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ABSTRACT: Wearable electrochemical sensors capable of non-invasive monitoring of chemical markers represent a rapidly emerging digital-health technology. Recent advances towards wearable continuous glucose monitoring (CGM) systems have ignited tremendous interest in expanding such sensor technology to other important fields. This article reviews for the first time wearable electrochemical sensors for monitoring therapeutic drugs and drugs of abuse. This rapidly emerging class of drug-sensing wearable devices addresses the growing demand for personalized medicine, towards improved therapeutic outcomes while minimizing the side effects of drugs and the related medical expenses. Continuous, non-invasive monitoring of therapeutic drugs within bodily fluids empowers the clinicians and patients to correlate the pharmacokinetic behaviour with optimal outcomes by realizing patient-specific dose regulation and tracking dynamic changes in pharmacokinetics behaviour while assuring the medication adherence of patients. Furthermore, wearable electrochemical drug monitoring devices can also serve as powerful screening tools in the hands of law enforcement agents to combat drug trafficking and support on-site forensic investigations. The review covers various wearable form factors developed for non-invasive monitoring of therapeutic drugs in different body fluids and towards on-site screening of drugs of abuse. The future prospects of such wearable drug monitoring devices is presented with the ultimate goals of introducing accurate real-time drug monitoring protocols and autonomous closed-loop platforms toward precise dose regulation and optimal therapeutic outcome. Finally, current unmet challenges and existing gaps are discussed for motivating future technological innovations regarding personalized therapy. The current pace of developments and the tremendous market opportunities for such wearable drug monitoring platforms are expected to drive intense future research and commercialization efforts.

KEYWORDS: *wearable sensors, electrochemical sensors, drug analysis, therapeutic drug monitoring, drugs of abuse, microneedle sensors, epidermal patches, glove sensors, personalized medicine.*

The use of drugs, either for therapeutic or recreational purposes, is deeply rooted in our society.[1] Drugs are classified into: (i) therapeutic drugs, which are universally prescribed by healthcare professionals to treat medical conditions, such as levodopa (l-Dopa) and theophylline to treat Parkinson's and lung diseases, respectively, or propofol to induce anaesthesia during surgery operations; (ii) licit drugs for recreational use, such as alcohol, nicotine and caffeine, commonly found in commercial products (e.g. caffeine in coffee), and provoke psychoactive effects when entering the body, and (iii) illicit drugs for recreational purposes constituting the majority of psychoactive drugs which strong effect the central nervous system and thus induce severe short- and long-term health problems.[2,3] While this category was evolved primarily for medicinal purposes, its therapeutic use was soon overshadowed by their abuse potential. For example, heroin was first marketed by Bayer in 1898 as a new ingredient in a cough suppressant formulation.[4]

The use of therapeutic drugs is constantly increasing, with a projected global spending of 1.52 trillion US dollars by 2023.[5] Such rapidly growing trend reflects primarily the aging world population and the spreading of new diseases and pandemics, such as the current novel COVID19.[6] Therapeutic drug monitoring (TDM) has long been established to manage therapy in patients, especially for drugs with narrow therapeutic ranges; therapeutic range is defined as the difference between the minimum effective concentration of a drug and the minimum toxic concentration of that drug.[7] However, different patients need different drug dosages to reach the optimal pharmacological effect, reflecting the wide inter-patient variation in the way drugs are absorbed and disposed of the body and in the way the body responds to the drugs.[8] Such variability can lead to administration of incorrect drug dosing and hence to adverse consequences. For instance, accurate dosing of propofol during surgical operations is critical for ensuring a safe and efficient medication in anesthetized patients, as underdosing leads to serious problems, such as pain, and intraoperative awareness. In contrast, overdosing of propofol may result in respiratory distress, decreased blood pressure and even death.[9] Another example is the dosage of antibiotics. While high antibiotic dosing can provoke serious intoxication, a suboptimal dosing leads antimicrobial

resistance, and poses threat to humans' lives.[10] Considering the narrow therapeutic range of major drugs, future TDM devices must meet several strict performance requirements, particularly in connection with closed loop systems where the sensor readings guide the medication dosage and an inaccurate measurement might trigger a fatal response. Accordingly, wearable sensors for monitoring drugs should be extremely reliable compared to on-body devices used for fitness or wellness applications. Owing to individualized dose-response characteristics of drugs, "precision medicine" has been introduced recently as a new paradigm aimed at customizing the dosage towards increased therapeutic efficiency and minimal toxic drug effects. In addition, the management of aging population commonly relies on multidrug dosage for treating multiple chronic conditions. This results in additional issues, such as drug-drug interactions and drug non-compliance and places additional burdens to the healthcare system.[11]

The rising prevalence of recreational drugs, especially illicit drugs, has turned to a major international crisis affecting public health, social and economic prosperity. According to National Institute of Health (NIH) data in 2018, 128 deaths were reported per day due to the opioid overdose in the US, leading to an enormous economic burden.[12] Similarly, the prevalence of drugs of abuse among European adults during 2019 was around 96 million people.[13]

As the use of drugs continues to grow, there are urgent needs for robust and rapid decentralized drug analysis tools to enhance their medical outcomes and limit their misuse and circulation of controlled substances. Current methods of drug analysis rely primarily on centralized laboratories, and are based on liquid chromatography (LC) or gas chromatography (GC) coupled with mass spectrometry (MS), enabling quantitative assays of multiple samples with low detection limits (LOD).[14–17] While such centralized techniques offer highly reliable results, the immense needs for rapid, readily affordable field detection tools have resulted in the emergence of portable analytical devices which offer tremendous promise for obtaining on-site qualitative or quantitative information about different drugs.[18,19] Such portable systems have been developed for testing both the therapeutic and recreational drugs. Examples include breathalyzers used by law enforcement officers for rapid field testing of blood alcohol content (BAC) of suspected drivers, or the single-use color tests and immunoassay kits for on-site identification of suspected narcotics. Several laboratory-based advanced portable instruments have also been adapted for field detection, including miniaturized MS instruments, ion mobility spectroscopy (IMS), infrared spectroscopy (IR) and Raman spectroscopy.[20] However, the widespread use of such portable devices has been

hindered mainly by their high costs, high power consumption, complex data analysis and maintenance.[20]

Current drug dosing practices are based on long processes, starting with prescribing by the physician, dispensing by pharmacist, and administration by the patient.[11] The dose is ultimately adjusted by the physician after observing the clinical outcomes over several repetitions. Such a process is considered a 'loose loop', as it involves human errors due to limited knowledge and judgement.[11] Since the first demonstration of the relationship between drug activity and its plasma concentration by Marshal in 1940s, plasma has been the gold standard matrix for clinical TDM analyses.[8,21] However, analysis of plasma is subject to important limitations including (i) the invasive nature of the sampling procedure through venipuncture, (ii) increased risk of infection, (iii) high cost of sample collection, transfer and analysis along with the long turnaround times, and (iv) challenges in estimating the concentration of the free (pharmacologically active) drug due to the dominance of protein-bound drugs. For recreational drug analysis, urine has been the preferred biofluid as it can retain drugs or their metabolites for longer periods of time; however, urine assays are time consuming, costly, and laborious, and are mainly used for qualitative screening.[22] The adaptation of the urine or plasma matrices for real-time continuous monitoring of dynamically-changing drug concentrations is extremely challenging. These limitations have stimulated considerable interests in using other biofluids which can be sampled in a minimally invasive or non-invasive manner for continuous monitoring purposes.

Here we review for the first time recent progress in the field of wearable electrochemical sensors for monitoring therapeutic drugs and drugs of abuse. Wearable devices have recently emerged as a major technological wave, taking advantage of tremendous advances in microfabrication, mobile and telemetric devices, material science, flexible electronics and their integration with the sensing modalities.[23–26] Wearable sensing devices can be easily worn and continuously monitor the wearer's health status in a non-invasive and non-obtrusive fashion.[24] Wearable chemical sensors can provide real-time physiological information by measuring dynamically-changing concentrations of biomarkers in biofluids such as interstitial fluid (ISF), sweat, saliva and tears.[27] Inspired by the tremendous commercial success of CGM devices for the treatment of diabetic patients, a dramatic recent surge in wearable electrochemical devices has illustrated the remarkable potential of these on-body sensing platforms.[28–34] Most of the initial applications of wearable electrochemical sensing devices have focused primarily on the fitness and

healthcare fields.

Driven by the immense needs for real-time, non-invasive or minimally-invasive drug monitoring and for on-the-spot screening of drugs of abuse, we have witnessed an intensive recent activity in development of wearable drug-monitoring systems. Wearable electrochemical devices are particularly attractive for drug measurements due to their distinct advantages such as selectivity toward important electroactive drugs, inherent miniaturization, low power requirements, low costs, high speed, and highly scalable fabrication through the use of screen-printing technology.[35–37] Electrochemical techniques have already shown immense potential in the in-vitro detection of drugs. For example, a screen-printed carbon electrode modified with ionic liquid has been used recently for fentanyl detection.[38] Another example is the detection of anaesthetic drug, propofol, in whole blood samples through carbon electrodes modified with plasticized polyvinyl chloride (PVC) outer membranes.[39] Some reports exploited the unique characteristics of nanomaterials for imparting higher sensitivity and selectivity in electrochemical detection of drugs. For instance, the combination of carbon nanotubes and the enzyme tyrosinase was employed toward amperometric detection of l-Dopa in human serum samples,[40] while graphene-modified electrodes were employed for simultaneous measurements of three opioid compounds, heroin, morphine and noscapine.[41] Several reports combined the favourable merits of electrochemical sensors with recognition capabilities of antibody bioreceptors,[42] or artificial receptors, including aptamers[43] and molecularly imprinted polymers (MIPs),[44] aiming to enhance the specificity of electrochemical drug detection systems. A notable example is an electrochemical aptamer-based sensor for continuous monitoring of the antibiotic vancomycin through binding-induced changes in electron transfer kinetics.[45] Despite such recent advances, further improvements are urgently needed to transfer the developed electrochemical sensors from in-vitro to on-body wearable devices.

Initial efforts aimed at developing wearable sensing devices for drugs of abuse have mainly been limited to monitoring drug-induced changes in vital signs.[22,46] Representative examples include a wristband exploiting changes in heart rate, skin temperature and conductance to monitor drug abuse[47], smart footwear which integrates pressure sensor in shoes and the corresponding changes in gait to sense alcohol consumption[48], and a wearable sensor which uses the opioid-induced decreased heart rate for triggering antidote delivery to tackle drug overdose problem.[49] While these wearable sensors have attracted commercial attention, they do not measure the drugs directly but rely only on the monitoring of physical parameters that can be easily influenced by

several non-related conditions (e.g. stress and anxiety).[22] To address these challenges, several research groups have recently focused on wearable devices capable of direct continuous monitoring of the drug concentration rather than its side effects on physical parameters. We have also witnessed growing use of wearable electrochemical devices for field screening of drugs of abuse for diverse forensic applications.

Major recent efforts have been directed into merging a plethora of wearable devices with different electrochemical techniques toward developing body-worn drug monitoring platforms. These activities have led to several innovative platforms and attractive strategies for on-body monitoring of drugs. **Figure 1** shows representative examples of the drug-sensing wearable devices. Such wearable sensors are classified into two categories, including glove-based wearable devices for external drug screening[50] (**Figure 1A**) and wearable sensors for monitoring dynamically-changing drug concentrations in various bodily fluids (**Figure 1B-E**). These include a skin-worn iontophoretic-based epidermal patch for the non-invasive tracking of the alcohol levels in stimulated sweat[51] (**Figure 1B**), a microneedle-based platform for minimally-invasive ISF monitoring of penicillin[10] (**Figure 1C**), various accessories that allow non-invasive detection of drugs, such as a ring-based device for simultaneous multiplexed detection of alcohol and Δ^9-tetrahydrocannabinol (THC) - the active ingredient of marijuana, in saliva[52] (**Figure 1D**), and an eyeglasses-based sensor merged with a fluidic sampling for tears alcohol analysis[53] (**Figure 1E**).

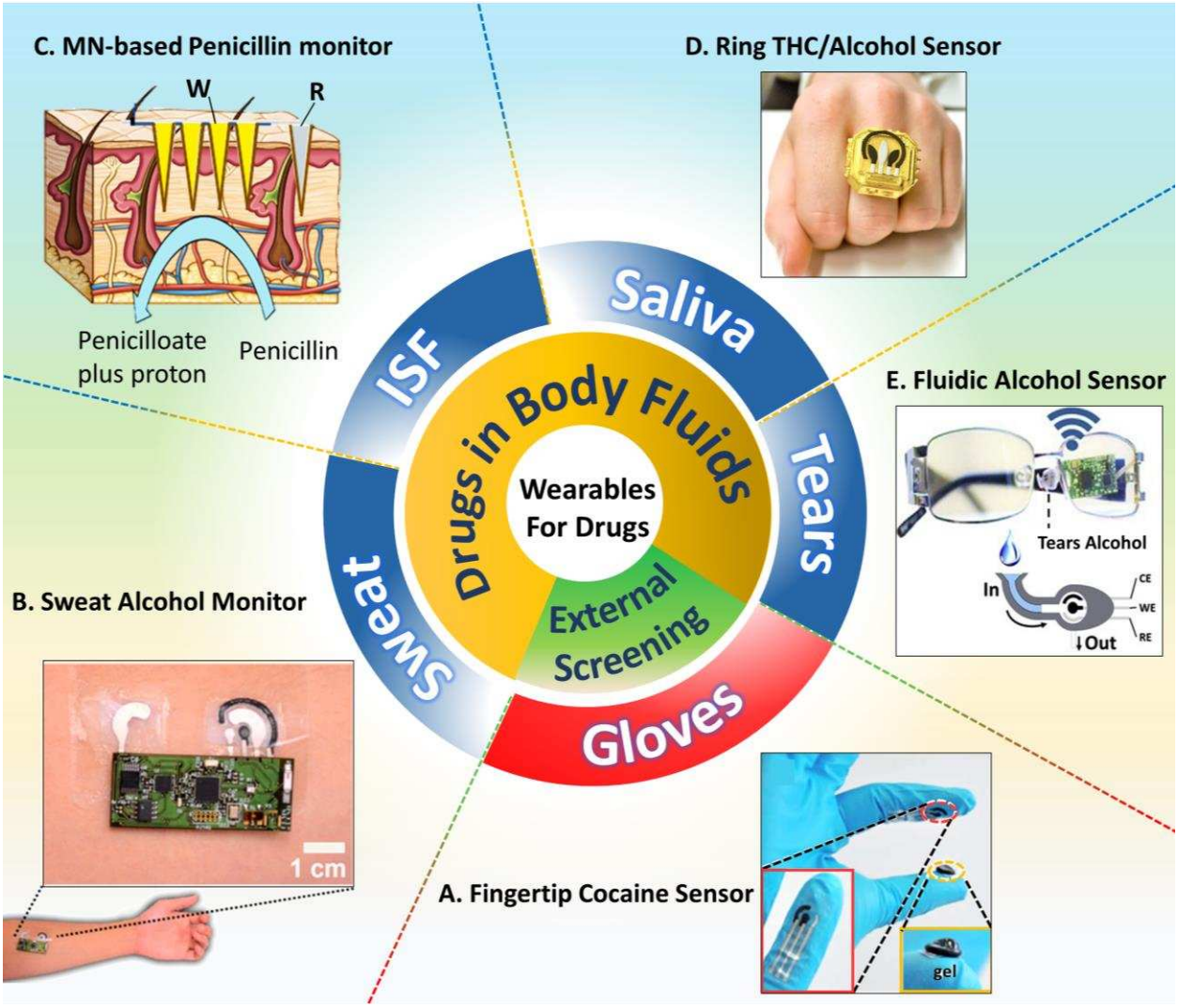

Figure 1. Representative examples of electrochemical wearables for drug analysis. A. External drug screening: *Wearable glove sensor for analysis of suspicious powder samples, showing screen-printed electrode onto the flexible finger, and a conductive gel immobilized upon the thumb. Adapted with permission from ref* [50]*. Copyright 2016 The Royal Society of Chemistry.* ***B-E. Drugs monitoring in body fluids. B. Sweat monitoring:*** *Image of an skin-worn alcohol iontophoretic-sensing tattoo device with integrated flexible electronic board. Adapted with permission from ref* [51]*. Copyright 2016 American Chemical Society.* ***C. ISF monitoring:*** *Microneedle biosensor for real-time drug monitoring of phenoxymethylpenicillin. Adapted with permission from ref* [10]*. Copyright 2019 Elsevier.* ***D. Saliva monitoring****: Ring-based THC/alcohol sensor. Adapted with permission from ref* [52]*. Copyright 2020 Elsevier.* ***E. Tears Monitoring:*** *Fluidic alcohol sensor; Photograph and schematics of the fluidic device and wireless electronics integrated into the eyeglass platform. Adapted with permission from ref* [53]*. Copyright 2019 Elsevier.*

Such wearable interfaces enable a variety of applications to meet the ever-increasing demands of

drug-related monitoring technology. External screening platforms such as glove-based sensors can be used to hinder drug trafficking by seizing cargos of illicit drugs or suspicious powders found in street samples.[54] They can also identify potential causes of criminal activity in toxicological and forensic investigations. Ring-based devices can enable law enforcement personnel to rapidly screen drivers toward addressing the growing concerns of drug-impaired driving habits. On another note, sweat-based epidermal patches and microneedle ISF sensing arrays have opened new opportunities toward on-site TDM through continuous tracking of drug concentrations, with an ultimate goal of developing an entirely closed-loop feedback-controlled drug dosing system. By customizing drug dosing according to the individual's metabolism, such systems addresses intra- and inter-patient variations that affect the drug pharmacokinetics.[9] Through tailoring the medicine to the patient, these devices will pave the way toward PM, and thus, offer great potential in reducing the financial and time expenditure while increasing the quality of life for patients.[55] Additionally, by providing continuous trends of variations in drug concentrations, these wearable devices automatically allow monitoring the drug adherence and drug-drug interactions. In case of drugs of abuse, closed-loop wearable devices can be employed to save lives through improving overdose prevention and reversal interventions by continuously watching the concentration of abused drugs and automated delivery of antidotes when a pre-set threshold is passed.[56,57] They can also monitor the drug abuse in individuals on probation toward a successful rehabilitation or in criminal justice and employment-based settings.[58]

To adapt these technologies to specific applications, there are key challenges that must be addressed. The first and most important is establishing reliable correlations between drug concentrations in blood and those in other bodily fluids in order to gain more accurate, reliable and comprehensive information regarding the distribution of different classes of drug compounds. Other challenges are related to the analytical performance of such wearable electrochemical sensors under varying conditions associated with on-body or on-site settings (e.g., changing temperature or sweat pH). The adaptation of bioaffinity electrochemical drug assays is also challenging due to their common washing, tagging, and receptor regeneration steps. In addition, unlike common metabolites (e.g. glucose, lactate) which are present at relatively high millimolar concentrations, therapeutic drugs are commonly present in ultralow (micromolar and nanomolar) concentration and would require highly sensitive EC techniques (such as square wave voltammetry, SWV). Ultimately, widespread clinical validation trials against laboratory-based

gold standard techniques will be necessary to completely ascertain their reliability toward practical pharmaceutical applications.

Over the last decade, wearable sensing devices have been reviewed in several articles, highlighting primarily technological advances and the significance of these next-generation platforms to the academic, clinical and industrial communities.[30,33,34,59–61] Particularly, recent reviews on wearable electrochemical sensors have addressed different applications,[28] materials,[62,63] designs[33,64] and target analytes.[65–67] The new arsenal of wearable devices can now offer continuous on-body monitoring and rapid, on-site testing of relevant chemical markers toward medical, wellness and security applications.

In the following sections we will review the opportunities and challenges of wearable electrochemical devices for detecting and monitoring drugs. Specifically, we will discuss key advances and features of various body-compatible electrochemical sensors toward rapid on-site drug screening and non-invasive monitoring of drugs in body fluids, from sweat over ISF to saliva and tears. Additionally, physiological information on the distribution of drugs in different body fluids will be discussed, mainly to guide future developments, including the need for comprehensive correlation trials between blood/plasma and external fluids. We conclude this review with discussion of existing technological challenges along with the potential solutions and of future prospects of such devices for monitoring therapeutic and illicit drugs toward widespread adaptation of wearable drug-sensing devices, meeting the growing societal and market needs.

WEARABLE DEVICES FOR DRUG MONITORING

External Screening of Drugs of Abuse (Glove-Based Sensors). While wearable sensors for the in situ chemical analysis of biofluids have attracted considerable attentions, the use of conformal devices for the screening of analytes in external samples (i.e., powders and liquids) has been less explored.[68] Wearable tools for decentralized chemical analysis of these substances is of utmost importance in countless applications (e.g., food, environmental, forensic, security) as they facilitate rapid decision-making processes in the field. In that sense, the chemical sensing at the fingertips, using glove-based electrochemical sensors, opens up new possibilities toward screening of target analytes in a decentralized manner (**Figure 2Ai**). Such smart glove sensors would satisfy the urgent need for a more rapid, user-friendly and cost-effective strategy toward on-site, real-time screening of drugs, in comparison to commercial presumptive color tests or bulky and more

expensive portable spectroscopic tools.

The miniaturization and integration of the 'lab-on-a-glove' sensing concept often require innovative materials and bioelectronic systems to fulfil desirable specifications.[68] For this purpose, tailor-made materials such as stress-enduring inks made of conductive nanomaterials and inherently stretchable polymers have been developed, which offer stretchability and resilience to the printed electrodes without affecting the tactile ability and user protection. Hence, engineered designs have been used to accommodate the strain from extreme mechanical deformations by unwinding of the serpentine microstructure during sampling procedure (**Figure 2Aii**). Besides, customized designs can be printed on each fingertip allowing multiplexed analysis of different analytes (**Figure 2Aiii**).[69] Glove-based wearables allow for an electrochemical direct detection of liquids (i.e., by dipping the fingertip on the solution), and powders (i.e., through a procedure known as "swiping method" where the sampling and the electrochemical steps are carried out in the thumb and index fingertip, respectively) (**Figure 2Aiv**). The latter involves the incorporation of a gel-based electrolyte on the index finger to complete the electrochemical circuit.

The integration of a miniaturized potentiostat is paramount to gain full wearability for on-site applications (**Figure 2Av**). Toward this, glove-based sensors have been integrated with miniaturized, portable potentiostats for the electrochemical detection of organophosphorus chemical threats, and for multiplexed detection of different targets in beverages.[69] The electrochemical reader as a re-usable module can be worn on the hand or suitably integrated in a wristband to increase the comfort of the user during the analysis. Finally, the wireless transmission of the data (e.g., via Bluetooth®) to a tablet or smartphone allows to visualize the data, thus coordinating the proper action with sufficient safety measures by law enforcement agencies (LEAs).

Glove-based devices have directly leveraged the impact of remote technology, although only few cases have been reported for the detection of drugs. A pioneering work by de Jong *et al.* reported a screening strategy for on-site fingerprinting of cocaine street samples.[50] The screen-printed sensor was built on a nitrile finger cot-based platform in order to directly analyze the suspicious powders (**Figure 2B)**. In this study, the selectivity of the sensor was examined by mixing the cocaine sample with a large panel of cutting agents (i.e., phenacetin, paracetamol, levamisole, caffeine, lidocaine, procaine, benzocaine, diltiazem, hydroxyzine, boric acid and sugars). Remarkably, levamisole showed a suppressing effect over cocaine signal, which was

deeply studied in further works.[70,71] To test the potential of the electrochemical approach in real scenarios, measurements of seized street samples of cocaine powder were conducted and the results were validated using GC-MS and gas chromatography-flame ionization detection (GC-FID) methods.

Barfidokht *et al.* have recently described a glove-based sensor for detection of fentanyl, an extremely potent synthetic opioid, that relies on its direct electrocatalytic oxidation on fingertip printed electrodes (**Figure 2C**).[72] The working electrode at the index fingertip was functionalized with a nanocomposite composed of carbon nanotubes and ionic liquid (4-(3-butyl-1-imidazolio)-1-butanesulfonate) to enhance the electrochemical performance. The resulting glove opioid sensor displayed high selectivity toward fentanyl detection in powder state in the presence of some common cutting agents (e.g., acetaminophen, caffeine and glucose), showing promises for on-site detection by excluding potential false positive/negative results. Caffeine (1,3,7-trimethylxanthine) is the most widely consumed central nervous system stimulant as it can be easily found in commercial products (e.g., coffee, chocolate) as well as in over-the-counter medications. However, caffeine intake might be accompanied by several adverse effects such as anxiety, insomnia, agitation or nervousness.[73,74] Hence, the chemical analysis of common beverages aimed at discriminating between caffeinated/decaffeinated products presents as an interesting utility in different sectors (i.e. food and medical industry). In this direction, a multiplexed glove-based device coupled to a robotic arm was successfully developed for selective discrimination of caffeine in beverages (**Figure 2D**).[69] This type of multiplexed sensing unfolds an exciting alternative for qualitative, as well as quantitative measurements of drugs in countless scenarios.

Despite the clear advantages that smart gloves can offer, there are still some challenges that this configuration needs to tackle to successfully be applied in real scenarios: (i) a low-cost screen-printing method for massive production of disposable smart gloves; (ii) selectivity issues which can be addressed by including tailor-made materials and broaden the database of electrochemical fingerprints; (iii) flawless integration within a miniaturized and comfortable wireless reader, (iv) use of secure data transmission systems (encrypted), and last but not least, (v) training of the users (i.e. LEAs, industry) on how to properly use the device in the field.

Overall, the use of these smart gloves for the rapid on-site analysis of seized cargos by customs services is presented as an attractive tool for safety and protection issues, and to a large extent, providing relevant drug-trafficking information. Besides, the introduction of a glove-based sensor

that allows accurate, rapid and real-time detection of multiple compounds could be of great interest for the fast analysis of chemical compositions in pharmaceutical and food industry.

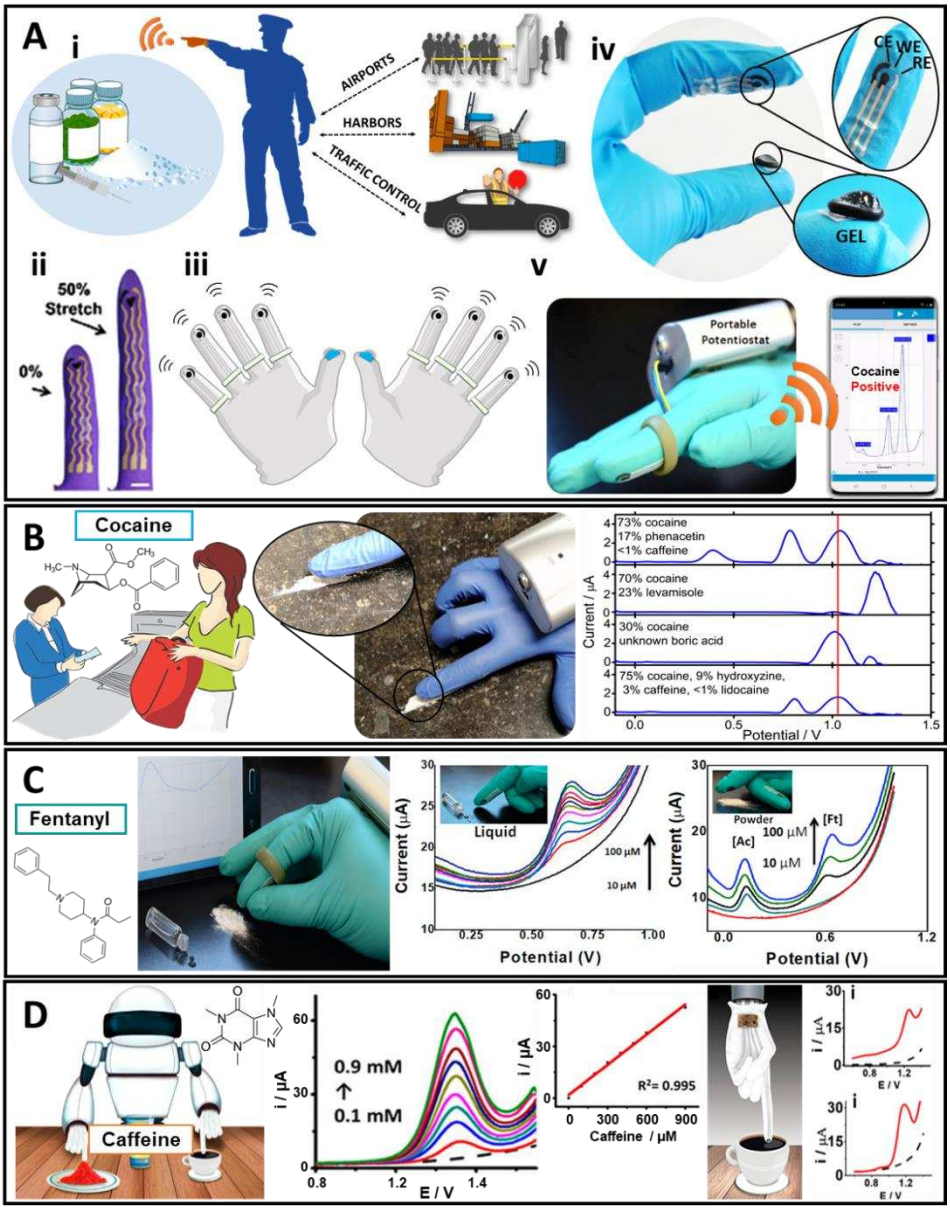

Figure 2: Overview and applications of glove-based wearable sensors for drug detection. *Images and schematics illustrating:* ***A. Concept and design****, (i) Applications, (ii) Robustness and stretchability of glove-based electrochemical sensors. Adapted with permission from ref* [75]*. Copyright 2017 American Chemical Society. (iii) Possibility of multiplexing. Adapted with permission from ref* [69]*. Copyright 2018 American Chemical Society. (iv) Ability to solid-phase detection (gel). Adapted with permission from ref* [50]*. Copyright 2016 The Royal Society of Chemistry. (v) Integration with a portable reader and data transmission. Adapted with permission from ref* [72]*. Copyright 2019 Elsevier.* ***B. Fingertip detection of cocaine*** *(powder), illustration of a drug-of-abuse test in the field involving swiping method, and corresponding*

electrochemical fingerprint of real samples. Adapted with permission from ref [50] Copyright 2016 The Royal Society of Chemistry. ***C. Smart glove for fentanyl determination*** *(liquid or powder), optical image of one-touch sample-to-answer setup and corresponding analytical responses in liquid and powder samples. Adapted with permission from ref [72]. Copyright 2019 Elsevier.* ***D. Glove-based sensor for caffeine****, schematics of the dipping finger action in solution to determine the presence of caffeine, along with the corresponding calibration curve for caffeine and analysis in real samples. Adapted with permission from ref [69]. Copyright 2018 American Chemical Society.*

WEARABLE DEVICES FOR DRUG MONITORING IN BODY FLUIDS

Drug pharmacokinetics. Drugs are mainly administered to the body orally using a pill or capsule formulation, although other routes are also used, including via intravenous, transdermal, or intramuscular pathways. When a drug enters the body, its fate is determined by three different processes. (i) Pharmacokinetics, which describes the action of the body on the drug and consists of the drug absorption, distribution, metabolism, and excretion; (ii) Pharmacodynamics, which describes the action of the drug on the body and consists of the biologic and physiologic effects of the drug in its target site; and (iii) Pharmacogenomics, which is the impact of genetic variations on the drug action and it is responsible for the observed inter-patient variability in terms of drug metabolism and response.[7] These processes are tightly interconnected and govern the ultimate action and fate of the drug. However, the distribution of drug molecules among the different biofluids is determined primarily through pharmacokinetics and subsequently, it will be discussed more in the following sections.

Which drugs should be monitored?

TDM has been evolved as a clinical discipline since late 1960s to help physicians toward safe and efficient drug dosing.[76] Among all the prescription and over-the-counter drugs, a few of them bear importance in terms of monitoring needs. To be considered beneficial for TDM, a specific drug must meet the following criteria.[7,77] First, the candidate drug should have a low therapeutic index (small difference between effective and toxic concentrations), where a same drug dose may cause therapeutic effects in one patient, but toxic effects in another patient. Second, the clinical effect of the drug should be strongly correlated with the drug concentration, but weakly correlated with the dosage. Third, the therapeutic and toxic concentrations of the respective drug should be well-established. Fourth, either under- or over-dosing should pose serious adverse and long-term effects, or lead to hospitalization, organ damage, or even death.[7] Most of the aforementioned criteria also satisfy the detection of illicit drugs, although there is much less information on the correlation of concentration with the clinical and/or fatal effects for these drugs compared to the

therapeutic drugs. Nonetheless, the very high number of drug-related deaths due to their accidental overdose among drug users should explain the necessity and urgency for their frequent monitoring.

Choosing appropriate body fluid for on-body drug monitoring.

TDM principally involves measuring the drug concentration in their site of action, where the strongest correlation exists between concentration and pharmacological effect.[77] However, owing to its accessibility, plasma has been accepted as the gold standard medium for analysis, with the assumption that drug concentration in plasma reflects that in the target site.[78] Consequently, the reference concentration ranges have mainly been established using plasma or related samples (whole blood or serum). **Table 1** summarizes therapeutic and toxic concentrations as well as other clinically important data on the clearance time of drugs from the body for a number of representative drugs. There are factors, however, which affect these reference ranges of concentrations. Apart from genetic variables and certain pathological conditions widely influencing the drug concentrations through affecting their metabolic pathways, the drug-drug interactions are the most important factors, albeit interactions between drug and food and herb have also been reported to cause changes in these ranges.

The use of plasma as the analysis matrix has numerous pitfalls, as discussed before, from invasiveness and the constant need for specialized personnel and venipuncture or phlebotomy-associated errors to the lack of adaptability to continuous monitoring systems. The latest advances in the field of wearable miniaturized devices have shifted the attention toward peripheral drugs monitoring in alternative biofluids (i.e., ISF, sweat, tear, saliva). These biofluids offer many advantages such as easy and painless sample collection (that obviates the need for specialized personnel), and the availability for real-time, on-site monitoring to provide temporal pharmacokinetic profiling, independent of the delays associated with central laboratories. In addition, unlike plasma, these external biofluids allow the detection of free protein-unbound drugs (i.e. a fraction of the drug molecules that is able to penetrate its targeted site and thus, produce the desired pharmacological effect).

While peripheral biofluids provide attractive characteristics, compared to traditional plasma medium, as sampling matrices for chemical monitoring, their use for wearable devices for drug monitoring is still in its infancy. In particular, understanding the correlation between drug concentrations in these external fluids and plasma besides gaining the desired information on physiology and distribution of drug molecules will require extensive studies. Nevertheless, the

small size and lipophilic nature of most drugs (either therapeutic or illicit) facilitate the passage of these molecules through the lipophilic capillary cell membranes without filtration and hence a nearly equal concentration ratio in external fluids and plasma is expected for most drug molecules.[27] In contrast, hydrophilic (e.g. penicillin and ibuprophen) or large drug molecules (e.g. hormones like insulin) are diluted to some extent, depending on the specific drug molecule and the sampling biofluid (with less dilution in ISF than in sweat, saliva or tears).

Additional factors need to be considered when designing a specific sensing platform. The administration route of a drug can also strongly affect drug levels in the biofluids. **Table 2** summarizes the administration route, clearance and drug levels for several illicit drugs. For example, concentrations of 3,4-methylenedioxy-methamphetamine (MDMA) after ingestion were reported to be higher in saliva (ca. 30x) than in plasma.[79] Similar trends were shown after smoking drugs (such as heroin and cocaine) in which higher salivary drug concentrations were observed compared to intravenous drug administration.[80] Peak plasma levels of cocaine range from 50 to 2000 ng mL^{-1}, depending on the mode of injection. The drug clearance time should also be considered. Some drugs are metabolized very quickly and have a short half-life in the body and consequently, the detection should target their metabolite rather than the original drug molecule. For example, cocaine is metabolized rapidly by ester hydrolysis and N-demethylation, and it is converted in the blood mainly to benzoylecgonine by nonenzymatic hydrolysis, and to ecgonine methyl ester, which might be ultimately detected in ISF or sweat.[81] Indeed, the times for reaching the peak concentrations of cocaine and its metabolites, benzoylecgonine and ecgonine methyl ester, range from 1 to 1.5 h, 6 to 8 h, and 3 to 4 h, respectively.[81] These considerations clearly show that the sensing platform should be designed and tailored based on the specific drug or its metabolite(s), target biofluid, administration route and the specific analytical application. In the following sections, the advances of wearable sensors for monitoring drugs in different body fluids will be presented in more detail.

Table 1. Drugs used in therapeutic monitoring.

Type of drugs	Compound	Matrix	Administration	PK / h	Therapeutic range / μM	Ref
Anesthetic	Propofol	Plasma	O / IV	0.3–1[a]	1–<60	[39,82]
Antineoplastic	5-Fluorouracil	Serum	IV (300–500 mg $kg^{-1}day^{-1}$)	0.45–0.69[b]	15.4–23.1	[83]

	Methotrexate		Serum	O / IV	1–4[b]	1.0–1000	[83]
	Tamoxifen		Serum	IV (20 mg day^{-1})	5[b]	≥0.02	[83]
Parkinson drug	Levodopa		Plasma	O (150–550 mg day^{-1})	> 4	0.5–<15	[84,85]
			Sweat	O (100–500 mg day^{-1})	0.83[a]	0.1–<2.5	[86,87]
Cardioactive drugs	Digoxin		Serum	O / IV (0.125–0.25 mg day^{-1})	1–3[b] (O) / 1.5–4[b] (IV)	$0.6x10^{-3}$–$1.3x10^{-3}$	[88]
	Digitoxin		Serum	O (0.05–0.2 mg day^{-1})	3–6[b]	0.01–0.04	[88]
	Disopyramide		Serum	O (300–600 mg day^{-1})	0.5–3[b]	5.9–14.7	[88]
	Flecainide		Serum	O (50–200 mg day^{-1})	2–3[b]	0.5–2.4	[88]
	Procainamide		Serum	O / IV (0.125–0.25 mg day^{-1})	1–2[b] (O) / 0.5[b] (IV)	14.7–36.8	[88]
Antidepressants	Amitriptyline		Serum	O (75–200 mg day^{-1})	4–8[b]	0.3–0.7	[89]
	Doxepin		Serum	O (75 mg day^{-1})	1–4[b]	0.5–0.8	[89]
	Amoxapine		Serum	O	10[a]	0.6–1.3	[89]
	Trazodone		Serum	O	4–11[a]	1.9–2.7	[89]
	Lithium		Serum	O (10–20 mg kg^{-1} day^{-1})	0.5–3[b]	600–1200	[89]
Antibiotic	Amikacin		Serum	IV (10–15 mg kg^{-1} day^{-1})	2–3[a]	25.6–42.6	[90]
	Gentamicin		Serum	IV or IM (3–5 mg kg^{-1} day^{-1})	2–3[a]	10.5–20.9	[90]
	Penicillin-type	PH	Plasma	O (150–550 mg day^{-1})	0.4–1.3[b]	C_{max} 1369.9–5822.1	[10,91,92]
		PP	Plasma	IV (4 g $dose^{-1}$)	0.8–4.1[a] /0.2[b]	C_{max} 140.5–1342.9	
		PP	ISF	IV (4 g $dose^{-1}$)	0.7–3.9[a]/0.2–1.1[b]	C_{max} 32.1–417.3	
	Vancomycin		Plasma	IV (2 g day^{-1})	0.5–1.0[a]	13.8–27.6	[90]
			ISF	IV (5–20 mg kg^{-1})	1.3±0.1[a]/1±0.7[b]	C_{max} 22.1±1.8	[92,93]
	Linezolid		Plasma	IV (600 mg $dose^{-1}$)	3.1–9.3[a]/0.5–2.7[b]	0.3–8.9	[92,94]
			ISF		3–6.5[a]/ 0.95–4[b]	0.3–3.6	
Analgesics	Acetaminophen		Serum	O / IV (1 g $dose^{-1}$)	0.5–2[b]	66.2–132.3	[95]
	Ibuprofen		Serum	O (200–800 mg day^{-1})	1–2[b]	72.7–145.4	[95]
	Indomethacin		Serum	O (75–150 mg day^{-1})	2[b]	0.8–8.4	[95]
	Naproxen		Serum	O (440–660 mg $dose^{-1}$)	1–2[b]	130.3–390.8	[95]
Immunosupressants	Ciclosporine		Blood	O / IV (4–18 mg kg^{-1} day^{-1})	1–6[b]	0.1–0.3[c]	[96]
	Everolimus		Blood	O (1–4 mg day^{-1})	1–3[b]	$3.1x10^{-3}$–$8.4x10^{-3}$	[96]
	Mycophenolic acid		Serum	O (1440–2000 mg day^{-1})	1–2.5[b]	3.1–10.9	[96]
	Sirolimus		Blood	O (1–6 mg day^{-1})	1–2[b]	$5.5x10^{-3}$–$21.9x10^{-3}$	[96]
	Tacrolimus		Blood	O / IV (0.05–0.3 mg kg^{-1} day^{-1})	0.5–6[b]	$6.1x10^{-3}$–$18.2x10^{-3}$	[96]
Antiepileptic	Carbamazepine		Serum	O (400–1200 mg day^{-1})	4–8[b]	16.9–50.8	[97]
	Ethosuximide		Serum	O (500 mg day^{-1})	1–2[b]	283.3–708.4	[97]
	Gabapentin		Serum	O (800–1800 mg day^{-1})	1.5–4[b]	11.7–116.8	[97]
	Lamotrigine		Serum	O (200–400 mg day^{-1})	1–3[b]	11.7–58.6	[97]
	Levetiracetam		Serum	O (1000–3000 mg day^{-1})	1[b]	58.8–352.5	[97]
Methylxanthine (airways obstruction)	Caffeine		Plasma	O (2.1–5 mg kg^{-1})	0.5–2[b]	5–25	[98,99]
			Sweat		-	5–25	
	Theophylline		Plasma	IH / IV (600 mg day^{-1})	1–3[b]	28–111	[99–101]
			Sweat	IV	0.9±0.1[a]	C_{max} 62.6±7.1	[102]

[a] Time required for a 50% decrease in concentration. [b] Time to maximum concentration. [c] Variable according to the transplanted organ. IH: inhaled administration; IM: intramuscular administration; ISF: interstitial fluid; IV: intravenous administration; O: oral administration; PH: Phenoxymethylpenicillin; PK: pharmacokinetics; PP: Piperacillin.

Table 2. Illicit drugs in biofluids.

Type of drugs	Compound	Biofluid	Administration / dose	Clearance / h	Biofluid levels	Ref
Opioids	Heroin	Blood	IH / IV	0.25–0.5	5.4–810 nM	[80,103]

		Sweat[b]	IV	0–24	6.9–157 ng patch^{-1}	[104,105]
	6-Acetylmorphine (heroin metabolite)	Blood	Intravenous	0.25–1	0.75–42.1 nM	[80]
		Sweat[b]		0–120	5.7–2386 ng patch^{-1}	[104,105]
	Morphine (heroin metabolite)	Blood	IH / IV	0.37–2 h / 20	6.7–389 nM	[103,106–108]
		Sweat[b]	IV (80–1000 mg)	-	1–271 ng patch^{-1}	[105,109]
	Codeine	Plasma	O (60 mg)	> 24	3.3–742.2 nM	[110]
		Sweat[b]	O (60–120 mg)	1–2	3.9–4018 ng patch^{-1}	[105,111]
	Fentanyl	Blood	IV (12.5–200 µg h^{-1})	> 8	3.15–10.81 nM (<233.71 postmortem)	[112,113]
		Sweat	TD (25 µg h^{-1})	-	505.2– 3031 nM	[114]
	Methadone	Plasma	O (6–80 mg day^{-1})	11–27	323.2–2908.4 nM	[115–117]
		Sweat[b]	O (20–90 mg day^{-1})	-	120–2160 ng patch^{-1}	[118]
CNS stimulant	Cocaine	Plasma	IV / IN	4–8	3.3–1226.3 nM	[80,103]
		Sweat[b]	IH	1–24	3.1–68.5 ng patch^{-1}	[104]
	Benzoylecgonine (cocaine metabolite)	Plasma	IH / IV / IN	24	3.5–826 nM	[80]
		Sweat[b]		2–24	2.8–7.8 ng patch^{-1}	[104]
	Ecgonine (cocaine metabolite)	Sweat[b]	IH / IV / IN	2–24	2.4–6.1 ng patch^{-1}	[104]
Alcohol	Ethanol	Blood	O (beverage)	<4	0–0.08 M nM	[119,120]
		Sweat		-	2.17 µM–43.4 mM	[121,122]
	Ethyl glucuronide (ethanol metabolite)	Plasma	O (beverage)	3.3	0.45–26.6 µM	[119]
		Sweat		> 9	7.7–464.0 nM	[123,124]
ATS	Amphetamine	Plasma	O (40–80 mg day^{-1})	46	5.02–2948.8 nM[a]	[125,126]
		Sweat[b]	O (10–20 mg day^{-1})	> 24	3.3–18.6[a] ng patch^{-1}	[127]
	Methamphetamine	Plasma	O (40–80 mg day^{-1})	48	10–5000 nM	[125]
		Sweat[b]	O (10–20 mg day^{-1})	> 24	3.1–103.4 ng patch^{-1}	[127]
	MDMA	Plasma	O (1–1.6 mg kg^{-1})	24	239.6–2407.8 nM	[128]
		Sweat[b]	O (100 mg)	1.5–> 24	3.2–1326 ng patch^{-1}	[129]
	MDA (MDMA metabolite)	Blood	O (100 mg)	1.5–>24	31.2–130 nM	[130]
		Sweat[b]			8.9–24.8 ng patch^{-1}	[105,129]
Cannabinoids	Δ^9-THC	Plasma	IH	3.5–5.5	6.04–349.8 nM	[131–133]
		Sweat[b]		4	0.4–38 ng patch^{-1}	[105,134,135]

[a]amphetamine as a metabolite from methamphetamine. Δ9-THC: Tetrahydrocannabinol; ATS: amphetamine-type substances; C_{max}: maximum concentration; IH: inhaled; IN: intranasal; IV: intravenous; MDA: 3,4-Methylenedioxyamphetamine; O: oral; TD: transdermal.
[b]Sweat analysis of illicit drugs was performed by the on-body collection of sweat during several days. It is a cumulative amount of illicit drug in the collecting pad.

Sweat. Sweat is a non-invasive biofluid with rich physiological information and is readily and vastly accessible due to the abundance of eccrine sweat glands all over the body.[29,136] Sweat can be obtained on-demand by either exercising or by stimulation using cholinergic agonist drugs.[136–138]

Important analytes, such as lactate, glucose, alcohol, uric acid, tyrosine, sodium, potassium, chloride, and cortisol, can be directly measured in sweat and correlated with blood.[30,34] Such abundance of analytes and the ease of sweat generation have led to tremendous activity toward the development and utilization of wearable devices for sweat sampling and sensing. A wide range of sweat monitoring wearable platforms has thus been developed.[136] These include conformal

temporary tattoos, patches or wrist bands, microfluidic flow-detection devices, textile-based sensors or various accessories such as eyeglasses.[51] For example, in an elegant work Gao et al. demonstrated fully-integrated wrist-band sensors for simultaneous multiplexed detection of five sweat metabolites and electrolytes.[26]

Sweat analysis has been intensely applied for the diagnostic of diseases and detection of drug abuse. For example, the gold standard methodology for the diagnostic of cystic fibrosis relies on measurements of elevated chloride levels in sweat.[136] Sweat alcohol ankle and wrist bands have been extensively used by law enforcement to determine if an individual has been drinking alcohol.[139,140] Small molecules, originated from food and/or medication, can easily partition into sweat (e.g. alcohol, glucose, vitamins, drugs) contributing to its composition.[136] Heavy metals, alcohol and drugs can also be found in sweat as the body attempts to reject such toxins.[141,142]

While most early activity has focused on the monitoring of sweat metabolites or electrolytes, wearable sweat drug sensing devices have introduced in recent years for both point-of-care screening and continuous monitoring toward precision medication.[22,143] Nowadays, sweat analysis of different types of drug is realized by using a commercial sweat patch. In this system, the drug is accumulated over a period of two weeks, after which the patch is removed and sent for laboratorial analysis.[144,145] The mechanism by which the drugs are partitioned into the sweat is not yet fully understood but it is thought to occur be via passive diffusion.[146]

Wearable sweat sensor for drug detection has been demonstrated. Alcohol (ethanol) is one of the most common analytes for sweat detection as it is a small polar molecule which can be found in a near unity ratio with respect to its level in blood.[147] Ethanol provokes a fast rise in concentration in blood and sweat, and it can be detected in the body 3 hours after its initial consumption.[147] Gamella et al. demonstrated a sweat alcohol sensor capable of detecting alcohol in situ, after sweat stimulation with a commercial iontophoretic pilocarpine system.[148] The procedure consisted of two steps: 30 minutes sweat stimulation with a rigid commercial device strapped in the forearm, followed by removal of the sweat stimulation device and placement of the electrochemical sensor strapped to the same forearm location. The alcohol signal was based on the amperometric response of the enzymatic reaction between AOx and ethanol. The sensor was able to distinguish between different levels of alcohol. The measurements showed strong correlation between sweat and blood alcohol levels with a 30 minutes time lag when the measurement was continually performed. The system was later optimized by Kim et al., who presented a flexible tattoo sensor for detection of

alcohol in sweat (**Figure 3Aa**).[51] The platform consisted on the integration of an AOx enzyme based electrochemical sensor with an iontophoretic system for pilocarpine delivery in a single platform. In a single step, the iontophoretic system was able to stimulate sweat directly on the electrode surface. The tattoo was able to detect different responses for subjects who had or not consumed alcohol, and it was also able to measure different levels of alcohol in sweat with no time lag. Non-enzymatic detection of alcohol levels on body has also been demonstrated. Selvam *et al.* demonstrate a wearable sweat-based sensor to monitor alcohol through detection of ethyl glucuronide (EtG), as a non-oxidative metabolite of ethanol marker.[124] The impedance-based immunoassay system composed of gold and zinc oxide electrodes modified with thiol linkers, anti-EtG antibodies and blocking agents is elegantly incorporated onto a conformal flexible electronic interface. The system demonstrated continuous measurement of EtG during 9 hours.

In addition to alcohol, the consumption of tobacco is largely spread with the effects of smoking affecting not only smokers but also those who are exposed to second-hand smoke. Thus, a tobacco monitoring system is necessary to access the risks in the non-smoking population. Recently, a sweat nicotine epidermal sensor was developed by Tai et al.[149] A gold electrode was modified with cytochrome P4502B6, a nicotine-oxidizing enzyme, and the sweat nicotine levels were monitored via chronoamperometry (+0.8V) during exercising. The device was able to successfully distinguish smokers and non-smokers through the sweat nicotine levels.

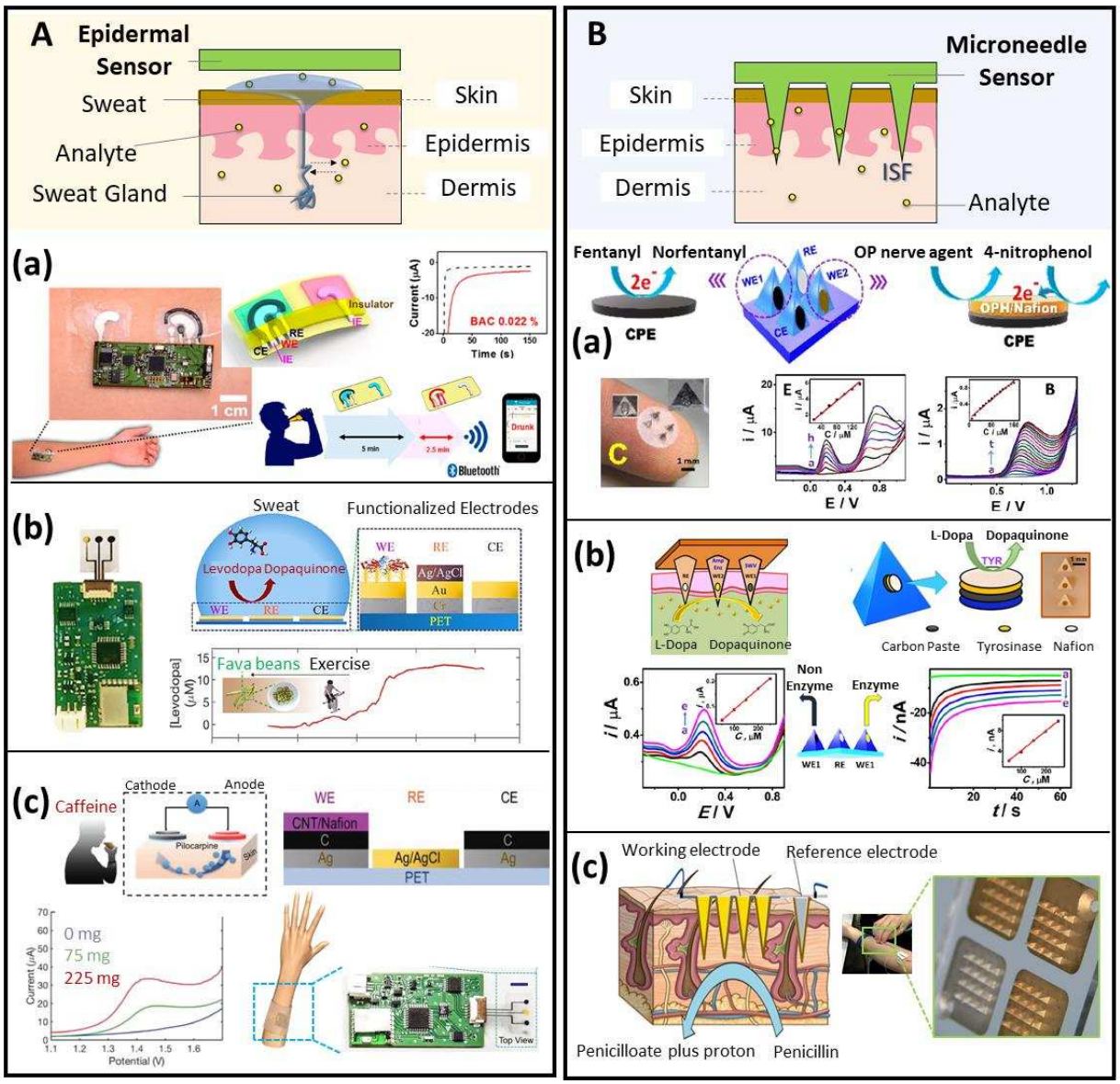

Figure 3. Schematic illustration of epidermal and microneedle-based electrochemical wearables for drug analysis. ISF analysis: A. Graphical demonstration of an epidermal patch sensing *including, skin multilayer models and sensor integration with skin.* ***B. Graphical demonstration of a microneedle transdermal sensing****, showing microneedle penetration, skin multilayers and ISF access. A****a****. **Epidermal tattoo sensor for alcohol monitoring****; schematics of the iontophoretic electrodes, tattoo sensor integrated with flexible electronics, complete wireless operation of the device and its representative amperometric response. Adapted with permission from ref* [51]*. Copyright 2016 American Chemical Society. A****b****. **l-Dopa monitoring sensing platform****; developed electronic board integrated with the gold electrodes, l-Dopa sensing mechanism and the sensor's cross-section along with an example of exercise-based drug monitoring with consumed fava beans. Adapted with permission from ref* [150]*. Copyright 2019 American Chemical Society. A****c****. **A sweat band platform for caffeine monitoring****; iontophoretic operation of pilocarpine delivery along with caffeine intake and sweat generation, optical image of the flexible board integrated with the sensing device with sensor's multilayers and its correspondence response to caffeine*

dosages. Adapted with permission from ref [151]*. Copyright 2018 John Wiley & Sons.* ***Ba. Opioid and nerve agent monitoring on a microneedle array****; mechanistic graphics of fentanyl and nerve agent reactions on the microneedle surface, simultaneous voltammetric detection of morphine and fentanyl, detection of MPOx and its calibration curve. Adapted with permission from ref* [152]*. Copyright 2020 American Chemical Society.* ***Bb. Microneedle sensor for l-Dopa detection****; Optical image and surface functionalities of the dual-mode microneedle system for enzymatic and non-enzymatic l-Dopa monitoring along with their corresponding voltammetric and amperometric curves. Adapted with permission from ref* [153]*. Copyright 2019 American Chemical Society.* ***Bc. Microneedle sensor for penicillin monitoring.*** *Schematics of the microneedle device based on potentiometric sensing with the corresponding optical images of the electrodes. Adapted with permission from ref* [10]*. Copyright 2019 Elsevier.*

Besides, the detection of drug of abuse in sweat, therapeutic drug monitoring is extremally important for implementing precise medicine and compliance. Precision medication is necessary for drugs with very narrow therapeutic range, drugs that are only effective if their concentration inside the body is kept at optimal level, for this, repetitive and sometimes excessive dosages are prescribed risking toxic levels or addiction. Wearable sensors for therapeutic drugs are necessary to map the drug pharmacokinetics. For example, Kilic et al. envisioned a closed loop e-patch capable of monitoring the drug used in the treatment of schizophrenia in sweat, which in turn was delivered by the same patch[154]. Differential pulse voltammetry (DPV) was used to test the sensor which presented great selectivity toward common sweat constituents and other medications. Schizophrenia patients are an example where wearable sensors can be used for compliance purposes once they might neglect taking the drugs as prescribed.

In **Figure 3Ab**, Tai et al. extended the developed technology to detect l-Dopa toward Parkinson disease management.[150] An enzymatic EC sensor based on tyrosinase drop-casted on Au/Cr conductive layer was fabricated on a flexible substrate of polyethylene terephthalate. In this method, sweat extraction was performed by both physical exercise and iontophoresis in human subjects after fava beans intakes. Caffeine, as already mentioned, is the world's most widely consumed psychoactive drug exhibiting potential health benefits and risks upon overconsumption. Therefore, developing sensors for in situ monitoring of caffeine levels is also of great importance. In this regard, Tai et al. introduced a wristband-type wearable sweat sensing platform toward detection of this methylxanthine-type stimulant after coffee consumption (**Figure 3Ac**).[151] This system relies on electrode arrays patterned on a flexible substrate and interfaced with a printed circuit boards (PCBs), along with iontophoretic sweat extraction. The CNT/Nafion modified carbon electrode offers direct differential pulse voltammetric oxidation and detection of the sweat

caffeine.

The above examples indicate the potential of using skin-worn devices for non-invasive monitoring of drugs in sweat. The development of reliable wearable sweat drug sensors will require large-scale validation studies, particularly toward precision medication and closed-loop operations.

ISF. The successful implementation and the rapidly growing acceptance of commercial CGM devices have stimulated extensive studies on exploiting ISF as an attractive biofluid for continuous on-body monitoring.[155–157] The feasibility of conducting TDM in ISF has been studied, demonstrating reliable correlations between blood and ISF concentrations for small drug molecules.[27,102] The potential of ISF as the fluid of choice for on-site TDM has also been highlighted in recent reviews.[77,78,92] However, the current studies are limited to a small number of therapeutic drugs and additionally, surveys on linking the ISF-blood levels for illicit drugs are rare. Thus, for ISF to be supplanting blood as the preferred analysis matrix for drugs, in-depth investigations using more comprehensive panel of drugs are needed to evaluate and establish strong correlations applicable for implementing on-site continuous, real-time monitoring of drugs. Unlike sweat and saliva, ISF is a more challenging biofluid to access, which partly explains the lack of information on distribution of drugs in ISF compared to other body fluids. Several non-invasive or minimally-invasive techniques have been developed to draw the ISF. Reverse iontophoresis, which depends on applying an electric field to drive an electro-osmotic flow of ISF across the skin, is the most common non-invasive ISF sampling method.[28] However, the sample dilution due to the paracellular diffusion pathway and the possible contamination with sweat are serious limitation of this method.[27] Similarly, while microdialysis has largely contributed to the current state of knowledge on correlations between drug levels in ISF versus blood,[78] the off-body analysis procedure and the long turnaround times are not amenable to wearable on-body or closed-loop applications.

Driven by advances in microfabrication techniques, microneedles have emerged as miniaturized replicas of hypodermic needles for ISF sampling, transdermal drug delivery and more recently for diagnostic purposes. The microneedles with microscale, sharp protrusions can easily pierce the stratum corneum, accessing ISF less than a millimeter into the skin while not reaching the pain receptors locating deeper in the tissue and thus, thus offering a pain-less, constant interaction with the ISF. Therapeutics (drug delivery) applications of microneedles have witnessed a tremendous

growth since the pioneering work of Henry et al in 1998,[158] with many recently reported innovative strategies for microneedle-assisted administration of proteins, vaccines, cells, etc.[159,160] Microneedles have also been used in ISF withdrawal,[161–163] albeit there has not still been a reliable strategy for extracting sufficient ISF volume essential for continuous monitoring applications. Nevertheless, good correlations between the microneedle-sampled ISF and the blood levels of several drugs, including theophylline and caffeine,[164] or vancomycin,[165] have been demonstrated. The development of wearable microneedle sensors to access the information-rich ISF in a minimally-invasive painless manner has attracted a tremendous recent attention,[166–168] These efforts have led to the development of microneedle-based electrochemical sensors capable of monitoring a wide variety of analytes.[169–171] These minimally-invasive devices rely on placing the electrode transducer at the tip of a solid or hollow microneedle, along with the corresponding reference and counter microneedle electrodes (**Figure 3B**). Integrating an array of multiple microneedle electrodes on a single miniaturized wearable patch has shown considerable promise not only in multiplexed detection of analytes,[152,172] but also for combining different sensing modalities for a single analyte[153] toward acquiring more comprehensive information and enhancing treatment efficacy. Furthermore, microneedles offer the possibility of merging real-time diagnostic and delivery procedures, and thus, can provide an attractive option for designing feedback-controlled closed-loop systems for timely controlled delivery of therapeutic drugs in personalized medicine as well as for life-saving drug overdose reversal patches in regular users of illicit drugs. Prolonged operation of such microneedle drug monitoring systems will require proper attention to the minimization of surface biofouling effects.

The first study of microneedle-based drug detection was reported by Mohan *et al.*,[169] where alcohol biosensing was achieved based on the biocatalytic alcohol oxidation onto the AOx enzyme modified electrodes. 100 μm-diameter Pt and Ag wires were incorporated within the apertures of a hollow polycarbonate-made microneedle platform and served as working and reference electrodes, respectively. The selective performance of the alcohol microneedle sensor was demonstrated in artificial ISF solution, while the potential of the strategy toward subcutaneous alcohol detection in ISF was investigated ex vivo in a mouse skin model. The same year, Sharma *et al.* proposed the use of microneedle array platforms toward in-situ detection of therapeutic drugs.[173] The Pt and Ag sputtered microneedle arrays were thus constructed and exploited for biocatalytic detection of the drug theophylline in connection to an immobilized xanthine oxidase

(XOx) and the subsequent amperometric oxidation of the generated H_2O_2.

A major recent advance toward multiplexed microneedle-based sensing toward continuous minimally-invasive detection of opioid drugs, along with other possible environmental or security threats, was recently reported through incorporation of fentanyl and nerve agent sensors on a wearable microneedle array platform (**Figure 3Ba**).[152] The simultaneous dual-threat detection strategy relied on unmodified and organophosphate hydrolase (OPH)-modified carbon paste microneedle electrodes for SWV oxidation of fentanyl and nerve agent target analytes, respectively. Such multimodal wearable platform, capable of distinguishing between the episodes of opioid overdose and nerve agent organophosphate poisoning, can provide real-time analytical information toward timely life-saving medical interventions. To meet the demands for nanomolar fentanyl detection in body fluids, a multi-layered, nanomaterials-based strategy was adopted, where a hybrid of gold nanoparticles and electrochemically reduced graphene oxide was electrodeposited on the microneedle electrode, followed by a PVC coating layer to impart the anti-biofouling characteristics toward prolonged, stable on-body operation. While the dual-target sensor has been tested in skin-mimicking phantom gel model, critical on-body assessments are required to evaluate and validate the potential utility of such a monitoring device.

The same group has demonstrated a multimodal microneedle-based sensing strategy for detection of the Parkinson disease l-Dopa drug possessing a narrow therapeutic range. Such multimodal l-Dopa microneedle arrays rely on unmodified and tyrosinase enzyme-modified carbon paste-packed hollow MN electrodes for simultaneous SWV and amperometric l-Dopa detection, respectively (**Figure 3Bb**).[153] The orthogonal l-Dopa monitoring using these independent electrodes on a single sensor patch offers a built-in redundancy and can be beneficial toward efficient treatment of PD patients via enhancing the information content of the sensing patch. The system exhibited linear dynamic ranges from 0.5 to 3 μM and from 0.25 to 3 μM for l-Dopa detection in artificial ISF using non-enzymatic SWV and enzyme-based amperometric methods, respectively, matching the reported physiological blood ranges of l-Dopa (Table 2). While there is no data available on ISF levels of l-Dopa, a unity ratio can be assumed between blood and ISF considering the molecular size and polarity of this therapeutic agent.[27] Current efforts aim at transferring the attractive analytical performance of the orthogonal l-Dopa detection demonstrated in skin-mimicking phantom gel and mice skin models, to on-body continuous drug monitoring of patients with Parkinson's disease toward improved treatment and future development of a metered

l-Dopa pump.

The first example of using microneedle-based sensing platforms toward real-time, in-vivo monitoring of therapeutic drugs in extracellular fluid (ECF) has recently been described toward individualized dose optimization of antibiotic drug, phenoxymethylpenicillin (**Figure 3Bc**).[10] The microneedle potentiometric sensor relied on measuring the local pH changes induced by the antibiotic drug reaction with an enzyme-modified microneedle electrode. The Au and Ag sputtered polycarbonate solid microneedle arrays were used as transducers, while β-lactamase enzyme-incorporated hydrogel layer, coated on the electrodeposited iridium oxide film, enabled the reaction of the target antibiotic drug to generate protons and the detection of pH changes. The enzyme-modified microneedle arrays were applied to the forearms of a total 10 healthy adult participants, along with a second control microneedle platform (without the β-lactamase enzyme) on each participant to serve as the control and thus, to compensate for the time-dependent changes in the sensor output. The sensing results during a 6 h-long pre- and post-drug administration study were calibrated against blood cannula sampling and the gold-standard ECF microdialysis sampling data, underscoring the initial potential of such microneedle sensing strategy toward real-time, continuous monitoring of penicillin antibiotics. The future trials of the system, however, should target enhancing the operational stability beyond 6 hours and expanding to larger scale subject populations.

Overall, while the aforementioned innovative examples highlight the prospects of using microneedles as wearable drug monitoring systems, intensive and multidisciplinary future efforts should target addressing several key issues. Similar to the current state-of-the-art CGM devices, future TDM applications of microneedle sensors will require large-scale validation prior to practical ISF monitoring, particularly in connection to closed-loop applications.

Saliva and Tears. Saliva and tears are important biofluids that can be employed for non-invasive monitoring of drugs. Till now, these biofluids have been less explored for drug monitoring compared to ISF and sweat-based drug detection systems. Nonetheless, the application of saliva and tears can be quite advantageous under specific scenarios. In this section, the potential and challenges of using saliva and tears for developing wearable drug detection platforms are discussed.

Saliva is a complex oral fluid that mainly stems from three salivary glands with varying

contributions: parotid, submandibular and sublingual.[174] Various materials can pass the bloodstream and enter into the oral cavity by passive or active diffusion.[28] While dominated by the paracellular partitioning route, the analytes face multiple barriers, including ISF, before entering into the saliva and thus, most analytes have smaller concentrations in saliva compared to the blood.[27] Salivary levels of drugs are dependent on their size, lipophilicity, protein binding and mainly, ionizability, as only unionized drugs have been shown to partition into the saliva.[78]

Saliva can be easily accessed in a non-invasive fashion either by stimulated or passive techniques. As such, saliva-based sensors have been exploited for detecting a wide range of analytes, exemplified by the well-recognized lateral flow assay for HIV by OraQuick[175] or the recent FDA-approved first home saliva test for coronavirus by Rutgers University[176]. Beside the advantage of easy collection, drugs are present in saliva in their free (non-protein-bound) state and thus, unlike blood or plasma, they obviate the need for additional steps in order to determine the clinically relevant drug concentrations.[77] Therefore, the potential utility of saliva has widely been explored toward monitoring of various classes of therapeutic drugs, including antibiotics,[177] psychiatrics[178,179] and antiepileptic[180] drugs, as well as for detection of drugs of abuse.[181,182]

A recent wearable design for on-site detection of drugs of abuse in saliva involves ring-based sensing platform toward simultaneous rapid roadside testing of THC and alcohol (**Figure 4Aa**).[52] A screen-printed carbon was used as working electrodes on the ring cap allowing selective direct voltammetric and enzyme-based amperometric quantitation of THC and alcohol, respectively, with no cross-talk between the two analytes. A wireless electronic board embedded within the ring case enabled the on-field drug screening. Furthermore, spring-loaded pins were mounted on the electronics board and aligned with the electrode contacts for rapid replacement of the electrode strips following each saliva assay. Despite the considerable promise of such a wearable accessory platform for addressing major concerns of drug-impaired driving, further improvements are required to target the detection in raw saliva samples and enhancing the THC detection sensitivity to nM range, as the minimum detectable THC level in saliva recommended by the US Department of Health and Human Services is 6.4 nM.[133]

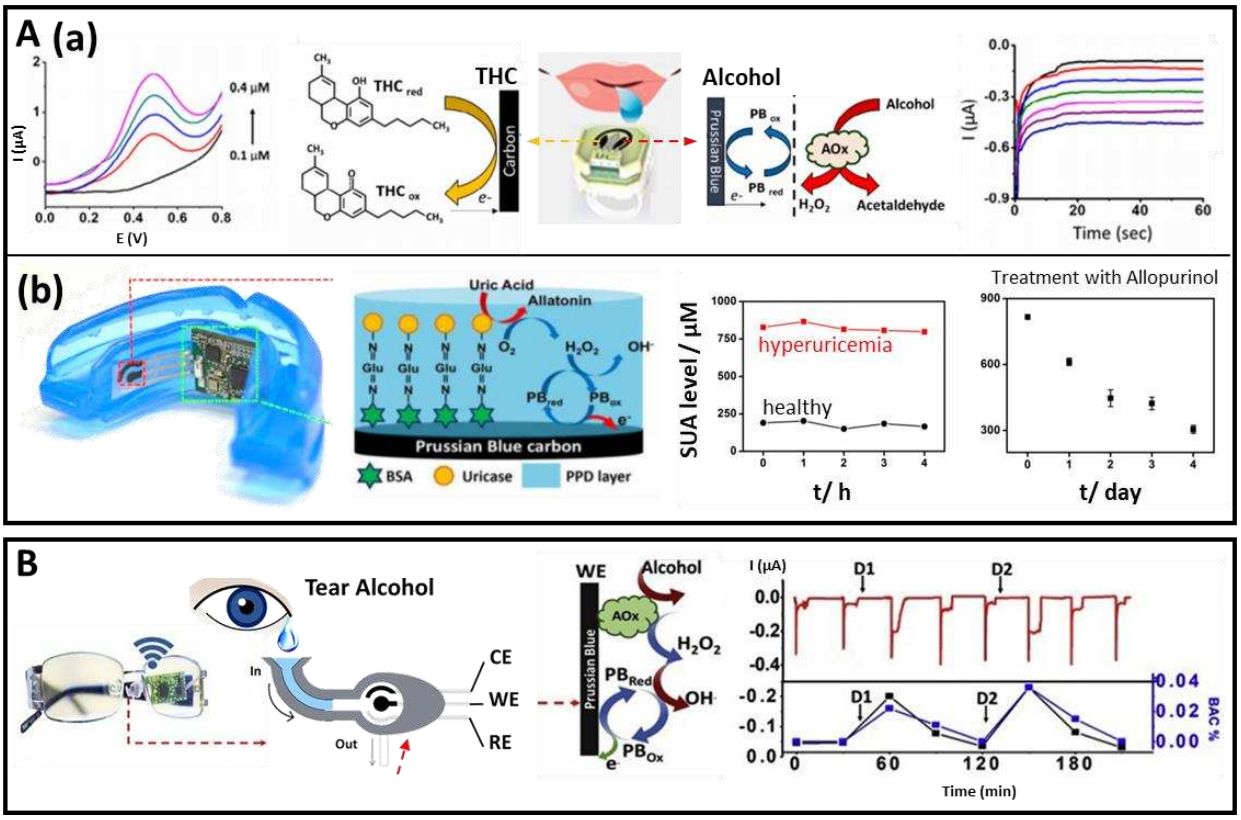

Figure 4. Wearable salivary and tear-based sensors for drug analysis. Aa. Ring-based sensor for simultaneous detection of alcohol and THC in diluted saliva; *square wave voltammograms of THC (left graph) and amperometric response of alcohol (right graph) in diluted saliva samples, along with their corresponding detection mechanisms. Adapted with permission from ref* [52]*. Copyright 2020 Elsevier.* ***Ab. Mouthguard biosensor for detecting salivary uric acid;*** *photograph of the fully integrated mouthguard with the sensor and electronic board, reagent layer and the sensing mechanism, monitored salivary uric acid level of a hyperuricemia patient and a healthy volunteer during 5 hours, hyperuricemia treatment with allopurinol and its effect on the salivary uric acid. Adapted with permission from ref* [183]*. Copyright 2015 Elsevier.* ***B. Eyeglasses-based fluidic sensor for tear alcohol;*** *graphic demonstration of the fluidic device with its integrated wireless electronics along with the detection scheme of alcohol, amperograms for a volunteer consuming two alcoholic drinks at D1 and D2 with the measured BAC levels (blue) and the observed tears alcohol current values (black). Adapted with permission from ref*[53] *Copyright 2019 Elsevier.*

While salivary diagnostics commonly relies on single use point-of-care in-vitro sensors, developing wearable in-mouth platforms for real-time, continuous drug monitoring is challenging. This reflects potential biofouling effects, possible contamination (from food or beverages),[18] and potential safety issues.[133] Additionally, the administration pathway of drugs has been found to largely affect their salivary composition. For example, when radioactively labelled THC was administered intravenously, no traces of radioactive THC were found in saliva, indicating that the presence of THC and its metabolites in saliva after smoking do not originate from salivary glands.[133] A number of oral-cavity sensing platforms have been introduced in recent years,[183–187]

of which the mouthguard biosensor has shown a distinct benefit. A salivary uric acid wearable biosensor was implemented through integration of a mouthguard platform with the uricase enzyme-modified screen-printed electrodes along with the anatomically-sized electronics including potentiostatic circuitry, microcontroller, and a Bluetooth wireless transceiver (**Figure 4Ab**).[183] Uric acid, the end product of purine metabolism, is a biomarker for several diseases such as hyperuricemia, gout, renal syndrome and Lesch–Nyhan syndrome.[183] Additionally, several types of drugs (e.g. l-Dopa and antitubercular drugs) have been identified which induce hyperuricemia and gout through increasing the levels of uric acid.[188] Such drug-induced diseases are emerging concerns in clinical practice and thus, continuous monitoring of uric acid levels can be extremely advantageous for individuals under certain medication treatments. The feasibility of the uric acid mouthguard biosensor was illustrated by comparing the quantities of salivary uric acids obtained for a hyperuricemia patient consuming allopurinol drug and a healthy volunteer.

Furthermore, tears or lachrymal fluid, can also be potentially explored for TDM purposes. The partition of analytes into tears is similar to their partitioning into saliva and sweat.[27] Tears has been shown useful for analysing several drugs such as acetaminophen, lithium, anticonvulsants, methotrexate and minocycline.[21] Additionally, tear is a more preferable matrix than saliva for antihistaminics, antibiotics and antimicrobial agents related to the treatment of conjunctivitis and ocular diseases.[21]

Contact lens-based sensing platforms have attracted interest for continuous monitoring of ocular biomarkers as they provide a constant contact between the sensing component and the basal tears. Representative examples are a self-powered contact lens sensing platform relying on the integration of an enzymatic glucose sensor and a biofuel cell with endogenous ascorbate as the fuel,[189] and a diabetic theragnostic contact lens device via coupling glucose sensing with a drug delivery module.[190] However, despite the attractive opportunities of using such devices toward investigating ocular pharmacokinetics and improving treatment protocols for certain eye-related diseases, there is no example of a contact lens for TDM.

A wearable eyeglasses-based sensor was recently described for non-invasive detection of tear biomarkers, including alcohol (**Figure 4B**).[53] Such wearable bioelectronic platform relied on an integrated microfluidic system, mounted on the nose bridge pad of the eyeglasses, to guide the stimulated tear sample to the AOx enzyme-based biodetector electrode. The tear alcohol sensing concept was illustrated for human volunteers over multiple drinking courses and the obtained

results were validated against BAC measured through commercial Breathalyzer.[53]

Overall, with further optimization in the design and operational characteristics of wearable accessories, such as ring-based devices, such platforms can provide reliable presumptive drug screening and thus hold great promise toward rapid, decentralized detection of drugs of abuse for forensic and law enforcement applications. On the other hand, contact lens-based wearables are expected to play an active role in TDM, especially for the ocular pharmacokinetics studies and toward the development of efficient theranostic devices.

CONCLUSION – PROSPECTS AND CHALLENGES

Dramatic innovations in wearable technology have paved the way for a paradigm shift in healthcare by moving from invasive routines to non-invasive measures for monitoring clinically relevant analytes. Wearable electrochemical sensors have been playing a key role towards on-body detection of chemical markers. While early developments have focused on non-invasive electrochemical monitoring of metabolites and electrolytes, recent efforts have demonstrated the potential of these devices for the monitoring of important therapeutic drugs and the detection of major drugs of abuse. These opportunities of wearable electrochemical sensors in the drug detection field have been the topic of the present review article. Such integration of electrochemical sensors with various wearable platforms, such as wrist-bands, tattoos, microneedles, or gloves, have shown considerable promise for continuous monitoring and on-site screening of drugs. However, there are still specific barriers to overcome for bridging the current gap between scientific and clinical communities. Here, we will briefly discuss the future prospects and remaining unmet challenges of this fast-moving field.

Prospects

Closing the loop. Fully automated closed-loop drug delivery systems would be a seismic shift in medical care toward optimal therapeutic outcomes. Such autonomous closed-loop devices offer automatic regulation of a process variable to a desired set point without human intervention.[191] The recent advances in CGM devices have greatly benefited the development of artificial pancreas systems. The landmark achievement of the FDA-approved hybrid closed-loop system in 2017 by the Medtronic 670G with Guardian 3 sensor[192] has been a major step forward for closing the loop

for people with diabetes.

Similarly, in the case of wearable drug monitoring devices, reliable closed-loop systems which account for wide inter- and intra-patient variations are urgently needed for avoiding ineffective underdosing or toxic overdosing events in patients. However, such systems remain in the early development stage due primarily to the absence of reliable sensors capable of continuous and accurate on-body therapeutic drugs monitoring. The only commercial system is a semi-closed-loop system for anaesthesia monitoring that operates through monitoring physical parameters (and not the direct drug concentration) to provide the anaesthesiologist with timely information for regulating the infusion rate of the anaesthetic drugs.[193] Such monitoring of physical parameters has major limitations as many drugs do not induce a measurable change in physical parameters, and it does not account for the individual physiological and genetic variability.

Recently there have been some progress toward closed-loop systems for therapeutic drugs based on chemical sensors monitoring the circulating drug concentrations. For example, an ex-vivo aptamer-based sensor was used for measuring the concentration of the anti-cancer doxorubicin drug in bloodstream of live rabbits in combination with a proportional–integral–derivative (PID) feedback algorithm and an infusion pump.[194] Another aptamer-based electrochemical sensor was incorporated into a 22-gauge catheter and deployed inside the jugular veins of live rats, which in combination with a PID-based control algorithm and an infusion pump, was used to adjust dosing rates every 7 s for up to 4 h.[195]

There have also been several recent advances in wearable drug delivery systems. For example, hollow microneedles have been shown considerable promise towards on-demand precise delivery of drugs. A microneedle-based multiplexed drug delivery, based on electrochemically-controlled polypyrrole ‘open/close’ nanoactuators, was shown useful for the on-demand delivery of different reagents.[196] Another example involved the integration of a thermally actuated polymeric microneedle to transcutaneously deliver the metformin drug along with the corresponding stretchable glucose monitoring sweat patch.[197] In another work, a microneedle patch consisting of an array of detachable microneedles were used as implantable therapeutic microreservoirs toward treating ocular diseases.[198] Multiplexed therapy was demonstrated through a double-layered microneedle, where quick release of anti-inflammatory diclofenac was followed by a sustained delivery of anti-angiogenic monoclonal antibody (DC101) to achieve synergistic therapeutic outcomes.[198] Miniaturized drug delivery modules have recently been merged also onto a contact

lens with real-time biometric analysis, where non-invasive and continuous diabetic diagnosis was integrated with on-demand diabetic retinopathy therapy enabled by electrical delivery of antiangiogenic genistein and glucose level-controlling metformin treatments.[190] Such advances, along with other reported miniaturized drug delivery modules, should enable multiplexed drug therapies with precise control of the drug infusion rate toward future integration with continuous drug-sensing devices, and ultimately, the realization of fully autonomous closed-loop devices.

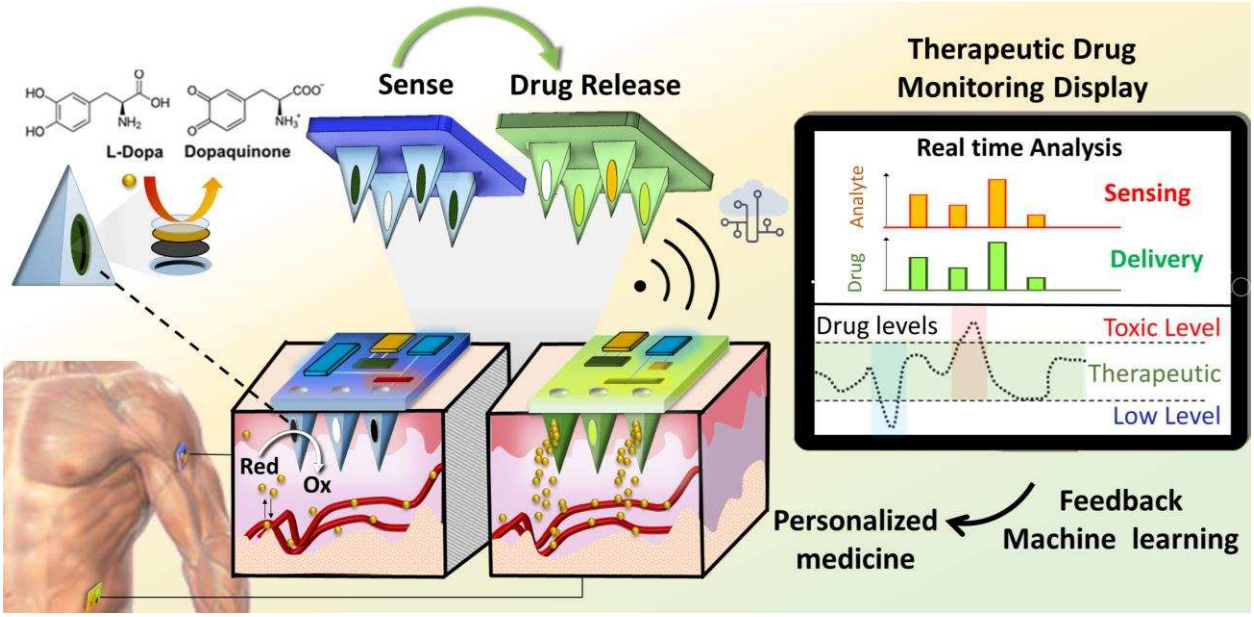

Figure 5. *Vision of a future feedback closed-loop autonomous microneedle system for therapeutic drug monitoring in ISF toward personalized therapy and optimal therapeutic outcome. An autonomous l-Dopa system is showed as an example. The closed-loop 'Sense-Act'' microneedle device is able to measure the ISF drug concentration and accordingly tune the delivery rate via control algorithm for maintaining the drug level within the desired safe therapeutic range.*

The achievement of feedback-controlled wearable closed-loop devices will greatly assist the clinical decision-making processes and the overall therapeutic outcomes. For example, during the treatment of Parkinson's disease, patients rely l-Dopa administration for restoring their motor and non-motor functions. However, due to the short half-life of l-Dopa, it should be taken at least three times a day. In addition, l-Dopa dosing involves a very narrow therapeutic range, as underdosing causes the patient to remain stiff, slow, and have tremors (off periods or akinesia) while overdosing leads to excessive, involuntary movements (on periods or dyskinesia).[199] Furthermore, as the

disease progresses, the therapeutic window becomes narrower, requiring higher l-Dopa doses at more frequent intervals.[199] **Figure 5** shows a hypothetical diagram of a fully automated closed-loop system toward personalized treatment of Parkinson's disease. The microneedle sensor is able to provide a continuous voltammetric measurement of dynamically changing l-Dopa ISF concentrations. The data are transferred in real-time to a smartphone controller with appropriate algorithm software to deliver or interrupt the drug infusion and hence to maintain the desired therapeutic range in the patient's body.[200]

A wearable continuous chemical sensor, capable of providing time-resolved data on drug concentrations, would minimize and even eliminate any drug-drug interactions through the monitoring of any unusual behaviour in the drug pharmacokinetics, to allow tailoring the drug dosing. In addition, wearable drug sensors can improve patient compliance to medication by sending alert messages to wearers and caregivers regarding the frequency of medication intake. All these applications of wearable drug monitoring systems and related wireless communications require critical attention to security and privacy concerns. In particular, data security is of utmost concern for closed-loop systems where potential cybersecurity threats can greatly risk the patient life.[201]

Illicit drugs screening. The recent developments of glove- or ring-based platforms have illustrated the great potential of wearable sensors toward on-site, rapid screening of illicit drugs and cutting agents in street samples and drug-impaired driving habits, respectively. With further developments and new capabilities, such wearable electrochemical systems can address the limitations of currently used portable analytical systems while maintaining the reliability of bench-top standard techniques for accurate and rapid decision-making process of the LEAs' personnel. Additionally, sweat and ISF-based monitoring wearables can offer unprecedented illicit-drug sensing opportunities, including remote monitoring of individuals on probation or in a closed-loop format for mitigating the drug overdose-related deaths.

Challenges. Wearable drug-monitoring sensor systems are required to provide extremely reliable results and hence to meet the high analytical performance expected for ensuring optimal therapeutic outcomes and on-site drug screening. High stability is a crucial for obtaining reliable signals over extended time periods, ranging from few hours (e.g., during surgery) to several days or weeks. While the sensor stability will depend on the specific biofluid, target drug or corresponding bioreceptor, special attention should be given for addressing the surface biofouling

and enzyme stability issues during prolonged operations. Attention should be given also to the storage stability in connection to single-use devices, such as drug-screening gloves, considering also that these sensors are often used in field settings and uncontrolled extreme conditions.

Another challenge associated with developing wearable sensors for drug analysis is the low concentrations (nM to μM) of many target drugs and their narrow therapeutic range. Realizing highly sensitive wearable drug sensors would require the systematic evaluation and incorporation of nanostructured materials that will offer specific electrocatalytic effects and increased available surface area.[152] However, more investigations should be done to ensure the biocompatibility and the safe deployment of such nanomaterials for on-body sensing applications considering the possible toxicity of these nanomaterials.

Considering that many electrochemical drug detection protocols are mainly based on nonenzymatic transduction methods, achieving selectivity is an important issue that needs to be addressed. Even in few cases where enzyme is used for the analyte detection, the enzyme usually possesses broad substrate specificity (such as tyrosinase enzyme for phenols and catechols) and thus, additional steps are necessary to impart high selectivity to the sensor. In particular, advanced permselective and protective surface coatings are critical for imparting the necessary selectivity and stability in the corresponding biofluids.

Furthermore, the increasing popularity of 'calibration-free' or so-called 'factory-calibrated' CGM sensors have elevated the expectations for commercial acceptance of any other type of wearable sensors. Designing such calibration-free sensors will require critical evaluation and correction of various factors that may affect the response of the target drug, such as pH, temperature, and ionic strength, (in connection to additional pH or temperature sensors[26,197] or control electrodes[10] for compensating for any time-dependent changes in the sensor output). Finally, the sensors should be extensively validated against gold standard LC-MS methods to establish the required precision and accuracy for the different target drugs and biofluids. These large-scale validation studies will establish also the correlation between the drug concentration in the corresponding biofluid and in plasma samples. Such large-scale, preclinical and clinical validation studies in human subjects or other animals are critical for demonstrating the suitability of the proposed sensor for a given drug. The commercial viability of rapidly emerging field of wearable drug monitoring systems depends on overcoming all these existing challenges and gaps through continued innovations and multidisciplinary collaborations of scientists, engineers, and clinicians in the coming years.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

BAC: blood alcohol content; CGM: continuous glucose monitoring; DPV: differential pulse voltammetry; ECF: extracellular fluid; EtG: ethyl glucuronide; GC: gas chromatography; ISF: interstitial fluid; LC: liquid chromatography; l-Dopa: levodopa; LEAs: law enforcement agencies; LOD: limit of detection; MDMA: 3,4-methylenedioxy-methamphetamine; MIPs: molecularly imprinted polymers; MS: mass spectrometry; PCBs: printed circuit boards; PID: proportional–integral–derivative; PVC: polyvinyl chloride; SWV: square wave voltammetry; TDM: Therapeutic drug monitoring; THC: Δ^9-tetrahydrocannabinol.

VOCABULARY

Pharmacokinetics- is described as 'what the body does to a drug' and focuses on the movement of a dosed drug and its metabolites into, through, and out of the body. **Pharmacodynamics**- is described as 'what a drug does to the body' and studies the relationship between drug concentration

in the site of action and its biochemical and physiologic effects. **Therapeutic Drug Monitoring (TDM)**- a clinical practice in which drug concentrations are measured in a patient's blood or plasma at designated time points to provide guidance on the effective dosage regimen. **Closed-Loop Feedback-Controlled Device**- a device that continuously monitors the quantity of a process variable and automatically adjusts drug dosage regimen. **Drug-Drug Interactions**- when a specific drug, supplement/food, or the body itself affects the metabolism of another drug through stimulating or inhibiting the action of special enzymes responsible for metabolizing the medications. **Medication Adherence**- the degree by which the patients follow the prescribed dosing regimen as provided by their physicians. **Personalized/Precision Medicine**- an emerging practice in health care, aimed at maximizing patient care through tailoring the therapy based on the unique characteristics of patients. **Wearable Chemical Sensors**- body-worn sensors capable of continuously gather the relevant physiological information via measuring the concentration of a target analyte in peripheral body fluids in a non-invasive and non-obtrusive manner. **Electrochemical Sensors-** devices that convert the analyte-electrode interaction into a measurable electrical signal (e.g. current, voltage) proportional to the analyte concentration.

REFERENCES

(1) Brownstein, H. H. *The Handbook of Drugs and Society*; 2015. https://doi.org/10.1002/9781118726761.

(2) Jané-Llopis, E.; Matytsina, I. Mental Health and Alcohol, Drugs and Tobacco: A Review of the Comorbidity between Mental Disorders and the Use of Alcohol, Tobacco and Illicit Drugs. *Drug Alcohol Rev.* **2006**, *25* (6), 515–536. https://doi.org/10.1080/09595230600944461.

(3) Van Amsterdam, J.; Opperhuizen, A.; Koeter, M.; Van Den Brink, W. Ranking the Harm of Alcohol, Tobacco and Illicit Drugs for the Individual and the Population. *Eur. Addict. Res.* **2010**, *16* (4), 202–207. https://doi.org/10.1159/000317249.

(4) John Peppin, Kelly Dineen, Adam Ruggles, J. C. *Prescription Drug Diversion and Pain: History, Policy, and Treatment*; Oxford University Press, 2018.

(5) Statista Global spending on medicine

https://www.statista.com/statistics/280572/medicine-spending-worldwide/.

(6) Lunenfeld, B.; Stratton, P. The Clinical Consequences of an Ageing World and Preventive Strategies. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2013**, *27* (5), 643–659. https://doi.org/10.1016/j.bpobgyn.2013.02.005.

(7) Dirckx, J. H. *Therapeutic Drug Monitoring*, 4th editio.; Elsevier Inc, Academic Press, 2007; Vol. 26. https://doi.org/10.1097/01.HDMAT.0000350916.30860.f0.

(8) Adam Nergusz, Gail AA, C. *Clarke's Analytical Forensic Toxicology*, Second edi.; Pharmaceutical Press, 2013.

(9) C. Moonla, K.Y. Goud, H. Teymourian, T. Tangkuaram, J. Ingrande, P. Suresh, J. W. An Integrated Microcatheter-Based Dual-Analyte Sensor System for Simultaneous, Real-Time Measurement of Propofol and Fentanyl. *Talanta* **2020**, *218*, 121205. https://doi.org/10.1016/j.talanta.2020.121205.

(10) Rawson, T. M.; Gowers, S. A. N.; Freeman, D. M. E.; Wilson, R. C.; Sharma, S.; Gilchrist, M.; MacGowan, A.; Lovering, A.; Bayliss, M.; Kyriakides, M.; et al. Microneedle Biosensors for Real-Time, Minimally Invasive Drug Monitoring of Phenoxymethylpenicillin: A First-in-Human Evaluation in Healthy Volunteers. *Lancet Digit. Heal.* **2019**, *1* (7), e335–e343. https://doi.org/10.1016/S2589-7500(19)30131-1.

(11) Tucker, G. T. Personalized Drug Dosage – Closing the Loop. *Pharm. Res.* **2017**, *34* (8), 1539–1543. https://doi.org/10.1007/s11095-016-2076-0.

(12) NIH - Opioid overdose crisis https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis.

(13) European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report*; 2019. https://doi.org/10.1097/JSM.0b013e31802b4fda.

(14) Płotka, J. M.; Biziuk, M.; Morrison, C. Common Methods for the Chiral Determination of Amphetamine and Related Compounds I. Gas, Liquid and Thin-Layer Chromatography. *TrAC - Trends Anal. Chem.* **2011**, *30* (7), 1139–1158. https://doi.org/10.1016/j.trac.2011.03.013.

(15) Ibáñez, M.; Sancho, J. V.; Bijlsma, L.; Van Nuijs, A. L. N.; Covaci, A.; Hernández, F. Comprehensive Analytical Strategies Based on High-Resolution Time-of-Flight Mass Spectrometry to Identify New Psychoactive Substances. *TrAC - Trends Anal. Chem.* **2014**, *57*, 107–117. https://doi.org/10.1016/j.trac.2014.02.009.

(16) Fiorentin, T. R.; Krotulski, A. J.; Martin, D. M.; Browne, T.; Triplett, J.; Conti, T.; Logan, B. K. Detection of Cutting Agents in Drug-Positive Seized Exhibits within the United States. *J. Forensic Sci.* **2019**, *64* (3), 888–896. https://doi.org/10.1111/1556-4029.13968.

(17) Petrović, M.; Hernando, M. D.; Díaz-Cruz, M. S.; Barceló, D. Liquid Chromatography-Tandem Mass Spectrometry for the Analysis of Pharmaceutical Residues in Environmental Samples: A Review. *J. Chromatogr. A* **2005**, *1067*, 1–14. https://doi.org/10.1016/j.chroma.2004.10.110.

(18) Anderson, C. Presumptive and Confirmatory Drug Tests. *J. Chem. Educ.* **2005**, *82* (12), 1809. https://doi.org/10.1021/ed082p1809.

(19) Choodum, A.; Nic Daeid, N. Rapid and Semi-Quantitative Presumptive Tests for Opiate Drugs. *Talanta* **2011**, *86*, 284– 292. https://doi.org/10.1016/j.talanta.2011.09.015.

(20) Forensic Technology Center of Excellence. *Landscape Study of Field Portable Devices for Presumptive Drug Testing.U.S. Department of Justice, National Institute of Justice, Office of Investigative and Forensic Sciences*; 2018.

(21) Raju, K. S. R.; Taneja, I.; Singh, S. P.; Wahajuddin. Utility of Noninvasive Biomatrices in Pharmacokinetic Studies. *Biomed. Chromatogr.* **2013**, *27* (10), 1354–1366. https://doi.org/10.1002/bmc.2996.

(22) Mahmud, M. S.; Fang, H.; Carreiro, S.; Wang, H.; Boyer, E. W. Wearables Technology for Drug Abuse Detection: A Survey of Recent Advancement. *Smart Heal.* **2019**, *13*, 100062. https://doi.org/10.1016/j.smhl.2018.09.002.

(23) Bandodkar, A. J.; Jia, W.; Yard, C.; Wang, X.; Ramirez, J.; Wang, J. Tattoo-Based Noninvasive Glucose Monitoring: A Proof-of-Concept Study. *Anal. Chem.* **2014**, *87* (1), 394–398.

(24) Windmiller, J. R.; Wang, J. Wearable Electrochemical Sensors and Biosensors : A Review. *Electroanalysis* **2013**, *25* (1), 29–46. https://doi.org/10.1002/elan.201200349.

(25) Bariya, M.; Shahpar, Z.; Park, H.; Sun, J.; Jung, Y.; Gao, W.; Yin Yin Nyein, H.; Sun Liaw, T.; Tai, L.-C.; Ngo, Q. P.; et al. Roll-to-Roll Gravure Printed Electrochemical Sensors for Wearable and Medical Devices. *ACS Nano* **2018**, *12* (7), 6978–6987. https://doi.org/10.1021/acsnano.8b02505.

(26) Gao, W.; Emaminejad, S.; Nyein, H. Y. Y.; Challa, S.; Chen, K.; Peck, A.; Fahad, H. M.; Ota, H.; Shiraki, H.; Kiriya, D.; et al. Fully Integrated Wearable Sensor Arrays for

Multiplexed in Situ Perspiration Analysis. *Nature* **2016**, *529* (7587), 509–514. https://doi.org/10.1038/nature16521.

(27) Heikenfeld, J.; Jajack, A.; Feldman, B.; Granger, S. W.; Gaitonde, S.; Begtrup, G.; Katchman, B. A. Accessing Analytes in Biofluids for Peripheral Biochemical Monitoring. *Nat. Biotechnol.* **2019**, *37* (4), 407–419. https://doi.org/10.1038/s41587-019-0040-3.

(28) Kim, J.; Campbell, A. S.; de Ávila, B. E.-F.; Wang, J. Wearable Biosensors for Healthcare Monitoring. *Nat. Biotechnol.* **2019**, *37*, 389–406. https://doi.org/10.1038/s41587-019-0045-y.

(29) Kim, J.; Jeerapan, I.; Sempionatto, J. R.; Barfidokht, A.; Mishra, R. K.; Campbell, A. S.; Hubble, L. J.; Wang, J. Wearable Bioelectronics: Enzyme-Based Body-Worn Electronic Devices. *Acc. Chem. Res.* **2018**, *51* (11), 2820–2828. https://doi.org/10.1021/acs.accounts.8b00451.

(30) Sempionatto, J. R.; Jeerapan, I.; Krishnan, S.; Wang, J. Wearable Chemical Sensors: Emerging Systems for On-Body Analytical Chemistry. *Anal. Chem.* **2020**, *92* (1), 378–396. https://doi.org/10.1021/acs.analchem.9b04668.

(31) Tu, J.; Torrente-Rodríguez, R. M.; Wang, M.; Gao, W. The Era of Digital Health: A Review of Portable and Wearable Affinity Biosensors. *Adv. Funct. Mater.* **2019**, *1906713*, 1906713. https://doi.org/10.1002/adfm.201906713.

(32) Yang, Y.; Gao, W. Wearable and Flexible Electronics for Continuous Molecular Monitoring. *Chem. Soc. Rev.* **2019**, *18* (48), 1465–1491. https://doi.org/10.1039/C7CS00730B.

(33) Choi, J.; Ghaffari, R.; Gutruf, P.; Bandodkar, A. J.; Krishnan, S.; Rogers, J. A.; Tian, L.; Ray, T. R. Bio-Integrated Wearable Systems: A Comprehensive Review. *Chem. Rev.* **2019**, *119* (8), 5461–5533. https://doi.org/10.1021/acs.chemrev.8b00573.

(34) Heikenfeld, J.; Jajack, A.; Rogers, J.; Gutruf, P.; Tian, L.; Pan, T.; Li, R.; Khine, M.; Kim, J.; Wang, J.; et al. Wearable Sensors: Modalities, Challenges, and Prospects. *Lab Chip* **2018**, *18*, 217–248. https://doi.org/10.1039/C7LC00914C.

(35) Shaw, L.; Dennany, L. Applications of Electrochemical Sensors: Forensic Drug Analysis. *Curr. Opin. Electrochem.* **2017**, *3* (1), 23–28. https://doi.org/https://doi.org/10.1016/j.coelec.2017.05.001.

(36) Florea, A.; de Jong, M.; De Wael, K. Electrochemical Strategies for the Detection of

Forensic Drugs. *Curr. Opin. Electrochem.* **2018**, *11*, 34–40. https://doi.org/10.1016/j.coelec.2018.06.014.

(37) Lima, H. R. S.; da Silva, J. S.; de Oliveira Farias, E. A.; Teixeira, P. R. S.; Eiras, C.; Nunes, L. C. C. Electrochemical Sensors and Biosensors for the Analysis of Antineoplastic Drugs. *Biosens. Bioelectron.* **2018**, *108* (November 2017), 27–37. https://doi.org/10.1016/j.bios.2018.02.034.

(38) Goodchild, S. A.; Hubble, L. J.; Mishra, R. K.; Li, Z.; Goud, K. Y.; Barfidokht, A.; Shah, R.; Bagot, K. S.; McIntosh, A. J. S.; Wang, J. Ionic Liquid-Modified Disposable Electrochemical Sensor Strip for Analysis of Fentanyl. *Anal. Chem.* **2019**, *91* (5), 3747–3753. https://doi.org/10.1021/acs.analchem.9b00176.

(39) Kivlehan, F.; Garay, F.; Guo, J.; Chaum, E.; Lindner, E. Toward Feedback-Controlled Anesthesia: Voltammetric Measurement of Propofol (2,6-Diisopropylphenol) in Serum-like Electrolyte Solutions. *Anal. Chem.* **2012**, *84*, 7670–7676. https://doi.org/10.1021/ac3006878.

(40) Brunetti, B.; Valdés-Ramírez, G.; Litvan, I.; Wang, J. A Disposable Electrochemical Biosensor for L-DOPA Determination in Undiluted Human Serum. *Electrochem. commun.* **2014**, *48*, 28–31. https://doi.org/10.1016/j.elecom.2014.08.007.

(41) Navaee, A.; Salimi, A.; Teymourian, H. Graphene Nanosheets Modified Glassy Carbon Electrode for Simultaneous Detection of Heroine, Morphine and Noscapine. *Biosens. Bioelectron.* **2012**, *31* (1), 205–211. https://doi.org/10.1016/j.bios.2011.10.018.

(42) Yilmaz Sengel, T.; Guler, E.; Gumus, Z. P.; Aldemir, E.; Coskunol, H.; Akbulut, H.; Goen Colak, D.; Cianga, I.; Yamada, S.; Timur, S.; et al. An Immunoelectrochemical Platform for the Biosensing of 'Cocaine Use.' *Sensors Actuators, B Chem.* **2017**, *246*, 310–318. https://doi.org/10.1016/j.snb.2017.02.087.

(43) Abnous, K.; Danesh, N. M.; Ramezani, M.; Taghdisi, S. M.; Emrani, A. S. A Novel Electrochemical Aptasensor Based on H-Shape Structure of Aptamer-Complimentary Strands Conjugate for Ultrasensitive Detection of Cocaine. *Sensors Actuators, B Chem.* **2016**, *224*, 351–355. https://doi.org/10.1016/j.snb.2015.10.039.

(44) Xiao, N.; Deng, J.; Cheng, J.; Ju, S.; Zhao, H.; Xie, J.; Qian, D.; He, J. Carbon Paste Electrode Modified with Duplex Molecularly Imprinted Polymer Hybrid Film for Metronidazole Detection. *Biosens. Bioelectron.* **2016**, *81*, 54–60.

https://doi.org/10.1016/j.bios.2016.02.041.

(45) Dauphin-Ducharme, P.; Yang, K.; Arroyo-Currás, N.; Ploense, K. L.; Zhang, Y.; Gerson, J.; Kurnik, M.; Kippin, T. E.; Stojanovic, M. N.; Plaxco, K. W. Electrochemical Aptamer-Based Sensors for Improved Therapeutic Drug Monitoring and High-Precision, Feedback-Controlled Drug Delivery. *ACS Sensors* **2019**, *4* (10), 2832–2837. https://doi.org/10.1021/acssensors.9b01616.

(46) Carreiro, S.; Wittbold, K.; Indic, P.; Fang, H.; Zhang, J.; Boyer, E. W. Wearable Biosensors to Detect Physiologic Change During Opioid Use. *J. Med. Toxicol.* **2016**, *12* (3), 255–262. https://doi.org/10.1007/s13181-016-0557-5.

(47) Howell, J.; Nag, A.; McKnight, M.; Narsipur, S.; Adelegan, O. A Low-Power Wearable Substance Monitoring Device. *IEEE Virtual Conf. Appl. Commer. Sensors* **2015**. https://doi.org/10.1109/VCACS.2015.7439567.

(48) Park, E.; Lee, S. I.; Nam, H. S.; Garst, J. H.; Huang, A.; Campion, A.; Arnell, M.; Ghalehsariand, N.; Park, S.; Chang, H. J.; et al. Unobtrusive and Continuous Monitoring of Alcohol-Impaired Gait Using Smart Shoes. *Methods Inf. Med.* **2017**, *56* (1), 74–82. https://doi.org/10.3414/ME15-02-0008.

(49) Device could automatically deliver drug to reverse opioid overdose https://www.sciencedaily.com/releases/2019/07/190725091855.htm.

(50) de Jong, M.; Sleegers, N.; Kim, J.; Van Durme, F.; Samyn, N.; Wang, J.; De Wael, K. Electrochemical Fingerprint of Street Samples for Fast On-Site Screening of Cocaine in Seized Drug Powders. *Chem. Sci.* **2016**, *7*, 2364–2370. https://doi.org/10.1039/C5SC04309C.

(51) Kim, J.; Jeerapan, I.; Imani, S.; Cho, T. N.; Bandodkar, A. J.; Cinti, S.; Mercier, P. P.; Wang, J. Non-Invasive Alcohol Monitoring Using a Wearable Tattoo-Based Iontophoretic-Biosensing System. *ACS Sensors* **2016**, *1*, 1011–1019. https://doi.org/10.1021/acssensors.6b00356.

(52) Mishra, R. K.; Sempionatto, J. R.; Li, Z.; Brown, C.; Galdino, N. M.; Shah, R.; Liu, S.; Hubble, L. J.; Bagot, K.; Tapert, S.; et al. Simultaneous Detection of Salivary Δ9-Tetrahydrocannabinol and Alcohol Using a Wearable Electrochemical Ring Sensor. *Talanta* **2020**, *211*, 120757.

(53) Sempionatto, J. R.; Brazaca, L. C.; García-Carmona, L.; Bolat, G.; Campbell, A. S.;

Martin, A.; Tang, G.; Shah, R.; Mishra, R. K.; Kim, J.; et al. Eyeglasses-Based Tear Biosensing System: Non-Invasive Detection of Alcohol, Vitamins and Glucose. *Biosens. Bioelectron.* **2019**, *137*, 161–170. https://doi.org/10.1016/j.bios.2019.04.058.

(54) European Monitoring Centre for Drugs and Drug Addiction. *EU Drug Markets Report*; 2019. https://doi.org/10.2810/53181.

(55) Mathur, S.; Sutton, J. Personalized Medicine Could Transform Healthcare (Review). *Biomedical Reports*. 2017. https://doi.org/10.3892/br.2017.922.

(56) Lankenau, S. E.; Wagner, K. D.; Silva, K.; Kecojevic, A.; Iverson, E.; McNeely, M.; Kral, A. H. Injection Drug Users Trained by Overdose Prevention Programs: Responses to Witnessed Overdoses. *J. Community Health* **2013**. https://doi.org/10.1007/s10900-012-9591-7.

(57) Green, T. C.; Zaller, N.; Palacios, W. R.; Bowman, S. E.; Ray, M.; Heimer, R.; Case, P. Law Enforcement Attitudes toward Overdose Prevention and Response. *Drug Alcohol Depend.* **2013**. https://doi.org/10.1016/j.drugalcdep.2013.08.018.

(58) Friedmann, P. D.; Taxman, F. S.; Henderson, C. E. Evidence-Based Treatment Practices for Drug-Involved Adults in the Criminal Justice System. *J. Subst. Abuse Treat.* **2007**. https://doi.org/10.1016/j.jsat.2006.12.020.

(59) Liu, Y.; Pharr, M.; Salvatore, G. A. Lab-on-Skin: A Review of Flexible and Stretchable Electronics for Wearable Health Monitoring. *ACS Nano* **2017**, *11* (10), 9614–9635. https://doi.org/10.1021/acsnano.7b04898.

(60) Choi, J.; Ghaffari, R.; Baker, L. B.; Rogers, J. A. Skin-Interfaced Systems for Sweat Collection and Analytics. *Sci. Adv.* **2018**, *4* (2), eaar3921. https://doi.org/10.1126/sciadv.aar3921.

(61) Bandodkar, A. J.; Jeerapan, I.; Wang, J. Wearable Chemical Sensors: Present Challenges and Future Prospects. *ACS Sensors* **2016**, *1* (5), 464–482. https://doi.org/10.1021/acssensors.6b00250.

(62) Kim, J.; Kumar, R.; Bandodkar, A. J.; Wang, J. Advanced Materials for Printed Wearable Electrochemical Devices: A Review. *Adv. Electron. Mater.* **2017**, *3* (1), 1600260. https://doi.org/10.1002/aelm.201600260.

(63) Yu, Y.; Nyein, H. Y. Y.; Gao, W.; Javey, A. Flexible Electrochemical Bioelectronics: The Rise of In Situ Bioanalysis. *Adv. Mater.* **2020**, *32* (15), 1902083.

https://doi.org/10.1002/adma.201902083.

(64) Bandodkar, A. J.; Jia, W.; Wang, J. Tattoo-Based Wearable Electrochemical Devices : A Review. *Electroanalysis* **2015**, *27* (3), 562–572. https://doi.org/10.1002/elan.201400537.

(65) Parrilla, M.; Cuartero, M.; Crespo, G. A. Wearable Potentiometric Ion Sensors. *TrAC - Trends Anal. Chem.* **2019**, *110*, 303–320. https://doi.org/10.1016/j.trac.2018.11.024.

(66) Lee, H.; Hong, Y. J.; Baik, S.; Hyeon, T.; Kim, D. H. Enzyme-Based Glucose Sensor: From Invasive to Wearable Device. *Adv. Healthc. Mater.* **2018**, *7* (8), 1–14. https://doi.org/10.1002/adhm.201701150.

(67) Kim, J.; Campbell, A. S.; Wang, J. Wearable Non-Invasive Epidermal Glucose Sensors: A Review. *Talanta* **2018**, *177*, 163–170. https://doi.org/10.1016/j.talanta.2017.08.077.

(68) Hubble, L. J.; Wang, J. Sensing at Your Fingertips: Glove-based Wearable Chemical Sensors. *Electroanalysis* **2019**, *31* (3), 428–436. https://doi.org/10.1002/elan.201800743.

(69) Ciui, B.; Martin, A.; Mishra, R. K.; Nakagawa, T.; Dawkins, T. J.; Lyu, M.; Cristea, C.; Sandulescu, R.; Wang, J. Chemical Sensing at the Robot Fingertips: Toward Automated Taste Discrimination in Food Samples. *ACS Sensors* **2018**, *3*, 2375–2384. https://doi.org/10.1021/acssensors.8b00778.

(70) De Jong, M.; Florea, A.; De Vries, A. M.; Van Nuijs, A. L. N.; Covaci, A.; Van Durme, F.; Martins, J. C.; Samyn, N.; De Wael, K. Levamisole: A Common Adulterant in Cocaine Street Samples Hindering Electrochemical Detection of Cocaine. *Anal. Chem.* **2018**, *90* (8), 5290–5297. https://doi.org/10.1021/acs.analchem.8b00204.

(71) De Jong, M.; Sleegers, N.; Florea, A.; Van Loon, J.; Van Nuijs, A. L. N.; Samyn, N.; De Wael, K. Unraveling the Mechanisms behind the Complete Suppression of Cocaine Electrochemical Signals by Chlorpromazine, Promethazine, Procaine, and Dextromethorphan. *Anal. Chem.* **2019**, *91* (24), 15453–15460. https://doi.org/10.1021/acs.analchem.9b03128.

(72) Barfidokht, A.; Mishra, R. K.; Seenivasan, R.; Liu, S.; Hubble, L. J.; Wang, J.; Hall, D. A. Wearable Electrochemical Glove-Based Sensor for Rapid and on-Site Detection of Fentanyl. *Sensors Actuators, B Chem.* **2019**, *296*, 126422. https://doi.org/10.1016/j.snb.2019.04.053.

(73) Nehlig, A.; Daval, J. L.; Debry, G. Caffeine and the Central Nervous System: Mechanisms of Action, Biochemical, Metabolic and Psychostimulant Effects. *Brain Res. Rev.* **1992**, *17*

(2), 139–170. https://doi.org/10.1016/0165-0173(92)90012-B.

(74) Kerrigan, S.; Lindsey, T. Fatal Caffeine Overdose: Two Case Reports. *Forensic Sci. Int.* **2005**, *153* (1), 67–69. https://doi.org/10.1016/j.forsciint.2005.04.016.

(75) Mishra, R.; Hubble, L. J.; Martín, A.; Kumar, R.; Barfidokht, A.; Kim, J.; Musameh, M. M.; Kyratzis, I. L.; Wang, J. Wearable Flexible and Stretchable Glove Biosensor for On-Site Detection of Organophosphorus Chemical Threats. *ACS Sensors* **2017**, *2* (4), 553–561. https://doi.org/10.1021/acssensors.7b00051.

(76) Booker, H. E.; Darcey, B. Serum Concentrations of Free Diphenylhydantoin and Their Relationship To Clinical Intoxication. *Epilepsia* **1973**, *14* (2), 177–184. https://doi.org/10.1111/j.1528-1157.1973.tb03954.x.

(77) Ates, H. C.; Roberts, J. A.; Lipman, J.; Cass, A. E. G.; Urban, G. A.; Dincer, C. On-Site Therapeutic Drug Monitoring. *Trends Biotechnol.* **2020**, 1–16. https://doi.org/10.1016/j.tibtech.2020.03.001.

(78) Kiang, T. K. L.; Ranamukhaarachchi, S. A.; Ensom, M. H. H. Revolutionizing Therapeutic Drug Monitoring with the Use of Interstitial Fluid and Microneedles Technology. *Pharmaceutics* **2017**, *9* (4). https://doi.org/10.3390/pharmaceutics9040043.

(79) Navarro, M.; Pichini, S.; Farré, M.; Ortuño, J.; Roset, P. N.; Segura, J.; De La Torre, R. Usefulness of Saliva for Measurement of 3,4-Methylenedioxymethamphetamine and Its Metabolites: Correlation with Plasma Drug Concentrations and Effect of Salivary PH. *Clin. Chem.* **2001**, *47* (10), 1788–1795. https://doi.org/10.1093/clinchem/47.10.1788.

(80) Jenkins, A. J.; Oyler, J. M.; Cone, E. J. Comparison of Heroin and Cocaine Concentrations in Saliva with Concentrations in Blood and Plasma. *J. Anal. Toxicol.* **1995**, *19* (6), 359–374. https://doi.org/10.1093/jat/19.6.359.

(81) Vidal, J. C.; Bertolín, J. R.; Bonel, L.; Asturias, L.; Arcos-Martínez, M. J.; Castillo, J. R. Rapid Determination of Recent Cocaine Use with Magnetic Particles-Based Enzyme Immunoassays in Serum, Saliva, and Urine Fluids. *J. Pharm. Biomed. Anal.* **2016**, *125*, 54–61. https://doi.org/10.1016/j.jpba.2016.03.004.

(82) Schüttler, J.; Ihmsen, H. Population Pharmacokinetics of Propofol: A Multicenter Study. *Anesthesiology* **2000**, *92* (3), 727–738. https://doi.org/10.1097/00000542-200003000-00017.

(83) Dasgupta, A.; Krasowski, M. D. Antineoplastic Drugs. *Ther. Drug Monit. Data* **2020**,

331–350. https://doi.org/10.1016/b978-0-12-815849-4.00015-3.

(84) Brooks, D. J. Optimizing Levodopa Therapy for Parkinson's Disease with Levodopa/Carbidopa/Entacapone: Implications from a Clinical and Patient Perspective. *Neuropsychiatr. Dis. Treat.* **2008**, *4* (1 A), 39–47. https://doi.org/10.2147/ndt.s1660.

(85) Nyholm, D. Pharmacokinetic Optimisation in the Treatment of Parkinson's Disease: An Update. *Clin. Pharmacokinet.* **2006**, *45* (2), 109–136. https://doi.org/10.2165/00003088-200645020-00001.

(86) Tsunoda, M.; Hirayama, M.; Tsuda, T.; Ohno, K. Noninvasive Monitoring of Plasma L-Dopa Concentrations Using Sweat Samples in Parkinson's Disease. *Clin. Chim. Acta* **2015**, *442*, 52–55. https://doi.org/10.1016/j.cca.2014.12.032.

(87) Sanghavi, B. J.; Wolfbeis, O. S.; Hirsch, T.; Swami, N. S. Nanomaterial-Based Electrochemical Sensing of Neurological Drugs and Neurotransmitters. *Microchim. Acta* **2015**, *182* (1–2), 1–41. https://doi.org/10.1007/s00604-014-1308-4.

(88) Dasgupta, A.; Krasowski, M. D. *Therapeutic Drug Monitoring of Cardioactive Drugs*; 2020. https://doi.org/10.1016/b978-0-12-815849-4.00012-8.

(89) Dasgupta, A.; Krasowski, M. D. Therapeutic Drug Monitoring of Antidepressants and Psychoactive Drugs. *Ther. Drug Monit. Data* **2020**, 199–227. https://doi.org/10.1016/b978-0-12-815849-4.00011-6.

(90) Dasgupta, A.; Krasowski, M. D. *Therapeutic Drug Monitoring of Antimicrobial, Antifungal and Antiviral Agents*; 2020. https://doi.org/10.1016/b978-0-12-815849-4.00010-4.

(91) Gowers, S. A. N.; Freeman, D. M. E.; Rawson, T. M.; Rogers, M. L.; Wilson, R. C.; Holmes, A. H.; Cass, A. E.; O'Hare, D. Development of a Minimally Invasive Microneedle-Based Sensor for Continuous Monitoring of B-Lactam Antibiotic Concentrations in Vivo. *ACS Sensors* **2019**, *4*, 1072–1080.

(92) Kiang, T. K. L.; Häfeli, U. O.; Ensom, M. H. H. A Comprehensive Review on the Pharmacokinetics of Antibiotics in Interstitial Fluid Spaces in Humans: Implications on Dosing and Clinical Pharmacokinetic Monitoring. *Clin. Pharmacokinet.* **2014**, *53* (8), 695–730. https://doi.org/10.1007/s40262-014-0152-3.

(93) Ito, Y.; Inagaki, Y.; Kobuchi, S.; Takada, K.; Sakaeda, T. Therapeutic Drug Monitoring of Vancomycin in Dermal Interstitial Fluid Using Dissolving Microneedles. *Int. J. Med. Sci.*

2016, *13* (4), 271–276. https://doi.org/10.7150/ijms.13601.

(94) Minichmayr, I. K.; Schaeftlein, A.; Kuti, J. L.; Zeitlinger, M.; Kloft, C. Clinical Determinants of Target Non-Attainment of Linezolid in Plasma and Interstitial Space Fluid: A Pooled Population Pharmacokinetic Analysis with Focus on Critically Ill Patients. *Clin. Pharmacokinet.* **2017**, *56* (6), 617–633. https://doi.org/10.1007/s40262-016-0463-7.

(95) Dasgupta, A.; Krasowski, M. D. Analgesics. In *Therapeutic Drug Monitoring Data*; 2020; pp 309–330. https://doi.org/10.1016/B978-0-12-815849-4.00014-1.

(96) Dasgupta, A.; Krasowski, M. D. Immunosuppressants. In *Therapeutic Drug Monitoring Data*; 2020; pp 271–307. https://doi.org/10.1016/B978-0-12-815849-4.00013-X.

(97) Dasgupta, A.; Krasowski, M. D. Antiepileptic Drugs. In *Therapeutic Drug Monitoring Data*; 2020; Vol. Chapter 9, pp 99–158. https://doi.org/10.1016/B978-0-12-815849-4.00009-8.

(98) Kovacs, E. M. R.; Stegen, J. H. C. H.; Brouns, F. Effect of Caffeinated Drinks on Substrate Metabolism, Caffeine Excretion, and Performance. *J. Appl. Physiol.* **1998**, *85* (2), 709–715. https://doi.org/10.1152/jappl.1998.85.2.709.

(99) Dasgupta, A.; Krasowski, M. D. Caffeine and Theophylline. *Ther. Drug Monit. Data* **2020**, 351–359. https://doi.org/10.1016/b978-0-12-815849-4.00016-5.

(100) Barnes, P. J. Theophylline. *Am. J. Respir. Crit. Care Med.* **2013**, *188* (8), 901–906. https://doi.org/10.1164/rccm.201302-0388PP.

(101) Turner-Warwick, M. Study of Theophylline Plasma Levels after Oral Administration of New Theophylline Compounds. *Br. Med. J.* **1957**, *2* (5036), 67. https://doi.org/10.1136/bmj.2.5036.67.

(102) Kiang, T. K. L.; Schmitt, V.; Ensom, M. H. H.; Chua, B.; Hafeli, U. O. Therapeutic Drug Monitoring in Interstitial Fluid: A Feasibility Study Using a Comprehensive Panel of Drugs. *J. Pharm. Sci.* **2012**, *101* (7), 2271–2280. https://doi.org/10.1002/jps.

(103) Maurer, H. H.; Sauer, C.; Theobald, D. S. Toxicokinetics of Drugs of Abuse: Current Knowledge of the Isoenzymes Involved in the Human Metabolism of Tetrahydrocannabinol, Cocaine, Heroin, Morphine, and Codeine. *Ther. Drug Monit.* **2006**, *28* (3), 447–453. https://doi.org/10.1097/01.ftd.0000211812.27558.6e.

(104) Cone, E. J.; Hillsgrove, M. J.; Jenkins, A. J.; Keenan, R. M.; Darwin, W. D. Sweat Testing

for Heroin, Cocaine, and Metabolites. *J. Anal. Toxicol.* **1994**, *18* (6), 298–305. https://doi.org/10.1093/jat/18.6.298.

(105) Kintz, P.; Tracqui, A.; Mangin, P.; Edel, Y. Sweat Testing in Opioid Users with a Sweat Patch. *J. Anal. Toxicol.* **1996**, *20* (6), 393–397. https://doi.org/10.1093/jat/20.6.393.

(106) Dasgupta, A. The Effects of Adulterants and Selected Ingested Compounds on Drugs-of-Abuse Testing in Urine. *Am. J. Clin. Pathol.* **2007**, *128* (3), 491–503. https://doi.org/10.1309/FQY06F8XKTQPM149.

(107) Vindenes, V.; Lund, H. M. E.; Andresen, W.; Gjerde, H.; Ikdahl, S. E.; Christophersen, A. S.; Øiestad, E. L. Detection of Drugs of Abuse in Simultaneously Collected Oral Fluid, Urine and Blood from Norwegian Drug Drivers. *Forensic Sci. Int.* **2012**, *219* (1–3), 165–171. https://doi.org/10.1016/j.forsciint.2012.01.001.

(108) Christo, P. J.; Manchikanti, L.; Ruan, X.; Bottros, M.; Hansen, H.; Solanki, D. R.; Jordan, A. E.; Colson, J. Urine Drug Testing in Chronic Pain. *Pain Physician* **2011**, *14* (2), 123–143.

(109) Kintz, P.; Brenneisen, R.; Bundeli, P.; Mangin, P. Sweat Testing for Heroin and Metabolites in a Heroin Maintenance Program. *Clin. Chem.* **1997**, *43* (5), 736–739. https://doi.org/10.1093/clinchem/43.5.736.

(110) Findlay, J. W. A.; Jones, E. C.; Butz, R. F.; Welch, R. M. Plasma Codeine and Morphine Concentrations after Therapeutic Oral Doses of Codeine-Containing Analgesics. *Clin. Pharmacol. Ther.* **1978**, *24* (1), 60–68. https://doi.org/10.1002/cpt197824160.

(111) Schwilke, E. W.; Barnes, A. J.; Kacinko, S. L.; Cone, E. J.; Moolchan, E. T.; Huestis, M. A. Opioid Disposition in Human Sweat after Controlled Oral Codeine Administration. *Clin. Chem.* **2006**, *52* (8), 1539–1545. https://doi.org/10.1373/clinchem.2006.067983.

(112) McClain, D. A.; Hug, C. C. Intravenous Fentanyl Kinetics. *Clin. Pharmacol. Ther.* **1980**, *28* (1), 106–114.

(113) Andresen, H.; Gullans, A.; Veselinovic, M.; Anders, S.; Schmoldt, A.; Iwersen-Bergmann, S.; Mueller, A. Fentanyl: Toxic or Therapeutic? Postmortem and Antemortem Blood Concentrations after Transdermal Fentanyl Application. *J. Anal. Toxicol.* **2012**, *36* (3), 182–194. https://doi.org/10.1093/jat/bks005.

(114) Schneider, S.; Ait-m-bark, Z.; Schummer, C.; Lemmer, P.; Yegles, M.; Appenzeller, B.; Wennig, R. Determination of Fentanyl in Sweat and Hair of a Patient Using Transdermal

Patches. *J. Anal. Toxicol.* **2008**, *32* (3), 260–264. https://doi.org/10.1093/jat/32.3.260.

(115) Eap, C. B.; Bourquin, M.; Martin, J. L.; Spagnoli, J.; Livoti, S.; Powell, K.; Baumann, P.; Déglon, J. J. Plasma Concentrations of the Enantiomers of Methadone and Therapeutic Response in Methadone Maintenance Treatment. *Drug Alcohol Depend.* **2000**, *61* (1), 47–54. https://doi.org/10.1016/S0376-8716(00)00121-6.

(116) Loimer, N.; Schmid, R. The Use of Plasma Levels to Optimize Methadone Maintenance Treatment. *Drug Alcohol Depend.* **1992**, *30* (3), 241–246. https://doi.org/10.1016/0376-8716(92)90058-K.

(117) Verebely, K.; Volavka, J.; Mulé, S.; Resnick, R. Methadone in Man: Pharmacokinetic and Excretion Studies in Acute and Chronic Treatment. *Clin. Pharmacol. Ther.* **1975**, *18* (2), 180–190. https://doi.org/10.1002/cpt1975182180.

(118) Fucci, N.; De Giovanni, N. Methadone in Hair and Sweat from Patients in Long-Term Maintenance Therapy. *Ther. Drug Monit.* **2007**, *29* (4), 452–454. https://doi.org/10.1097/FTD.0b013e31811f1bbe.

(119) Høiseth, G.; Morini, L.; Polettini, A.; Christophersen, A.; Mørland, J. Blood Kinetics of Ethyl Glucuronide and Ethyl Sulphate in Heavy Drinkers during Alcohol Detoxification. *Forensic Sci. Int.* **2009**, *188* (1–3), 52–56. https://doi.org/10.1016/j.forsciint.2009.03.017.

(120) Roine, R. P.; Gentry, R. T.; Lim, R. T.; Baraona, E.; Lieber, C. S. Effect of Concentration of Ingested Ethanol on Blood Alcohol Levels. *Alcohol. Clin. Exp. Res.* **1991**, *15* (4), 734–738. https://doi.org/10.1111/j.1530-0277.1991.tb00589.x.

(121) Bhide, A.; Muthukumar, S.; Saini, A.; Prasad, S. Simultaneous Lancet-Free Monitoring of Alcohol and Glucose from Low-Volumes of Perspired Human Sweat. *Sci. Rep.* **2018**, *8* (1), 1–11. https://doi.org/10.1038/s41598-018-24543-4.

(122) Pawan, G. L.; Grice, K. Distribution of Alcohol in Urine and Sweat after Drinking. *Lancet* **1968**, *2* (7576), 1016. https://doi.org/10.1016/S0140-6736(68)91302-0.

(123) Schummer, C.; Appenzeller, B. M. R.; Wennig, R. Quantitative Determination of Ethyl Glucuronide in Sweat. *Ther. Drug Monit.* **2008**, *30* (4), 536–539. https://doi.org/10.1097/FTD.0b013e318180c83d.

(124) Selvam, A. P.; Muthukumar, S.; Kamakoti, V.; Prasad, S. A Wearable Biochemical Sensor for Monitoring Alcohol Consumption Lifestyle through Ethyl Glucuronide (EtG) Detection in Human Sweat. *Sci. Rep.* **2016**, *6*, 23111. https://doi.org/10.1038/srep23111.

(125) Nakashima, K.; Kaddoumi, A.; Ishida, Y.; Itoh, T.; Taki, K. Determination of Methamphetamine and Amphetamine in Abusers' Plasma and Hair Samples with HPLC-FL. *Biomed. Chromatogr.* **2003**, *17* (7), 471–476. https://doi.org/10.1002/bmc.278.

(126) Peters, F. T.; Kraemer, T.; Maurer, H. H. Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic-Mass Spectrometric Assay for Determination of Amphetamine and Methamphetamine Enantiomers and Its Application to Toxicology Cases. *Clin. Chem.* **2002**, *48* (9), 1472–1485. https://doi.org/10.1093/clinchem/48.9.1472.

(127) Barnes, A. J.; Smith, M. L.; Kacinko, S. L.; Schwilke, E. W.; Cone, E. J.; Moolchan, E. T.; Huestis, M. A. Excretion of Methamphetamine and Amphetamine in Human Sweat Following Controlled Oral Methamphetamine Administration. *Clin. Chem.* **2008**, *54* (1), 172–180. https://doi.org/10.1373/clinchem.2007.092304.

(128) Hartman, R. L.; Desrosiers, N. A.; Barnes, A. J.; Yun, K.; Scheidweiler, K. B.; Kolbrich-Spargo, E. A.; Gorelick, D. A.; Goodwin, R. S.; Huestis, M. A. 3,4-Methylenedioxymethamphetamine (MDMA) and Metabolites Disposition in Blood and Plasma Following Controlled Oral Administration. *Anal. Bioanal. Chem.* **2014**, *406* (2), 587–599. https://doi.org/10.1007/s00216-013-7468-y.

(129) Pichini, S.; Navarro, M.; Pacifici, R.; Zuccaro, P.; Ortuño, J.; Farré, M.; Roset, P. N.; Segura, J.; De la Torre, R. Usefulness of Sweat Testing for the Detection of MDMA after a Single-Dose Administration. *J. Anal. Toxicol.* **2003**, *27* (5), 294–303. https://doi.org/10.1093/jat/27.5.294.

(130) Pizarro, N.; Ortuno, J.; Farre, M.; Hernandez-Lopez, C.; Pujadas, M.; Llebaria, A.; Joglar, J.; Roset, P. N.; Mas, M.; Segura, J.; et al. Determination of MDMA and Its Metabolites in Blood and Urine by Gas Chromatography-Mass Spectrometry and Analysis of Enantiomers by Capillary Electrophoresis. *J. Anal. Toxicol.* **2002**, *26* (3), 157–165. https://doi.org/10.1093/jat/26.3.157.

(131) Lindgren, J. E.; Ohlsson, A.; Agurell, S.; Hollister, L.; Gillespie, H. Clinical Effects and Plasma Levels of Δ9-Tetrahydrocannabinol (Δ9-THC) in Heavy and Light Users of Cannabis. *Psychopharmacology (Berl).* **1981**, *74* (3), 208–212. https://doi.org/10.1007/BF00427095.

(132) Schwope, D. M.; Karschner, E. L.; Gorelick, D. A.; Huestis, M. A. Identification of Recent Cannabis Use: Whole-Blood and Plasma Free and Glucuronidated Cannabinoid

Pharmacokinetics Following Controlled Smoked Cannabis Administration. *Clin. Chem.* **2011**, *57* (10), 1406–1414. https://doi.org/10.1373/clinchem.2011.171777.

(133) Klimuntowski, M.; Alam, M. M.; Singh, G.; Howlader, M. M. R. Electrochemical Sensing of Cannabinoids in Biofluids: A Noninvasive Tool for Drug Detection. *ACS Sensors* **2020**, *5* (3), 620–636. https://doi.org/10.1021/acssensors.9b02390.

(134) Huestis, M. A.; Scheidweiler, K. B.; Saito, T.; Fortner, N.; Abraham, T.; Gustafson, R. A.; Smith, M. L. Excretion of Δ9-Tetrahydrocannabinol in Sweat. *Forensic Sci. Int.* **2008**, *174* (2–3), 173–177. https://doi.org/10.1016/j.forsciint.2007.04.002.

(135) Gambelunghe, C.; Fucci, N.; Aroni, K.; Bacci, M.; Marcelli, A.; Rossi, R. Cannabis Use Surveillance by Sweat Analysis. *Ther. Drug Monit.* **2016**, *38* (5), 634–639. https://doi.org/10.1097/FTD.0000000000000327.

(136) Bariya, M.; Nyein, H. Y. Y.; Javey, A. Wearable Sweat Sensors. *Nat. Electron.* **2018**, *1* (3), 160–171. https://doi.org/10.1038/s41928-018-0043-y.

(137) Simmers, P.; Li, S. K.; Kasting, G.; Heikenfeld, J. Prolonged and Localized Sweat Stimulation by Iontophoretic Delivery of the Slowly-Metabolized Cholinergic Agent Carbachol. *J. Dermatol. Sci.* **2017**, *89* (1), 40–51. https://doi.org/10.1016/j.jdermsci.2017.10.013.

(138) Sonner, Z.; Wilder, E.; Gaillard, T.; Kasting, G.; Heikenfeld, J. Integrated Sudomotor Axon Reflex Sweat Stimulation for Continuous Sweat Analyte Analysis with Individuals at Rest. *Lab Chip* **2017**, *17* (15), 2550–2560. https://doi.org/10.1039/c7lc00364a.

(139) Wang, Y.; Fridberg, D. J.; Leeman, R. F.; Cook, R. L.; Porges, E. C. Wrist-Worn Alcohol Biosensors: Strengths, Limitations, and Future Directions. *Alcohol* **2019**. https://doi.org/10.1016/j.alcohol.2018.08.013.

(140) Kilmer, B. The Future of DIRECT Surveillance: Drug and Alcohol Use Information from REmote and Continuous Testing. *J. Drug Policy Anal.* **2008**. https://doi.org/10.2202/1941-2851.1004.

(141) Kim, J.; de Araujo, W. R.; Samek, I. a.; Bandodkar, A. J.; Jia, W.; Brunetti, B.; Paixão, T. R. L. C.; Wang, J. Wearable Temporary Tattoo Sensor for Real-Time Trace Metal Monitoring in Human Sweat. *Electrochem. commun.* **2015**, *51*, 41–45. https://doi.org/10.1016/j.elecom.2014.11.024.

(142) De Giovanni, N.; Fucci, N. The Current Status of Sweat Testing For Drugs of Abuse: A

Review. *Curr. Med. Chem.* **2013**, *20* (4), 545–561. https://doi.org/10.2174/0929867311320040006.

(143) Brunelle, E.; Thibodeau, B.; Shoemaker, A.; Halámek, J. Step toward Roadside Sensing: Noninvasive Detection of a THC Metabolite from the Sweat Content of Fingerprints. *ACS Sensors* **2019**, *4* (12), 3318–3324. https://doi.org/10.1021/acssensors.9b02020.

(144) Uemura, N.; Nath, R. P.; Harkey, M. R.; Henderson, G. L.; Mendelson, J.; Jones, R. T. Cocaine Levels in Sweat Collection Patches Vary by Location of Patch Placement and Decline Over Time. *J. Anal. Toxicol.* **2004**, *28* (4), 253–259. https://doi.org/10.1093/jat/28.4.253.

(145) Koster, R. A.; Alffenaar, J.-W. C.; Greijdanus, B.; VanDerNagel, J. E. L.; Uges, D. R. A. Application of Sweat Patch Screening for 16 Drugs and Metabolites Using a Fast and Highly Selective LC-MS/MS Method. *Ther. Drug Monit.* **2014**, *36* (1), 35–45. https://doi.org/10.1097/FTD.0b013e3182a04feb.

(146) Kidwell, D. A.; Holland, J. C.; Athanaselis, S. Testing for Drugs of Abuse in Saliva and Sweat. *J. Chromatogr. B Biomed. Sci. Appl.* **1998**, *713* (1), 111–135. https://doi.org/https://doi.org/10.1016/S0378-4347(97)00572-0.

(147) Hauke, A.; Simmers, P.; Ojha, Y. R.; Cameron, B. D.; Ballweg, R.; Zhang, T.; Twine, N.; Brothers, M.; Gomez, E.; Heikenfeld, J. Complete Validation of a Continuous and Blood-Correlated Sweat Biosensing Device with Integrated Sweat Stimulation. *Lab Chip* **2018**, *18*, 3750–3759. https://doi.org/10.1039/C8LC01082J.

(148) Gamella, M.; Campuzano, S.; Manso, J.; Rivera, G. G. de; Lopez-Colino, F.; Reviejo, A. J.; Pingarron, J. M. A Novel Non-Invasive Electrochemical Biosensing Device for in Situ Determination of the Alcohol Content in Blood by Monitoring Ethanol in Sweat. *Anal. Chim. Acta* **2014**, *806*, 1–7. https://doi.org/10.1016/j.aca.2013.09.020.

(149) Tai, L.; Ahn, C. H.; Yin, H.; Nyein, Y. Nicotine Monitoring with Wearable Sweat Band. *ACS Sensors* **2020**, *5* (6), 1831–1837. https://doi.org/10.1021/acssensors.0c00791.

(150) Tai, L.-C.; Liaw, T. S.; Lin, Y.; Nyein, H. Y. Y.; Bariya, M.; Ji, W.; Hettick, M.; Zhao, C.; Zhao, J.; Hou, L.; et al. A Wearable Sweat Band for Noninvasive Levodopa Monitoring. *Nano Lett.* **2019**, *19* (9), 6346–6351. https://doi.org/10.1021/acs.nanolett.9b02478.

(151) Tai, L. C.; Gao, W.; Chao, M.; Bariya, M.; Ngo, Q. P.; Shahpar, Z.; Nyein, H. Y. Y.; Park, H.; Sun, J.; Jung, Y.; et al. Methylxanthine Drug Monitoring with Wearable Sweat

Sensors. *Adv. Mater.* **2018**, *30* (23), 1–8. https://doi.org/10.1002/adma.201707442.

(152) Mishra, R. K.; Goud, K. Y.; Li, Z.; Moonla, C.; Mohamed, M. A.; Tehrani, F.; Teymourian, H.; Wang, J. Continuous Opioid Monitoring along with Nerve Agents on a Wearable Microneedle Sensor Array. *J. Am. Chem. Soc.* **2020**, *142* (13), 5991–5995.

(153) Goud, K. Y.; Moonla, C.; Mishra, R. K.; Yu, C.; Narayan, R.; Litvan, I.; Wang, J. Wearable Electrochemical Microneedle Sensor for Continuous Monitoring of Levodopa: Toward Parkinson Management. *ACS Sensors* **2019**, *4* (8), 2196–2204. https://doi.org/10.1021/acssensors.9b01127.

(154) Kilic, T.; Brunner, V.; Audoly, L.; Carrara, S. Smart E-Patch for Drugs Monitoring in Schizophrenia. *2016 IEEE Int. Conf. Electron. Circuits Syst. ICECS 2016* **2017**, 57–60. https://doi.org/10.1109/ICECS.2016.7841131.

(155) Akturk, H. K.; Garg, S. Technological Advances Shaping Diabetes Care. *Curr. Opin. Endocrinol. Diabetes Obes.* **2019**, *26* (2), 84–89. https://doi.org/10.1097/MED.0000000000000467.

(156) Facchinetti, A. Continuous Glucose Monitoring Sensors: Past, Present and Future Algorithmic Challenges. *Sensors (Switzerland)* **2016**, *16* (12), 1–12. https://doi.org/10.3390/s16122093.

(157) Waltz, E. Sweet Sensation. *Nat. Biotechnol.* **2019**, *37*, 340–344. https://doi.org/10.1038/s41587-019-0086-2.

(158) Henry, S.; McAllister, D. V.; Allen, M. G.; Prausnitz, M. R. Microfabricated Microneedles: A Novel Approach to Transdermal Drug Delivery. *J. Pharm. Sci.* **1998**. https://doi.org/10.1021/js980042+.

(159) Tang, J.; Wang, J.; Huang, K.; Ye, Y.; Su, T.; Qiao, L.; Hensley, M. T.; Caranasos, T. G.; Zhang, J.; Gu, Z.; et al. Cardiac Cell–Integrated Microneedle Patch for Treating Myocardial Infarction. *Sci. Adv.* **2018**. https://doi.org/10.1126/sciadv.aat9365.

(160) Lopez-Ramirez, M. A.; Soto, F.; Wang, C.; Rueda, R.; Shukla, S.; Silva-Lopez, C.; Kupor, D.; McBride, D. A.; Pokorski, J. K.; Nourhani, A.; et al. Built-In Active Microneedle Patch with Enhanced Autonomous Drug Delivery. *Adv. Mater.* **2020**, *32* (1), 1905740. https://doi.org/10.1002/adma.201905740.

(161) Samant, P. P.; Prausnitz, M. R. Mechanisms of Sampling Interstitial Fluid from Skin Using a Microneedle Patch. *Proc. Natl. Acad. Sci.* **2018**, 201716772.

https://doi.org/10.1073/pnas.1716772115.

(162) Chang, H.; Zheng, M.; Yu, X.; Than, A.; Seeni, R. Z.; Kang, R.; Tian, J.; Khanh, D. P.; Liu, L.; Chen, P.; et al. A Swellable Microneedle Patch to Rapidly Extract Skin Interstitial Fluid for Timely Metabolic Analysis. *Adv. Mater.* **2017**, *29* (37), 1–8. https://doi.org/10.1002/adma.201702243.

(163) Tran, B. Q.; Miller, P. R.; Taylor, R. M.; Boyd, G.; Mach, P. M.; Rosenzweig, C. N.; Baca, J. T.; Polsky, R.; Glaros, T. Proteomic Characterization of Dermal Interstitial Fluid Extracted Using a Novel Microneedle-Assisted Technique. *J. Proteome Res.* **2018**, *17* (1), 479–485. https://doi.org/10.1021/acs.jproteome.7b00642.

(164) Caffarel-Salvador, E.; Brady, A. J.; Eltayib, E.; Meng, T.; Alonso-Vicente, A.; Gonzalez-Vazquez, P.; Torrisi, B. M.; Vicente-Perez, E. M.; Mooney, K.; Jones, D. S.; et al. Hydrogel-Forming Microneedle Arrays Allow Detection of Drugs and Glucose in Vivo: Potential for Use in Diagnosis and Therapeutic Drug Monitoring. *PLoS One* **2015**. https://doi.org/10.1371/journal.pone.0145644.

(165) Kolluru, C.; Williams, M.; Yeh, J. S.; Noel, R. K.; Knaack, J.; Prausnitz, M. R. Monitoring Drug Pharmacokinetics and Immunologic Biomarkers in Dermal Interstitial Fluid Using a Microneedle Patch. *Biomed. Microdevices* **2019**, *21* (1), 14. https://doi.org/10.1007/s10544-019-0363-3.

(166) Babity, S.; Roohnikan, M.; Brambilla, D. Advances in the Design of Transdermal Microneedles for Diagnostic and Monitoring Applications. *Small* **2018**, *14* (49), 1803186. https://doi.org/10.1002/smll.201803186.

(167) Microneedle-Based Glucose Monitoring: Biolinq. Available from: Https://Www.Biolinq.Me/.

(168) Madden, J.; O'Mahony, C.; Thompson, M.; O'Riordan, A.; Galvin, P. Biosensing in Dermal Interstitial Fluid Using Microneedle Based Electrochemical Devices. *Sens. Bio-Sensing Res.* **2020**, *29*, 100348. https://doi.org/10.1016/j.sbsr.2020.100348.

(169) Mohan, A. M. V.; Windmiller, J. R.; Mishra, R. K.; Wang, J. Continuous Minimally-Invasive Alcohol Monitoring Using Microneedle Sensor Arrays. *Biosens. Bioelectron.* **2017**, *91*, 574–579. https://doi.org/10.1016/j.bios.2017.01.016.

(170) Parrilla, M.; Cuartero, M.; Padrell, S.; Rajabi, M.; Roxhed, N.; Niklaus, F.; Crespo, G. A. Wearable All-Solid-State Potentiometric Microneedle Patch for Intradermal Potassium

Detection. *Anal. Chem.* **2019**, *91* (2), 1578−1586. https://doi.org/10.1021/acs.analchem.8b04877.

(171) Ventrelli, L.; Marsilio Strambini, L.; Barillaro, G. Microneedles for Transdermal Biosensing: Current Picture and Future Direction. *Adv. Healthc. Mater.* **2015**, *4* (17), 2606–2640. https://doi.org/10.1002/adhm.201500450.

(172) Teymourian, H.; Moonla, C.; Tehrani, F.; Vargas, E.; Aghavali, R.; Barfidokht, A.; Tangkuaram, T.; Mercier, P. P.; Dassau, E.; Wang, J. Microneedle-Based Detection of Ketone Bodies along with Glucose and Lactate: Toward Real-Time Continuous Interstitial Fluid Monitoring of Diabetic Ketosis and Ketoacidosis. *Anal. Chem.* **2020**, *92* (2), 2291–2300. https://doi.org/10.1021/acs.analchem.9b05109.

(173) Sharma, S.; Saeed, A.; Johnson, C.; Gadegaard, N.; Cass, A. E. Rapid, Low Cost Prototyping of Transdermal Devices for Personal Healthcare Monitoring. *Sens. Bio-Sensing Res.* **2017**, *13*, 104–108. https://doi.org/10.1016/j.sbsr.2016.10.004.

(174) Nunes, L. A. S.; Mussavira, S.; Bindhu, O. S. Clinical and Diagnostic Utility of Saliva as a Non-Invasive Diagnostic Fluid: A Systematic Review. *Biochem. Medica* **2015**, *25* (2), 177–192. https://doi.org/10.11613/BM.2015.018.

(175) First in-home oral HIV test http://www.oraquick.com/.

(176) First at-home saliva test for Coronavirus https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-diagnostic-test-using-home-collection-saliva.

(177) Kiang, T. K. L.; Ensom, M. H. H. A Qualitative Review on the Pharmacokinetics of Antibiotics in Saliva: Implications on Clinical Pharmacokinetic Monitoring in Humans. *Clin. Pharmacokinet.* **2016**, *55* (3), 313–358. https://doi.org/10.1007/s40262-015-0321-z.

(178) Pichini, S.; Papaseit, E.; Joya, X.; Vall, O.; Farré, M.; Garcia-Algar, O.; De Latorre, R. Pharmacokinetics and Therapeutic Drug Monitoring of Psychotropic Drugs in Pediatrics. *Ther. Drug Monit.* **2009**, *31* (3), 283–318. https://doi.org/10.1097/FTD.0b013e31819f3328.

(179) Suherman, A. L.; Rasche, B.; Godlewska, B.; Nicholas, P.; Herlihy, S.; Caiger, N.; Cowen, P. J.; Compton, R. G. Electrochemical Detection and Quantification of Lithium Ions in Authentic Human Saliva Using LiMn 2 O 4 -Modified Electrodes. *ACS Sensors* **2019**, *4* (9), 2497–2506. https://doi.org/10.1021/acssensors.9b01176.

(180) Patsalos, P. N.; Berry, D. J. Therapeutic Drug Monitoring of Antiepileptic Drugs by Use of Saliva. *Ther. Drug Monit.* **2013**, *35* (1), 4–29. https://doi.org/10.1097/FTD.0b013e31827c11e7.

(181) Goodwin, A.; Banks, C. E.; Compton, R. G. Tagging of Model Amphetamines with Sodium 1,2-Naphthoquinone-4-Sulfonate: Application to the Indirect Electrochemical Detection of Amphetamines in Oral (Saliva) Fluid. *Electroanalysis* **2006**, *18* (18), 1833–1837. https://doi.org/10.1002/elan.200603596.

(182) Stevenson, H.; Bacon, A.; Joseph, K. M.; Gwandaru, W. R. W.; Bhide, A.; Sankhala, D.; Dhamu, V. N.; Prasad, S. A Rapid Response Electrochemical Biosensor for Detecting Thc In Saliva. *Sci. Rep.* **2019**, *9* (1), 1–11. https://doi.org/10.1038/s41598-019-49185-y.

(183) Kim, J.; Imani, S.; de Araujo, W. R.; Warchall, J.; Valdés-Ramírez, G.; Paixão, T. R. L. C.; Mercier, P. P.; Wang, J. Wearable Salivary Uric Acid Mouthguard Biosensor with Integrated Wireless Electronics. *Biosens. Bioelectron.* **2015**, *74*, 1061–1068. https://doi.org/10.1016/j.bios.2015.07.039.

(184) Mannoor, M. S.; Tao, H.; Clayton, J. D.; Sengupta, A.; Kaplan, D. L.; Naik, R. R.; Verma, N.; Omenetto, F. G.; McAlpine, M. C. Graphene-Based Wireless Bacteria Detection on Tooth Enamel. *Nat. Commun.* **2012**, *3*, 763. https://doi.org/10.1007/s13398-014-0173-7.2.

(185) Tseng, P.; Napier, B.; Garbarini, L.; Kaplan, D. L.; Omenetto, F. G. Functional, RF-Trilayer Sensors for Tooth-Mounted, Wireless Monitoring of the Oral Cavity and Food Consumption. *Adv. Mater.* **2018**, *30* (18), 1703257. https://doi.org/10.1002/adma.201703257.

(186) Lee, Y.; Howe, C.; Mishra, S.; Lee, D. S.; Mahmood, M.; Piper, M.; Kim, Y.; Tieu, K.; Byun, H.-S.; Coffey, J. P.; et al. Wireless, Intraoral Hybrid Electronics for Real-Time Quantification of Sodium Intake toward Hypertension Management. *Proc. Natl. Acad. Sci.* **2018**, *115* (21), 5377–5382. https://doi.org/10.1073/pnas.1719573115.

(187) Arakawa, T.; Kuroki, Y.; Nitta, H.; Chouhan, P.; Toma, K.; Sawada, S. ichi; Takeuchi, S.; Sekita, T.; Akiyoshi, K.; Minakuchi, S.; et al. Mouthguard Biosensor with Telemetry System for Monitoring of Saliva Glucose: A Novel Cavitas Sensor. *Biosens. Bioelectron.* **2016**, *84*, 106–111. https://doi.org/10.1016/j.bios.2015.12.014.

(188) Ben Salem, C.; Slim, R.; Fathallah, N.; Hmouda, H. Drug-Induced Hyperuricaemia and Gout. *Rheumatology* **2016**, *56* (5), 679–688.

https://doi.org/10.1093/rheumatology/kew293.

(189) Falk, M.; Andoralov, V.; Silow, M.; Toscano, M. D.; Shleev, S. Miniature Biofuel Cell as a Potential Power Source for Glucose-Sensing Contact Lenses. *Anal. Chem.* **2013**, *85* (13), 6342–6348. https://doi.org/10.1021/ac4006793.

(190) Keum, D. H.; Kim, S.-K.; Koo, J.; Lee, G.-H.; Jeon, C.; Mok, J. W.; Mun, B. H.; Lee, K. J.; Kamrani, E.; Joo, C.-K.; et al. Wireless Smart Contact Lens for Diabetic Diagnosis and Therapy. *Sci. Adv.* **2020**. https://doi.org/10.1126/sciadv.aba3252.

(191) Li, J.; Liang, J. Y.; Laken, S. J.; Langer, R.; Traverso, G. Clinical Opportunities for Continuous Biosensing and Closed-Loop Therapies. *Trends in Chemistry*. 2020. https://doi.org/10.1016/j.trechm.2020.02.009.

(192) Nimri, R.; Audon, P.; Pinsker, J. E.; Dassau, E. Closing the Loop. *Diabetes Technol. Ther.* **2018**, *20* (S1), S41–S54. https://doi.org/10.1089/dia.2018.2504.

(193) Khodaei, M. J.; Candelino, N.; Mehrvarz, A.; Jalili, N. Physiological Closed-Loop Control (PCLC) Systems: Review of a Modern Frontier in Automation. *IEEE Access* **2020**. https://doi.org/10.1109/ACCESS.2020.2968440.

(194) Mage, P. L.; Ferguson, B. S.; Maliniak, D.; Ploense, K. L.; Kippin, T. E.; Soh, H. T. Closed-Loop Control of Circulating Drug Levels in Live Animals. *Nat. Biomed. Eng.* **2017**, *1* (70), 1–10. https://doi.org/10.1038/s41551-017-0070.

(195) Arroyo-Currás, N.; Ortega, G.; Copp, D. A.; Ploense, K. L.; Plaxco, Z. A.; Kippin, T. E.; Hespanha, J. P.; Plaxco, K. W. High-Precision Control of Plasma Drug Levels Using Feedback-Controlled Dosing. *ACS Pharmacol. Transl. Sci.* **2018**, *1* (2), 110–118. https://doi.org/10.1021/acsptsci.8b00033.

(196) Valdés-Ramírez, G.; Windmiller, J. R.; Claussen, J. C.; Martinez, A. G.; Kuralay, F.; Zhou, M.; Zhou, N.; Polsky, R.; Miller, P. R.; Narayan, R.; et al. Multiplexed and Switchable Release of Distinct Fluids from Microneedle Platforms via Conducting Polymer Nanoactuators for Potential Drug Delivery. *Sensors Actuators, B Chem.* **2012**, *161* (1), 1018–1024. https://doi.org/10.1016/j.snb.2011.11.085.

(197) Lee, H.; Choi, T. K.; Lee, Y. B.; Cho, H. R.; Ghaffari, R.; Wang, L.; Choi, H. J.; Chung, T. D.; Lu, N.; Hyeon, T.; et al. A Graphene-Based Electrochemical Device with Thermoresponsive Microneedles for Diabetes Monitoring and Therapy. *Nat. Nanotechnol.* **2016**, *11*, 566–572. https://doi.org/10.1038/nnano.2016.38.

(198) Than, A.; Liu, C.; Chang, H.; Duong, P. K.; Cheung, C. M. G.; Xu, C.; Wang, X.; Chen, P. Self-Implantable Double-Layered Micro-Drug-Reservoirs for Efficient and Controlled Ocular Drug Delivery. *Nat. Commun.* **2018**, *9* (4433), 1–12. https://doi.org/10.1038/s41467-018-06981-w.

(199) Thanvi, B. R.; Lo, T. C. N. Long Term Motor Complications of Levodopa: Clinical Features, Mechanisms, and Management Strategies. *Postgraduate Medical Journal*. 2004. https://doi.org/10.1136/pgmj.2003.013912.

(200) Pravika, M.; Jacob, J.; K, P. J. PID Controlled Fully Automated Portable Duodopa Pump for Parkinson's Disease Patients. *Biomed. Signal Process. Control* **2019**, *50*, 178–187. https://doi.org/10.1016/j.bspc.2019.01.025.

(201) Klonoff, D.; Han, J. The First Recall of a Diabetes Device Because of Cybersecurity Risks. *J. Diabetes Sci. Technol.* **2019**, *13* (5), 817–820. https://doi.org/10.1177/1932296819865655.

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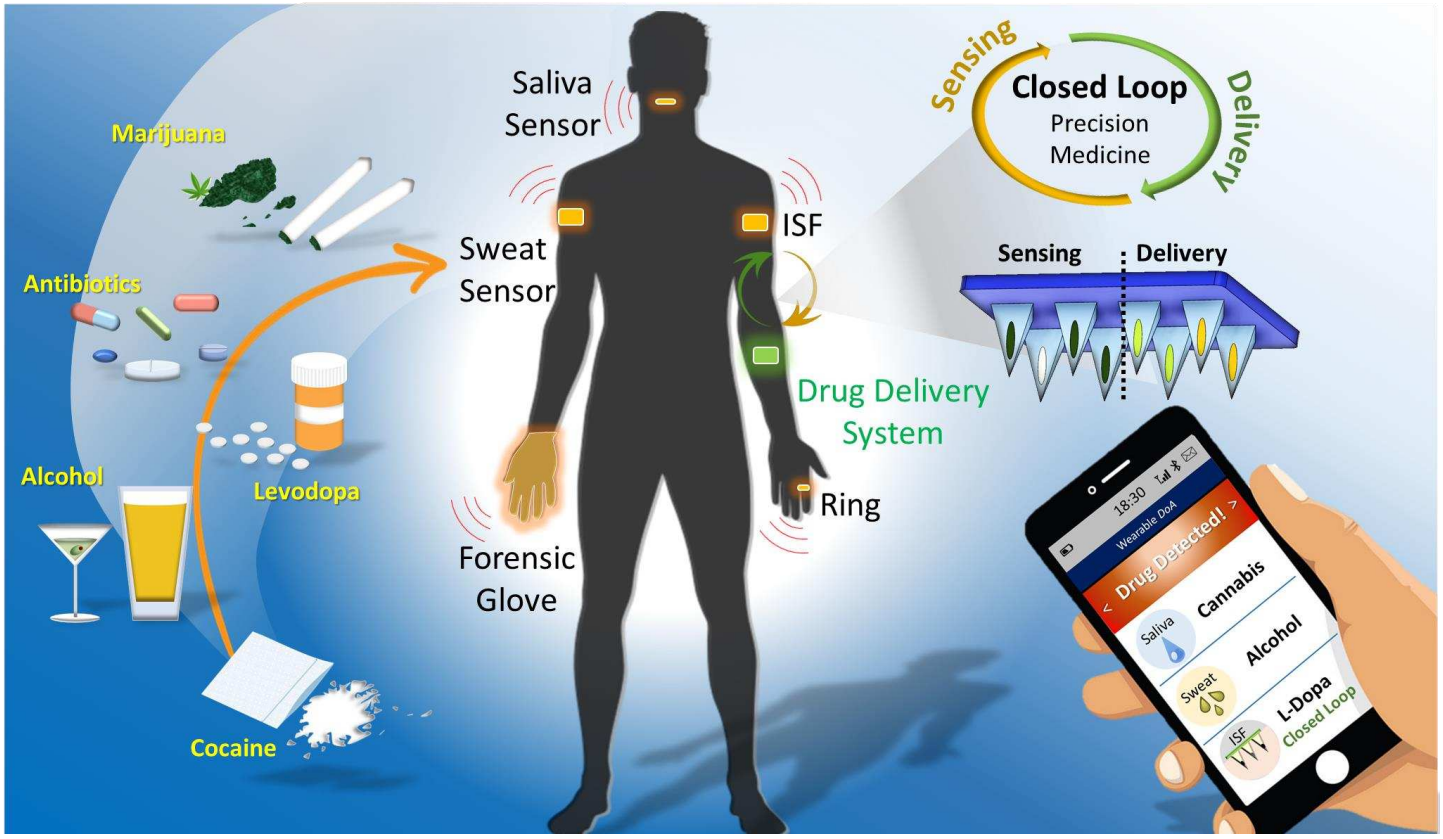
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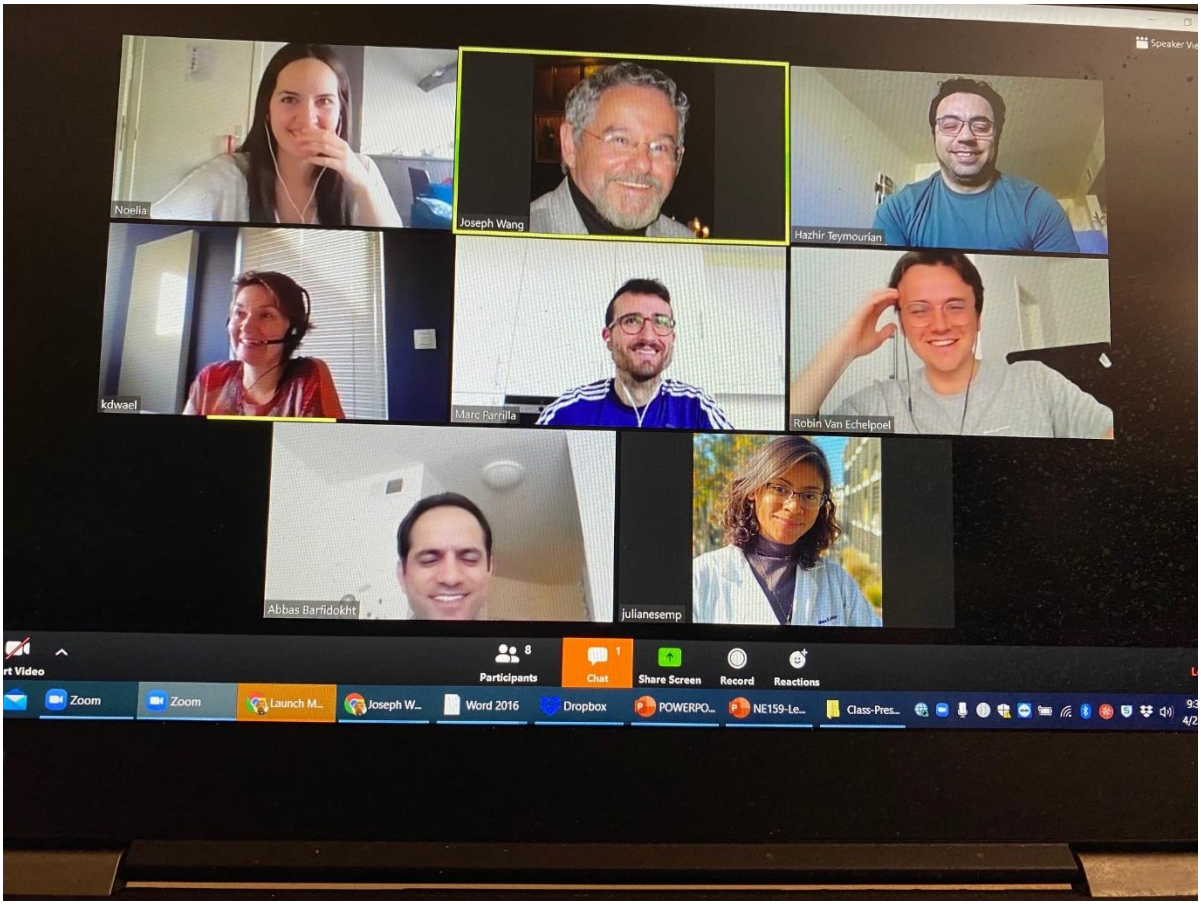
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