56. The broader electrochemical literature on acetaminophen, paracetamol, dexamethasone, chloroquine, citalopram, ceftriaxone, codeine, and 5-hydroxytryptophan adds valuable context for analyte selection, electrode design, and calibration strategies that can migrate into paper-based devices40, 59-61, and 64-66.

Several low-cost paper and portable electrochemical strategies extend this theme to caffeine, ibuprofen, diclofenac, and other pharmaceutically relevant compounds. Syahputra et al. reported paper-based electrochemical detection of caffeine in beverages, while Li et al. developed a paper-based sensor for ibuprofen. Costa-Rama et al. and Seguro et al. addressed diclofenac using electro analytical approaches that reinforce the importance of preconcentration and molecular imprinting for pharmaceutical targets67-70. These studies show that pad-oriented drug analysis is expanding beyond a small number of model analyses toward a more diverse pharmaceutical portfolio.

Drugs and Clinically Relevant Analyses in Biological Samples

Biological matrices are analytically demanding but highly relevant to decentralized health monitoring. Gautama et al. integrated blood–plasma separation with electrochemical ascorbic acid sensing in a biodegradable Expand, demonstrating a practical route for whole-blood-derived analysis62. Martins et al. reported electrochemical paper detection of 8-hydroxy-2′-deoxyguanosine, and Nontawong et al. extended this approach to simultaneous determination of 8-OHdG and 3-nitrotyrosine using a dual-imprinted pad validated against HPLC53, 71. Sonnet et al. further demonstrated simultaneous paper-based detection of vanillylmandelic acid and 5-hydroxyindole-3-acetic acid in urine and plasma using a dual-imprinted origami 3D-ePAD54.

Not all clinically oriented electrochemical assays are drug assays in the strict regulatory sense, but they are highly informative for pad translation because they address sample pretreatment, matrix tolerance, bio fouling, selective recognition, and portable validation. For example, paper or microfluidic systems for creatinine and multimarket blood analysis show how integrated sample-processing architectures can support real-world analytical demands72, 73. This is directly relevant to future pad development for therapeutic drug monitoring and pharmacodynamics biomarker assessment.

Counterfeit and Substandard Medicine Screening

Substandard and falsified medicines remain a global public-health concern, especially for antibiotics, antimalarial, and high-volume essential products. The World Health Organization continues to identify substandard and falsified medical products as a major international health problem, and bibliometric work confirms rising attention to this field74, 75. Paper analytical devices have been proposed for rapid field screening of beta-lactam antibiotics and ant tuberculosis pharmaceuticals, and economic modeling suggests they can reduce screening costs in low-resource settings76, 77. Drug-testing

reviews also emphasize that paper platforms are increasingly adaptable to chemically diverse matrices and decentralized screening workflows78. More recent studies extend field screening through vibrational or spectroscopic tools such as SERS and handheld NIR, offering complementary methods to paper electrochemistry79, 80.

Within the pad literature itself, da Silva et al. developed a functionalized-bio char paper electrochemical device for paracetamol screening in substandard medicines, directly addressing real commercial samples and on-site pharmaceutical quality control63. Paper microfluidic platforms have also been used for electrochemical ketamine sensing and on-site ketamine screening with multimodal output, illustrating the relevance of paper-based drug- testing strategies beyond conventional dosage-form analysis81, 82. The combination of paper disposability, low instrumentation requirements, and quantitative electrochemical readout makes ePADs attractive for preliminary screening, although confirmatory regulatory testing still requires validated reference methods. This distinction is critical: ePADs are highly promising triage tools, but translational claims should be calibrated against the analytical scope and validation depth of each study20, 21.

Simultaneous or Multiplex Analysis

Multiplexing increases the value of paper devices when clinical or pharmaceutical decisions depend on analyte panels rather than isolated markers. Nontawong et al. and Sonnet et al. demonstrated dual-analyte determination in urine and plasma using molecular imprinting, showing how recognition chemistry and device geometry can combine to support simultaneous readout53, 54. Multiplexing is also central to emerging wearable sensor arrays capable of measuring combinations of electrolytes and metabolites in sweat, saliva, and urine83, 84.

For direct pharmaceutical translation, multiplex ePADs could eventually enable simultaneous assessment of combination products, degradation markers, or co-administered drugs. At present, however, truly drug-specific multiplex ePADs remain less common than biomarker- focused or wearable multiplex systems. This gap defines a clear opportunity for future research2, 3.

Environmental and Residue Monitoring Of Drugs

Environmental and food-residue monitoring is a rapidly expanding domain for paper electro analysis. Qi et al. developed a foldable paper-based photo electrochemical biosensor for ampicillin in milk, tap water, and river water, demonstrating ultra-trace antibiotic analysis

In real matrices85. Paper-based sensors for sulfamethoxazole and trimethoprim, paracetamol monitoring in wastewater, and broader enzyme-based electrochemical systems for pharmaceutical residues in wastewater reinforce the importance of decentralized environmental surveillance44, 86, and 87. Recent reviews on antibiotic electrochemical detection further emphasize the analytical importance of residue monitoring in relation to antimicrobial resistance concerns88.

Adjacent electrochemical studies on tetracycline, rifampicin, norfloxacin, ofloxacin, ciprofloxacin, and lab-made 3D-printed tetracycline sensors illustrate the rapid development of high-sensitivity antibiotic sensors, even when the platforms are not strictly paper-based. These reports are relevant because they identify promising recognition materials, electrode architectures, and selectivity strategies that may be adapted to pad formats88-91. Thus, environmental pharmaceutical analysis is likely to remain a major driver of pad innovation.

Analytical Performance and Validation Aspects

The utility of ePADs depends not only on low detection limits but also on robust analytical validation. Core validation characteristics include selectivity, calibration range, and limit of detection, limit of quantification, accuracy, precision, repeatability, intermediate precision, matrix recovery, interference tolerance, sample stability, device-to-device reproducibility, and agreement with a reference method. Modern pharmaceutical analytical development increasingly emphasizes lifecycle thinking and scientifically justified method validation, as reflected in ICH Q2 (R2) and ICH Q1420, 21.

Several pad studies illustrate encouraging validation practice. Nontawong et al. reported low detection limits, real biological matrices, and HPLC benchmarking for oxidative/nutritive stress biomarkers53. Gautama et al. evaluated ascorbic acid sensing in plasma-derived samples with practical sample-separation architecture62. Da Silva et al. applied their substandard- medicine paper sensor to commercial dosage forms and reported recovery and selectivity data63. Ferreira et al. combined paper electrodes with a 3D-printed BIA system and demonstrated repeatability, reproducibility, lifetime, analytical frequency, and agreement with UV–vies spectrophotometry40.

Despite this progress, many papers still emphasize sensitivity more strongly than translational robustness. A low Nano molar detection limit is not sufficient if electrode fabrication varies between batches, calibration slopes drift with humidity, or the device is not evaluated under realistic storage conditions. The next stage of pharmaceutical pad development therefore requires larger sample cohorts, inter-operator studies, and batch-to-batch fabrication analysis, stability under transport and storage, and transparent comparison with accepted analytical reference methods2, 5, and 17.

Advantages Of ePADs Over Conventional Analytical Methods

The principal strengths of ePADs are low cost, portability, disposability, low reagent and sample consumption, capillary-driven fluid transport, and potential compatibility with handheld readout systems. These features align with the needs of decentralized pharmaceutical screening, low-resource analysis, rapid triage, and point-of-need testing1, 3, 10, 38.

Electrochemical readout adds several advantages over purely colorimetric PADs: quantitative signal generation, compatibility with miniaturized potentiostats, improved sensitivity for many analyses, and stronger potential for digital data transfer. Recent efforts toward battery- less NFC potentiostats, Bluetooth-linked handheld electrochemical readers, and portable point-of-care devices demonstrate how ePADs can be coupled to modern compact instrumentation92-94. Such integration is important for future pharmaceutical workflows where

The analytical device may need to support traceable data capture rather than only visual pass/fail screening.

Sustainability is another advantage. Paper reduces the use of plastics and can minimize reagent waste, while disposable low-mass devices are well suited to single-use field applications. Sustainable sensor perspectives increasingly frame paper and fabric-based platforms as components of eco-conscious point-of-care systems, particularly when paired with low-power electronics and recyclable or low-material manufacturing19, 38.

Limitations and Translational Challenges

Despite their promise, ePADs remain less standardized than established chromatographic methods. Paper introduces heterogeneity in thickness, porosity, capillary transport, surface adsorption, and humidity response. Each of these factors can alter analyte delivery and

electrochemical signal magnitude. Modified electrodes add further complexity because nanoparticles, conductive polymers, imprinted layers, and enzyme or tamer coatings may vary across batches2, 3, and 5.

Shelf-life and matrix tolerance are major barriers. Biological fluids can foul electrodes, food and environmental samples may contain electro active interferes, and commercial dosage forms include excipients that affect wetting, adsorption, or redox background. Potentiometric paper sensors must also address response drift, potential reproducibility, and calibration maintenance, especially if used outside controlled laboratory conditions17, 55.

Manufacturing scale-up remains another challenge. Wax printing, screen printing, laser processing, and additive manufacturing can each produce promising laboratory devices, but translation to routine pharmaceutical use requires tight process control, device QC, packaging, calibration strategy, and regulatory interpretation. These considerations are closely aligned with the analytical-development mindset emphasized by ICH Q14 and the validation expectations of ICH Q2 (R2)20, 21. The field has moved beyond asking whether paper electrochemical devices can generate a signal; the central question is now whether they can generate reliable, reproducible, clinically or pharmaceutically meaningful data under real operating conditions.

Emerging Trends and Future Perspectives

Several converging trends are likely to define the next phase of pad research. First, laser- derived electrodes and advanced patterning may improve reproducibility and simplify fabrication. Laser-induced grapheme and laser-directed electrochemical paper platforms offer direct conductive structuring and may reduce dependence on multistep ink deposition36, 37, and 45.

Second, wearable and continuously monitored paper hybrids are expanding the conceptual scope of paper electro analysis. Wearable paper microfluidic systems have already been used for cortisol sensing, sweat biomarker analysis, multicomponent electrochemical arrays, and hybrid colorimetric–electrochemical readouts84, 95-99. Fully integrated wearable sensor arrays capable of monitoring electrolytes and metabolites across sweat, saliva, or urine further demonstrate the broader direction of decentralized electrochemical health analytics83, 100.

Third, affinity and hybrid recognition strategies will become more important. A tamer-based paper sensors, MIP-enabled devices, and dual-recognition electrochemical systems can improve selectivity for structurally similar drugs or low-abundance biomarkers. Emerging examples in estradiol sensing, general biomarker autosensing, and dexamethasone recognition support this trajectory51, 52, and 61. Such advances may be crucial for future therapeutic monitoring applications in which selectivity is more important than detection limit alone.

Fourth, smartphone-connected and battery-light instrumentation can bring ePADs closer to practical pharmaceutical deployment. NFC-powered potentiostats, Bluetooth-enabled portable systems, and handheld readers suitable for small disposable electrodes can support field analysis and data logging92-94. In combination with stable device manufacturing and validated analytical workflows, this may enable distributed networks for medicine quality screening or environmental residue surveillance.

Finally, the future of ePADs will depend on rigorous translational evidence. New studies should prioritize reference-method benchmarking, storage stability, inter-batch evaluation, matrix-specific calibration, and performance assessment across independent operators. Reviews increasingly emphasize that practical utility

requires more than proof-of-concept sensitivity; it requires robust analytical behavior under realistic use conditions2, 3, and 19.

CONCLUSION

Electrochemical paper-based analytical devices have matured into a diverse and increasingly credible platform for pharmaceutical analysis. Their major advantage lies in the integration of low-cost paper microfluidics with quantitative electrochemical detection, enabling compact devices that can be tailored for API analysis, quality screening, residue monitoring, and biological measurements. The literature now includes compelling examples of drug detection in formulations, substandard medicine screening, biomarker analysis in complex samples, environmental antibiotic monitoring, potentiometric pharmaceutical sensing, multiplex paper architectures, and wearable or portable systems.

Nevertheless, routine pharmaceutical adoption will depend on solving reproducibility, stability, standardization, and validation challenges. Future pad research should focus on scalable fabrication, matrix-robust sensing chemistry, portable but traceable instrumentation, and regulatory-style analytical validation. With these advances, ePADs could become an important complement to laboratory-based analytical chemistry, especially in decentralized, resource-sensitive, and time-critical pharmaceutical contexts.

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