Wearable Monitoring of Drugs

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Precision medicine, particularly therapeutic drug monitoring (TDM), is essential for optimizing drug dosage and minimizing toxicity. However, current TDM methods have limitations, including the need for skilled operators, patient discomfort, and the inability to monitor dynamic drug level changes. Wearable sensors have emerged as a promising solution for drug monitoring. These sensors offer real-time and continuous measurement of drug concentrations in biofluids, enabling personalized medicine and reducing the risk of toxicity.

Keywords: wearable sensors ; therapeutic drug monitoring ; personalized medicine

1. Introduction

Throughout the ongoing battle against illnesses, humans have gradually accumulated substantial experience in drug usage, resulting in a constant enrichment of our pharmacological practice. The use of drugs has become deeply ingrained in our society, assuming a pivotal role in disease treatment and physical regulation [1][2][3][4]. However, due to the physiologically-based pharmacokinetics, it is imperative for each p-atient to determine the appropriate dosage based on factors such as absorption, distribution, metabolism, and elimination rates in order to achieve optimal therapeutic effects [5]. Therefore, the development of precision medicine holds immense significance in mitigating drug toxicity.

Therapeutic drug monitoring (TDM) serves as a valuable approach within precision medicine, effectively minimizing drug side effects arising from individual differences. TDM involves the modern analytical techniques guided by pharmacokinetic (PK) principles to quantitatively determine drug and metabolite concentrations in patients' biofluids post-treatment. TDM enables the design or adjustment of personalized drug delivery plans, thereby enhancing treatment efficacy, minimizing drug side effects, and facilitating personalized medicine [6][7]. To date, various techniques such as chromatography [8][9], immunoassay [10], nuclear magnetic resonance [11], isotope tracing [12], and capillary electrophoresis [13] have been employed to measure drug concentrations in biofluids for TDM purposes. TDM also aims to facilitate the development of precision drugs and personalized medicine with its high accuracy and low detection limits [14].

However, several limitations associated with TDM warrant attention. Firstly, TDM requires skilled operators to maintain complex instruments, and frequent blood sampling may cause discomfort for patients. Additionally, the specific storage requirements for biofluid samples could compromise the detecting accuracy by inducing drug degradation and transformation within the samples [15]. Furthermore, most TDM methods capture drug concentrations at a specific time, lacking the ability to monitor dynamic changes in drug levels continuously. Consequently, developing novel techniques for real-time in vivo monitoring of therapeutic drugs becomes imperative to overcome these limitations and enhance drug monitoring efficiency [16].

In recent years, the potential of wearable sensors for biomedical applications and health monitoring has drawn increasing attention [17]. These sensors have achieved significant advancements in miniaturization, multifunction, and algorithm, owing to the development of integrated devices and artificial intelligence. By enabling non-invasive or minimally invasive sample collection, wearable sensors possess the capability to monitor physiological signals, facilitate early disease diagnosis, and enable remote monitoring of various conditions. Furthermore, wearable sensors can play a crucial role in drug concentration monitoring within the blood and other biofluids, providing real-time signal transmission to assist patients in regulating drug dosage and minimizing the risk of drug toxicity. Additionally, these sensors can continuously monitor dynamic changes in drug levels over extended periods, supplying vital data necessary for optimal therapeutic effects. As a result, wearable multifunctional sensors are poised to become an essential component of healthcare systems, effectively catering to the personalized medicine requirements of diverse patients while reducing resource waste and associated healthcare costs.

2. Wearable Monitoring of Drugs

Therapeutic drug monitoring is an increasingly vital area with significant potential for enhancing patient outcomes. Nevertheless, several challenges, such as non-linear pharmacokinetics, low therapeutic indices, narrow safety ranges, and the potential for life-threatening side effects, have limited the successful implementation of wearable monitoring systems for drug monitoring. Conventional analytical methods for measuring in vivo drug concentrations require precise timing of blood sampling to accurately determine steady-state concentrations. **Table 1** summarizes therapeutic and toxic concentrations for a number of representative drugs. In contrast, wearable technology has the capacity to revolutionize drug therapy by enabling real-time monitoring of drug concentration changes, thereby enhancing detection accuracy.

Table 1. The concentration of drugs that require treatment monitoring in biofluids.

Type of Drugs	Compound	Martrix	Biofluid Level	Ref
Immunosuppressants	Tacrolimus	Serum	0.01–0.015 μg mL^{-1}	[18]
	Cyclosporin	Serum	80–1000 μg mL^{-1}	[19][20]
Antiepileptic	Carbamazepine	Serum	6000–8000 μg mL^{-1}	[21]
	Phenytoin sodium	Serum	10–20 μg mL^{-1}	[22][23]
	Phenobarbital	Serum	10–40 μg mL^{-1}	[24]
	Valproic acid	Serum	50–100 μg mL^{-1}	[25]
	Lamotrigine	Serum	2.5–15 μg mL^{-1}	[26]
	Levetiracetam	Serum	12–46 μg mL^{-1}	[26]
Antimicrobial drugs	Vancomycin	Serum	0.005–0.04 μg mL^{-1}	[27]
		Sweat	8.7–50.7 μg mL^{-1}	[28]
	Meropenem	Serum	8–32 μg mL^{-1}	[29]
	Linezolid	Serum	2–7 μg mL^{-1}	[30]
		ISF	0.101–1.2 μg mL^{-1}	[31]
	Tobramycin	Serum	4–6 μg mL^{-1}	[32]
	Voricnazole	Serum	0.5–5 μg mL^{-1}	[30]
Cardioactive drugs	Digoxin	Serum	0.001–0.0025 μg mL^{-1}	[33]
Antidepressants	Lithium	Serum	44.4–66.6 μg mL^{-1}	[34]
Analgesics drugs	Fentanyl	Serum	1–3 μg mL^{-1}	[35]
		Sweat	0.17–1.02 μg mL^{-1}	[36]
	Methadone	Serum	0.08–0.7 μg mL^{-1}	[37]
		Sweat	120–2160 ng $patch^{-1}$	[38]
Anti-asthmatic drugs	Theophylline	Serum	5–15 μg mL^{-1}	[39]
Antipsychotic drugs	Clozapine	Serum	0.35–0.5 μg mL^{-1}	[40]
	Risperidone	Serum	0.02–0.06 μg mL^{-1}	[40]
	Perphenazine	Plasma	0.0012–0.0024 μg mL^{-1}	[41]
	Fluphenazine	Plasma	0.0002–0.002 μg mL^{-1}	[41]
	Thiothixene	Plasma	0.002–0.015 μg mL^{-1}	[41]
	Olanzapine	Serum	0.002–0.004 μg mL^{-1}	[40]

2.1. Anti-Parkinson's Drugs

Parkinson's disease (PD) is a neurodegenerative disorder primarily affecting middle-aged and elderly individuals, with a prevalence second only to Alzheimer's disease [42]. PD patients have fewer nigrostriatal dopaminergic neurons in their brains, leading to motor symptoms, including resting tremor, bradykinesia, rigidity, postural instability, and impaired self-care [43][44][45]. The current gold standard for improving early disease symptoms is levodopa (L-Dopa), which serves as a dopamine precursor but lacks inherent pharmacological activity. After being catalyzed by dopamine decarboxylase, L-Dopa is converted to dopamine, a vital neurotransmitter that enhances nociceptor function and regulates motor neuron pathways [46]. Despite its effectiveness in early-stage PD treatment, L-Dopa's pharmacokinetics can be significantly influenced by factors such as dietary intake, age, gender, and prior dosing history [47].

L-Dopa overdose may cause depression by elevating malondialdehyde levels. Therefore, wearable sensors for continuous L-Dopa monitoring have potential clinical applications by enabling accurate identification of individual drug metabolism differences and dosage adjustments [48]. In wearable sensors, sweat-based detection of L-Dopa is a promising approach. Researchers have used high-performance liquid chromatography to simultaneously measure blood drug concentrations, which validates the accuracy of the sweat detection process. One study reported a correlation of 0.678 between sweat and blood L-Dopa concentrations [49]. Dopamine in sweat can be detected by electrochemical methods, including enzyme-based chronoamperometry methods or cyclic voltammetry based on inorganic materials.

Moon et al. developed a wearable enzyme-based electrochemical biosensor for the real-time detection of L-Dopa in sweat [50]. The sensor utilized a screen-printed carbon paste substrate and immobilized tyrosinase on the surface to create a specific working electrode. By collecting sweat with a hydrogel covering the finger, the electrode detected L-Dopa through oxidation by tyrosinase, generating an electrochemical signal. The sensors showed a minimum detection limit of 300 nM L-Dopa and exhibited similar pharmacokinetic profiles to blood samples. The wearable sensor also exhibited high selectivity for L-Dopa, with a signal response to C-Dopa that is only 5% of that of L-Dopa. This non-invasive approach holds potential for monitoring drug pharmacokinetics and can be extended to other important drugs.

The real-time detection of L-Dopa through wearable enzyme-based sensors has shown promising promising results. However, long-term enzyme stability has remained a significant concern for researchers [51][52]. To address this challenge, Xiao et al. reported a noninvasive and wearable enzyme-based electrochemical sensor for detecting L-Dopa in sweat based on metal-organic frameworks (MOFs) [53]. Zeolite imidazolate framework (ZIF-8) and tyrosinase were co-precipitated on the surface of graphene oxide (GO), resulting in ZIF-8/GO composites with a wide linear response range of 1 to 95 µM and a lower detection limit of 0.45 µM, indicating high sensitivity and stability.

A novel sensing paradigm has emerged in the pursuit of achieving accurate signal measurements of L-Dopa. Goud et al. reported a minimally invasive microneedle sensing platform for orthogonal electrochemical monitoring of L-Dopa [54]. This platform utilized two sensing modes, redox and enzyme-catalyzed, simultaneously on both unmodified and tyrosinase-modified carbon paste microneedle electrodes. These parallel and independent modes enabled non-enzymatic voltammetry and enzyme-catalyzed amperometric detection of L-Dopa, resulting in an impressive L-Dopa detection limit of approximately 0.5 µM.

In summary, wearable detection of levodopa primarily relies on the use of specific enzymes to enhance electrode functionality, thereby improving selectivity and sensitivity. However, the practical application of these methods is limited by the inherent instability of enzymes. As a result, current detection methods have primarily emphasized the sensitivity of individual measurements, while long-term sensor sensitivity remains an area that requires further exploration.

2.2. Antimicrobial Drugs

Antibiotics play a vital role in treating infectious diseases, such as sepsis, burns, organ transplants, and obesity, by interfering with the growth and development of bacteria. In the early stages of the disease, antibiotics exhibit promising therapeutic effects, and timely administration can save patients' lives. However, in the clinical use of antibiotics, the pharmacokinetics of individual patients greatly varied, making it difficult to assess the appropriate dose. Although several biosensing technologies are available for antibiotic detection in vitro, wearable detection has only been implemented for vancomycin, kanamycin, tobramycin, and phenoxymethylpenicillin, utilizing interstitial fluid and blood as test samples, where the drug concentration quickly equilibrates to reflect blood drug concentration levels.

Vancomycin is a crucial antibiotic used to treat infections caused by penicillin-resistant staphylococci and can serve as an alternative medication for patients with severe β-lactam antibiotic allergy [55]. However, it has a very narrow therapeutic window (5–40 µg mL^{-1}) and if inappropriately dosed for a period, it may result in adverse reactions such as ototoxicity,

nephrotoxicity, peripheral venous complications, and allergies [56]. Due to its non-linear pharmacokinetics, indirect measurement of vancomycin's peak and trough concentrations may have limited practicality. The current wearable detection technologies for vancomycin have primarily focused on electrochemical, aptamer-based (E-AB) sensors. In a recent study by Dauphin-Ducharme et al. [28], an E-AB sensor was placed in the vein of a rat through a catheter to enable real-time detection of vancomycin concentration in plasma. Aptamers were immobilized onto the working electrode surface, with methylene blue serving as the redox reporter. Upon binding of vancomycin to the aptamers, the distance between the methylene blue and the electrode increases, or the transfer of electrolyte is hindered, resulting in a decrease in the electrochemical signal. By analyzing the change in electron transfer rate, the concentration of vancomycin can be derived. The sensor exhibited a stable response signal 9 s after injection of 10 μM vancomycin, with a linear detection range of approximately 6–35 μM. These results successfully demonstrated the high signal accuracy of the E-AB sensor. Moreover, under controlled administration, the E-AB sensor maintained a therapeutic window concentration of ±2 μM for several hours (<6 h), significantly improving the therapeutic effect.

Tobramycin is a commonly used drug to treat cystic fibrosis (CF) caused by *Pseudomonas aeruginosa.* Its therapeutic window is relatively narrow, typically requiring concentrations of 4–6 μg mL^{-1} in the blood [32]. Unfortunately, a common side effect is hearing loss, which can fluctuate [57]. To address this challenge, researchers have developed an electrochemical aptamer-based detection technology using microneedles. 3D printing was utilized to fabricate poly(methyl methacrylate) microneedle arrays, which were coated with conductive layers and sensitive elements. Tobramycin aptamers were then bonded to the microneedle electrodes to enable the detection of tobramycin in interstitial fluids. The elimination half-life of tobramycin was 23 ± 2 min, consistent with the results measured in blood [58]. This approach offers a potential solution to monitor the tobramycin concentration in real-time, enabling more precise and effective treatments for CF patients.

Kanamycin, an aminoglycoside antibiotic isolated from *Streptomyces kanamyceticus*, is mainly known for interfering with ribosomal RNA and the inhibiting of bacterial protein synthesis. It also destroys the integrity of bacterial cell membranes and has been proven effective against infections caused by Gram-negative bacteria. However, the effective concentration range of kanamycin is narrow, ranging from 15–30 μg mL^{-1}. As kanamycin cannot be metabolized in the body and is mainly excreted through glomerular filtration, overdose can lead to severe renal toxicity, neuromuscular blockade, and allergic reactions. Unfortunately, there is no specific antagonist to treat kanamycin overdose, and the only way to remove it from the body is through large amounts of water supplementation, followed by hemodialysis or peritoneal dialysis. To address this issue, wearable detection methods of kanamycin have been developed, including electrochemical aptamer detection and photoacoustic imaging. Chien et al. fabricated a chronoamperometry sensor implantable in a vein to directly measure changes in electron transfer kinetics at the far end of the aptamer [56]. During the measurement process, a sample-and-hold circuit was employed to decrease the device power consumption from 5.2 mW to 0.22 mW and improve the molecular detection limitation from 57 to 12.3 μM. Kaefer et al. developed an optical imaging method to detect kanamycin concentrations in real time [59]. Gold nanoparticles were embedded into macro-porous hydrogel scaffolds and exhibited excellent biocompatibility. The hydrogels facilitated the growth of cells and blood vessels within their structure, overcoming the obstructing physical exchange between the sensor and adjacent tissues. By leveraging the plasmon effect, the gold nanoparticles absorbed and scattered near-infrared light of specific wavelengths and utilized the plasmon effect to detect a variety of drug molecules. Specifically, the concentration of kanamycin was determined by inducing a change in the refractive index of the gold nanoparticles, resulting in a shift in the plasma absorption wavelength. This implantable sensor demonstrated long-term stability and enabled continuous monitoring of the pharmacokinetic process of kanamycin in vivo for several weeks.

Phenoxymethylpenicillin is a semi-synthetic penicillin with a similar antimicrobial spectrum to penicillin that is effective against Gram-positive bacteria. Recently, microneedle electrochemical sensors based on β-lactamases have been developed for the detection of phenoxymethylpenicillin [60]. The polycarbonate microneedle surface was plated with gold to enhance its conductivity, followed by iridium oxide coating as a pH-sensitive layer, and a hydrogel layer containing β-lactamase was applied to the microneedle array. When the sensor was inserted into the skin, phenoxymethylpenicillin in interstitial fluid diffused through the hydrogel and was hydrolyzed by β-lactamase to penicillin thiazoles and protons. This reaction caused a decrease in the local pH of the sensor, which disrupted the oxidation equilibrium of iridium oxide and induced a change in the current.

The importance of wearable detection of antibiotics in preserving human health cannot be overstated, particularly in light of the widespread use of antibiotics to treat infectious diseases and the growing prevalence of antibiotic-resistant bacteria [61]. While combination therapy involving multiple antibiotics can enhance therapeutic efficacy, it also carries the inherent risk of adverse reactions, potentially resulting in severe consequences. Consequently, the advancement of non-invasive

sensing and wearable detection techniques holds great promise for optimizing drug dosages and mitigating the emergence of drug resistance.

2.3. Analgesic Drugs

Acetaminophen (APAP) is an analgesic and antipyretic drug prone to overdose during acute fever, resulting in hepatic centrilobular necrosis [62]. Upon entry into the body, APAP is metabolized by CYP-dependent cytochrome P450 to produce the highly cytotoxic n-acetyl-p-benzoquinone imine (NAPQI). NAPQI initially binds with glutathione in the liver, and after depletion of glutathione, it binds to the mitochondrial proteins, interfering with their normal function and causing irreversible liver damage [63][64]. Due to the absence of effective antidotes, preventing APAP overdose is the most efficient approach. Given APAP's relatively short half-life, timely detection of blood drug peaks by blood sampling may be difficult, and APAP concentrations exceeding 1.1 μM may lead to hepatotoxicity [65]. Wearable APAP sensors have been developed, which employ differential pulse voltammetry (DPV) to measure the concentration of APAP in sweat and saliva, capitalizing on its electrochemical activity.

The presence of electrochemically active interferents in sweat can lead to the overlapping of signal peaks between target molecules, resulting in distorted signals that reduce the sensitivity of APAP detection. To address this challenge and effectively separate the redox peaks of interferents from APAP, Lin et al. used Nafion-coated and hydrogen-terminated boron-doped diamond electrodes (Nafion/H-BDDE) to construct the sensing interface [66]. Voltammetry was used to detect the redox peak of APAP, and the concentration change of the target molecule could be reflected by analyzing the peak strength. The Nafion/H-BDDE sensing interface utilized surface engineering strategies to reduce the adsorption of other electrochemical active molecules, effectively preventing the signal peaks of target molecules from being buried and generating distorted signals. The modified sensing interface could separate the target molecule and the redox peak of the interfering substance, accurately measured the electron transfer reaction rate constant and the concentration of APAP in sweat and saliva, and its detection limit can reach 1 μM. There was a similar dynamic distribution in the two matrices, indicating a similar distribution mechanism of analytes from the blood. The sensing mechanisms could also inspire researchers to monitor electrochemical active molecules and broaden the scope of drug monitoring.

A wearable sensor integrated onto plastic gloves has been developed for the detection of APAP in sweat and saliva. This sensor utilizes screen-printed carbonaceous nanomaterials to facilitate the electrooxidation of APAP [67]. Notably, the wearable glove sensor exhibits excellent stretching and bending capabilities, making it suitable for practical applications. The APAP detection limit reached 2.47×10^{-7} M, which falls within the clinically relevant concentration range for therapeutic drugs. Furthermore, the glove sensor mitigates the risk of infection associated with prolonged wearing and is particularly well-suited for individuals with fragile and sensitive skin [65]. By simply sliding the glove sensor across the skin surface, real-time monitoring of drug molecule concentrations in biofluids can be achieved, minimizing the potential for sample contamination and molecule degradation [68].

Fentanyl, a synthetic opioid used for anesthesia and analgesia, possesses pharmacological effects similar to morphine [69][70]. However, due to its narrow safe concentration range, it requires careful monitoring during its administration. The safe concentration range for analgesia is 1–3 mg L^{-1}, and concentrations above 5 mg L^{-1} can easily lead to hypoxia, respiratory failure, and death [35][71][72]. Although fentanyl has a shorter onset time compared to other analgesic drugs, its lipophilicity increases the risk of exceeding the safe concentration range, leading to serious toxic reactions [73]. Mishra et al. developed a wearable microneedle electrochemical sensor that analyzes the intensity of redox peaks to detect fentanyl concentration [74]. Similar work was done by Joshi et al., who used 3D printed E-Shell 200 materials to fabricate a hollow microneedle platform for fentanyl detection [75]. The platform responded linearly with a dynamic detection range between 6.4 and 51.2 μg L^{-1} and an LOD value of 9.2 μg L^{-1}.

The development of wearable sensors utilizing body fluids as detection samples has successfully generated pharmacokinetic curves for analgesic drugs in various bodily fluids, showcasing their real-time and dependable quantitative capabilities. This holds great promise for future medical monitoring applications, enabling timely intervention and prevention of adverse events such as liver failure, respiratory failure, and even fatal outcomes resulting from drug overdose.

2.4. Psychoactive Drugs

Abuse of psychoactive drugs has emerged as a major global concern because it poses a serious threat to public health, social stability, and economic growth [76][77][78]. Psychoactive drugs exert their effects by binding to specific receptors in the central nervous system, resulting in euphoria and excitement [79]. Therefore, timely monitoring of the blood concentration of psychoactive drugs is necessary to ensure the safety and effectiveness of treatment [80]. Existing testing

technologies require collecting samples and subsequent in vitro testing, which is relatively cumbersome and time-consuming [81]. Recently, wearable sensors that use sweat as a sample have been developed to detect psychoactive drugs. These sensors employ electrochemical or surface-enhanced Raman spectroscopy sensing technologies to achieve continuous and quantitative monitoring of different drugs based on their unique chemical signatures.

Caffeine, the most widely consumed psychoactive substance in daily life, is considered relatively safe in daily intake. However, the chronic overdose of caffeine can lead to several health problems, including rhabdomyolysis and chronic kidney failure [82]. Toxicity can occur at caffeine concentrations exceeding 15 mg L^{-1} in the blood [83]. Therefore, researchers have studied wearable detection of caffeine. Researchers have thus explored the potential of wearable devices for monitoring caffeine levels. Tai et al. developed a flexible vinyl terephthalate substrate with a carbon nanotube-modified working electrode to detect caffeine levels in sweat [84]. Caffeine can be oxidized on a working electrode with a sensitivity of about 110 nA mm^{-1} at 1.4 V potential. During the measurement process, the authors observed that the peak concentration of caffeine appeared 60 min after oral intake, which is consistent with the previous literature reporting on caffeine metabolism [85][86][87][88].

Synthetic cathinone is a class of psychoactive substances that are obtained by modifying natural cathinone and includes about 30 different compounds. These drugs primarily promote sympathetic nerve stimulation and are commonly used for recreational purposes, leading to restlessness, aggressive behavior, and violent tendencies [89][90]. Zhang et al. reported on an E-AB sensor with two adapters (Apt1 and Apt2) capable of accurately identifying six different types of synthetic cathinone in sweat. The researchers prepared three working electrodes coated with Apt1, Apt2, and a mixture of both to verify the ability of each to detect multiple psychoactive drugs. Mixed aptamers carried more negative charges, resulting in diverse folded structures with higher sensitivity, recognition ability, and anti-interference ability. The two adapters showed high specificity and low cross-target reactivity, indicating their potential for the accurate detection of synthetic cathinone in sweat [91].

Methamphetamine is a potent central nervous system stimulant and is the primary component of methamphetamine. The abuse of methamphetamine is widespread, and doses exceeding 50 mg can cause neurotoxicity, acute and chronic cardiovascular complications [92][93][94]. In order to monitor and combat drug abuse, wearable sensors have been developed using 2-Fluoromethamphetamine (2-FMA) as a substitute for methamphetamine. Koh et al. utilized surface-enhanced Raman spectroscopy (SERS) to detect 2-FMA in sweat [95]. To improve detection accuracy, silk fibroin film (SFF) was employed to prepare sweat absorption pads, which not only possessed blocking properties but also facilitated the long-term retention of drug molecules in the patch. The incorporation of silver nanowires (AgNWs) into the silk fibroin film (SFF) further enhanced the intensity of the Raman signals. During the detection process, a portable Raman spectrometer was used to irradiate the patch, generating SERS signals that were subsequently processed and converted into the corresponding drug concentration. In addition, the researchers verified the drug concentrations using 2-FMA as a fluorescent probe, which yielded consistent results with the SERS patch.

The diverse range of psychoactive drugs and the concurrent use of multiple substances by users to pursue excitement presents significant challenges for wearable drug detection. It necessitates the development of highly selective sensing technologies capable of detecting multiple drugs simultaneously. However, the majority of existing sensing technologies fall short in meeting these detection requirements. Therefore, it is crucial to optimize existing sensing technologies or develop new ones to broaden the scope of drug monitoring, especially for the monitoring of psychoactive ionic drugs, which will greatly contribute to health and law enforcement monitoring work.

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