INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print) 2222-5234 (Online)
http://www.innspub.net
Vol. 24, No. 4, p. 149-159, 2024

REVIEW PAPER OPEN ACCESS

Bioelectronic systems in controlled drug delivery systems- A novel dosage form

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Key words: Biological systems, Efficiency, Bioelectronic systems, Drug regimens

http://dx.doi.org/10.12692/ijb/24.4.149-159 Article published on April 15, 2024

Abstract

Electronic drug delivery systems (EDDS) are an interesting advancement in drug delivery technology. They are portable, interactive, wirelessly networked, and enable patient-administered medication, which lowers overall healthcare costs. Controlled DDS maintains drug plasma levels constantly by releasing the definite dose of the drug at each time point for a predetermined duration. This helps in reducing the dose and dosing frequency and improves patient compliance. Lesser drug exposure to the biological environment reduces drug toxicity and adverse effects. Among controlled release. Transdermal delivery mode (referred to as patches) is more preferably used among them because of great patient compliance. Bioelectronic systems play a crucial role in electronically controlled drug delivery systems by integrating electronic components with biological systems to deliver drugs with precision and efficiency. Their efficiency is further increased when integrated into remotely operated systems. One of the main motivations for developing EDDS was to increase patient adherence to recommended drug regimens. Moreover, EDDS have demonstrated the ability to administer drugs to specific body locations on demand. This review concentrates on electronic medication delivery systems, despite the fact that there are many different types of drug delivery devices on the market. Along with their mechanism of actions are also discussed.

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Introduction

Controlled drug delivery system

This is the drug delivery system in which a constant level of a drug is maintained in blood and tissue for an extended period. Controlled DDS maintains drug plasma levels constantly by releasing the definite dose of the drug at each time point for a predetermined duration (Tekade *et al.*, 2018). This helps in reducing the dose and dosing frequency and improves patient compliance. Lesser drug exposure to the biological environment reduces drug toxicity and adverse effects.

Evolution of the controlled release dosage forms

First-generation: This generation of dosage forms mainly involves four types of mechanisms for drug release, which include the oral and transdermal formulations. The mechanisms involved are dissolution, osmosis, diffusion, and ion exchange. Diffusion and dissolution-controlled systems are the most widely used mechanisms of drug delivery. The success of the first generation of drugs is mainly the development of the oral and transdermal routes (Park *et al.,* 2014).

Second-generation: These are not widely used. Electrically delivery systems were developed for introducing insulin. Due to its lesser bioavailability, it is administered many times higher per dose than is required, which results in toxicity. In the last decade of the second generation, nanoparticles that target genes and tumors were studied.

The third generation: involves the delivery of poorly water-soluble drugs, long-term and non-invasive technology for delivering proteins/nucleic acids/peptides, and drug delivery to the targeted site using nanoparticles (Yun *et al.,* 2015).

Formulations of controlled-release medication

Oral, intravenous, and transdermal patches are easily developed. Among controlled release, transdermal delivery mode (referred to as patches) is more preferably used among them because of great patient compliance.

Advantages

1. Include decreased frequency of drug administered
2. An improvement in patient compliance.
3. Reducing the amount of blood drug fluctuation.
4. Lowering medication use in comparison to traditional therapy.
5. Reduced medication buildup during long-term therapy.
6. Reduction in the drug's toxicity, either systemic or local.

Disadvantages

1. Include higher chances of dose dumping.
2. Dose adjustment is more difficult in controlled-release drug delivery system.
3. Have higher chances of dosage form breaking; resulting hence controlled release is lost (Ummadi *et al..,* 2013).

Bioelectronic systems in EDDS

Bioelectronic systems play a crucial role in electronically controlled drug delivery systems by integrating electronic components with biological systems to deliver drugs with precision and efficiency. These systems typically involve sensors to monitor physiological parameters, microcontrollers to process data and control drug release, and actuators to deliver the drug. Some of the bioelectronic systems present are given below (Fig. 1).

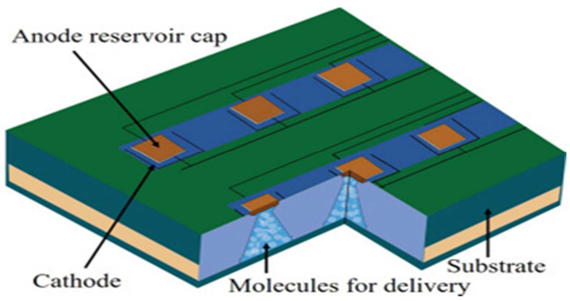

Fig. 1. Microchip devices

An implanted medication delivery systems called a microchip holds and deliver medication from tiny reservoirs (Santini *et al.,* 2000). The electronic gadget is composed of hundreds of micro-reservoirs, each of which has a metal membrane covering on top. A microprocessor or input device drives the final circuitry in each micro reservoir. The medication and device combination were determined to be safe, bio compatible, and free of adverse immunological reactions. The amount of drug to be released is scheduled by a pre-programmed dosage system. This system is mostly used to treat breast cancer, multiple sclerosis, osteoporosis, and Alzheimer's (Farra*et al.,* 2012).

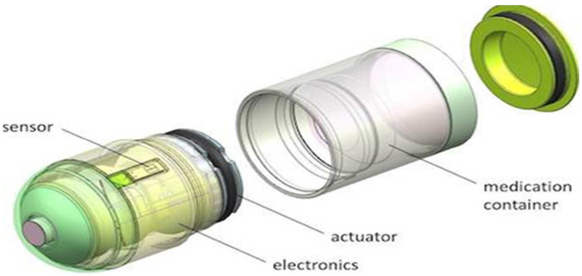

Fig. 2. The electronic capsule

Fig. 3. Electronic pumps

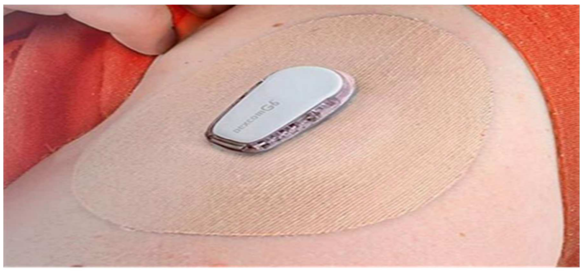

Fig. 4. Electronic transdermal patches

The electronic capsule is a type of oral electronic drug delivery system and is also used as a patient monitoring capsule that is used to deliver one drug or a combination of many types of drugs (Fig. 2). The capsule is made of a microprocessor, medication reservoir, fluid pump, wireless transmitter, pH and temperature sensors, and battery (Van Der Schaar *et al.,* 2013).

One of its salient features is that it is capable to deliver drug to a specific portion of the GI tract by measuring the pH of the GI tract. This capsule can transmit data via a wireless transmitter to an external control device that the patient wears. The electronic capsules allow caretakers to track the capsule's path through the GI tract and administer appropriate medication release (Grimm *et al.,* 2013).

Electronic pumps are mostly used in cases of diabetes management (Fig. 3). The pump, reservoir, and infusion set make up the insulin pump system. The insulin reservoir and a cannula deliver the insulin to the patient through the subcutaneous route and are connected by tubing that helps in infusion. An adhesive component holds the cannula in place at the injection site. Administering the needle can be done in the upper arm, upper thigh, or abdomen. Every two to three days, the insulin reservoir and infusion set need to be replaced. The reservoir can retain insulin for up to three days. Insulin dosages are tailored to each patient's specific requirements, and the insulin pump provides both on-demand bolus doses at the time of meal and continuously provides pre-set basal insulin throughout the day (Peyrot *et al.,* 2009).

In most cases, sensors, memory, electrical circuits, and drug delivery components are included in the construction of an electronic transdermal patch (Fig. 4). The data gathered is used to decide when to provide the medicine, which is kept inside the patch. This electronic patch is a revolutionary nanoparticle-based patch system with minimal electrical consumption and programmable thermal actuators for regulated transdermal medication administration. It is made up of data storage modules, diagnostic instruments, and therapeutic actuating components. These sensors are specialized to identify any movement in cases such as tremors in Parkinson's disease or epilepsy, and then apply the right amount of medication via the skin (Lin *et al.,* 2016).

The majority of technologies employ iontophoresis, which is the process of delivering charged molecules through the skin by applying electromotive force and low-level electric current. The two main processes by which medication ions are transported through the skin and into the systemic circulation during iontophoresis are electromigration and electroosmosis. The maximum acceptable value for current for in vivo applications is 0.5 mA/cm^2. Hydrogel formulations have become appealing due to their ability to offer an electroconductive basis along with an additional advantage of being easily applied to conform to the body's contours. It has been observed that drug that is released from a hydrogel matrix by passive diffusion obeys the Higuchi equation, according to which the total quantity of drug released is proportional to the square root of time. On the other hand, it seems from drug release data that the rate of drug release for electronic transdermal patches is constant when the electricity is applied and decreases when electricity is cut off. These electronic patches have the ability to release peptides, proteins, and many medications simultaneously.

Another extensively studied method for electrically assisted trans dermal medication delivery is electroporation. In the process of electroporation, the lipid bi layers of the stratum corneum in the skin are temporarily disturbed by the applying high voltage pulses, which results in the development of transitory hydrophilic holes. Thus, the medication passes more easily through the skin owing to these pores.

Sonophoresis is a method employed in the product "SonoPrepT". The FDA authorized this SonoPrepT in 2004 for the topical administration of lidocaine to produce a local anesthetic effect (Mitragotri *et al.,* 2004).

Microfluidic devices

These use very precise fluid manipulation and medication delivery through the use of microscale chambers and channels. Drug distribution can be monitored and controlled in real-time by integrating them with sensors and actuators.Typically, a controlled-release microreservoir device comprises drug-filled reservoirs, release mechanisms, and membranes made of biodegradable polymers or metallic layers. The pharmaceuticals are sealed in the reservoirs, keeping them away from the outside world. The reservoir's polymer or metallic layer covering is broken down or opened upon command, revealing its contents to the body. Single and multiple reservoir systems are included in the architecture of microreservoir-based devices. Different methods, such as temperature, pH, magnetic fields, and electric fields, can trigger the covering (Gao *et al.,* 2013).

Various micro-electro-mechanical systems (MEMS) used in electrically controlled drug delivery systems

These are technological devices that can be defined as miniaturized mechanical and electro-mechanical elements creating miniature integrated systems or devices. Their structure may differ from simple units to complex compounds with moving parts under the control of combined microelectronics. MEMS shows biocompatibility and carefully release drugs into the body from micro-chambers hosted in the device, eliminating the need for injections or needles. They are highly used to administer antibiotics, anti-inflammatories, analgesics, or even hormones, as in the case of archetypical insulin. They are classified as follows:

A. Implants
- i. Single reservoir-based
  - Mechanical micropumps
    1. Magnetic based micropumps
    2. Piezoelectric micropumps
    3. Electrostatic micropumps
    4. Phase change-based micropumps
  - Non- mechanical micropumps
    1. Electro micropumps
- ii Multiteservoir based micropumps
  1. Electro thermal
  2. NIR irradiation

B. Transdermal Drug delivery
- i. Needle- based transdermal drug delivery
  1. Silicon/carbon microneedles-based devices
  2. Polymeric microneedles-based devices
- ii. Needle free injectors for drug delivery (Nisar *et al.,* 2008).

Implantable micro electro mechanical system for electronically controlled drug delivery devices

Implants are highly used microsystems in electronically controlled drug delivery systems.

Implantable devices are characterized by containing reservoirs loaded with drugs to be released, which are the most critical parts of them. Reservoir material constitution must not only be biocompatible on the outside but also inert on the inside. Thus, polydimethylsiloxane (PDMS), polyacrylamide (PAA), medical-grade silicone rubber, and Pyrex are highly used in the preparation of the reservoir. To assure the exact amount of drug is released, MEMS drug delivery devices are either single or multiple reservoirs where drugs are loaded (Villarruel Mendoza *et al.,* 2020).

Single reservoir-based devices

In this device total drug is loaded single reservoir and exact dose is released by pumps using different actuation mechanisms to achieve controlled release of the drug by using micropump-based devices. They generate fluid movement to show controlled release. Small and compact pumps are incorporated into delivery devices, and precise control of the dosage to be released into the body is maintained. Micropumps are usually classified into mechanical (displacement) and non-mechanical (dynamic).

Mechanical micropumps

Mechanical micropumps use the movement of components such as oscillating diaphragms to pump fluid by applying pressure. These mechanical micropumps include a flexible membrane or diaphragm, an actuator, a pumping chamber, an inlet, and an outlet. Magnetic, piezoelectric, electric, and material phase change are among the physical driving forces used in mechanical micro pumps (Villarruel Mendoza *et al.,* 2020; Mohith *et al.,* 2019).

Magnetic-based micropumps: Since most drug delivery systems rely on integrated batteries to function, the electronics and battery size constrain the total size of the device, preventing it from becoming any smaller. Magnetic micropumps rely on the manipulation of an external magnetic field to act as essential parts of electronically controlled drug delivery systems.

Mechanism of working

These devices having a single reservoirmembrane or diaphragm that reacts to an applied magnetic field and a chamber that houses the drug reservoir. The diaphragm or membrane of the pump deforms in response to interaction between the field and a magnetic component, such as a magnetized membrane or fluid particles, changing the pumping chamber's volume and producing fluid flow. Medication dosage can be precisely and programmablyadjusted (Pirmoradi *et al.,* 2011).

Piezoelectric micropump: It is an electrically controlled active device that can administer medications against blood pressures ranging from 8mmHg to 12mmHg in veins and higher than 120mmHg in arteries.

Working mechanism

It contains a piezoelectric disk attached to a diaphragm, a pumping chamber and valves. The piezoelectric micropump is activated by applying large amount of force on piezoelectric materials. Piezoelectric actuation involves the strain induced by an applied electric field on the piezoelectric crystal; displacement of diaphragm would increase with either the increase of driving voltage or decrement of piezoelectric material thickness (Joshitha *et al.,* 2017).

Electrostatic micropumps: Due to their ability to manipulate electric fields, electrostatic micropumps are essential components of electronically controlled medication delivery systems. Electrode pairs are usually positioned along the length of microchannels in these tiny devices.

Working mechanism

Generally, an electroosmotic flow is produced when a voltage is applied across these electrodes, which creates an electric field that causes ions in the surrounding fluid to move. To further aid in fluid flow, certain designs also use electrodes that have the ability to attract or repel charged particles in the fluid.

The rate and amount of medication delivery can be accurately controlled by adjusting the applied voltage, which enables customized dosage schedules and targeted administration (Nisar *et al.,* 2008; Cabuz *et al.,* 2001).

Electroactive polymer-composite micropumps: Electroactive polymer-composite micropumps are apparatuses that produce fluid motion or flow by integrating electroactive polymers (EAPs) into composite constructions.

Working mechanism

These micropumps can work by subjecting the EAP material to an electrical current, which will cause it to distort and encourage fluid circulation inside the device. Depending on the exact design and configuration of the micro pump, this deformation can lead to a variety of pumping methods, including bending, twisting, or expanding.

Use

These devices find use in medication delivery, lab-on-a-chip devices, microfluidic systems, and other sectors that demand accurate micro scale fluid manipulation (Xu *et al..,* 2005).

Phase-change-based micro pumps: These micropumps create pressure and push the medication through micro channels by taking advantage of the phase change phenomena, which usually involves the vaporization and condensation of fluid.

Working mechanism:

The mechanism uses electrical components like resistive heaters to heat the working fluid, which is typically liquid water, over its boiling point. When the liquid reaches the boiling point, it vaporizes quickly and causes a pressure spike inside the microchannel. The medication payload is then propelled towards the delivery location by this pressure. The cycle is finished when the vapor cools down and condenses, returning it to its liquid condition. Accurate medication delivery is made possible by the precise regulation of the dosage and pumping rate through electrical input modulation (Sim *et al.,* 2003).

Non-mechanical micropumps

In this type of micropump, there are no moving parts of any type in the non-mechanical micropump's functioning. To provide the necessary kinetic momentum for fluid movement in microfluidic components, certain methods must be incorporated to transform non-mechanical energy into kinetic energy. Non-mechanical micropumps may be classified into a number of distinct types, including evaporation type, magneto-hydrodynamic, electro-chemical, electrowetting, and electroosmotic (Mebert *et al.,* 2017).

Electro-chemical micropump: It is an aqueous electrolyte solution-based reversible electrochemical process.

Working mechanism: N/A

Electro-chemical micropumps permit gas bubble expansion and reduction through electrolysis, and are the basis for the electrochemical micropump's basic operating principle. The production and spread of gas bubbles facilitate the flow of liquid through the tubes in micro- or milliliter-sized volumes (Suzuki *et al.,* 2002).

Electro-wetting micropump: Electro-wetting micropump utilizes a microfluidic phenomenon in which a voltage potential is used to modulate the surface energy between a conductive liquid and an electrode covered in dielectric. It is a reversible process; the system reverts to its initial state when the potential is withdrawn. The electro-wetting approach's capacity to manipulate discrete liquid volumes and produce finite-volume drops inside of microdevices is one of its strongest features (Yun *et al.,* 2002).

Multi-reservoir-based devices

Multi-reservoir-based devices are essential parts of electronically controlled drug delivery systems that allow for the exact and programmable administration of several drugs. These gadgets are made up of sections that hold various medications or dosages along with electronic parts for monitoring and control, such as microcontrollers and sensors. These systems provide feedback mechanisms to alter administration in real-time based on physiological reactions or drug levels, and they also distribute medications as needed by setting parameters including time, dosage, and patient-specific characteristics. Some of the examples include the following.

Electro thermal micropumps: With their complex mechanism that allows for exact and customizable drug administration, are crucial parts of electronically controlled drug delivery systems. These micropumps have several reservoirs with microchannels connecting them, each holding a different drug or solution. The process entails using electrical energy to create localized temperature gradients inside the microchannels, which causes fluid to flow and makes it possible for drugs to be released from the reservoirs selectively. The electrical inputs are regulated by electronic controls, which provide precise drug administration timing and dosage. Through the use of this mechanism, medical professionals can improve patient outcomes and therapeutic efficacy by managing numerous medications at once, dynamically adjusting dosages, and customizing treatment plans based on the needs of each patient (Jonas *et al.,* 2015).

Transdermal drug delivery

Transdermal drug delivery involves administering drugs across the skin, allowing them to enter the bloodstream and exert their effects throughout the body (Arunachalam *et al.,* 2010). They are widely classified into two types based on the devices used for administration:

Needle-based transdermal drug delivery devices and

Chemical enhancer based traditional TDD systems have not been able to provide perfectly self-controlled pharmacological behavior and high Effectiveness in delivery as a result of restrictions on absorption and penetration. To improve drug delivery efficiency and control, a method was proposed to create bigger transport channels through skin by employing arrays of small needles with a length less than 1 mm as TDD MEMS. By increasing the skin's permeability, they provide minimal invasion facilitated delivery of macromolecules into the dermis while staying painless, reliable, and capable of self-administration.

Working mechanism

The device consists of two components: a primary structure with an integrated MEMS-based medication delivery mechanism plus a modular reservoir made up of single-use disposable cartridges. The main component and loaded modular reservoir would be physically built before being attached to the skin. The primary framework consisted of multiple parts: a lower hollow MN array that allowed for a minimally invasive TDD, an upper hollow MN that linked to the modular reservoir via a septum on construction, micropumps, valves, control circuitry, and a power source that allowed for controlled obtaining of the drug loaded in the modular reservoir (Rosen *et al.,* 2017).

Use

They are used in the release of acyclovir for the treatment of herpes labialis, dihydroergotamine mesylate for the management of acute migraine, and vitamin K during bleeding (Pamornpathomkul *et al.,* 2018).

Based on the type of material used as needles, there are two types:

1. Silicon/carbon microneedles based devices
2. Polymeric microneedles based devices (Rosen *et al.,* 2017).

The microsystem for electrically controlled drug delivery

(EDD) comprises four main components: a frontend delivery system, an infusion system, a backend control system, and a reservoir that holds the drug. The conductive interconnections (made of metal or conductive polymer), the power management unit, the feedback control unit, and/or the communication module are the electronic interfaces of an EDD (Razzacki *et al.,* 2004).

Materials for soft ECDD micro-systems

1. Substrate
2. Interconnections, electrodes, and Electrode Coatings

3. Matrices and Drug Reservoirs
4. Drugs and Drug Carriers
5. Encapsulations
6. Micropumps
i. OEIPs
ii. Piezoelectric Micropumps
iii. Electroactive Polymer-Composite Micropumps
iv. Electrostatic Micropumps
v. Electrochemical, drugs micropumpsadiativend Electrothermal Micropumps (Mariello *et al.*, 2023)

ECDD devices and applications

Research on EDD devices has drawn a lot of interest from both academic and industry sources. There is a growing recognition of these devices' potential in a range of clinical settings. Benefits include better patient compliance, fewer side effects, and customized therapy alternatives. These state-of-the-art technologies are revolutionizing medicine delivery, resulting in more effective and efficient healthcare treatments. Examples of these technologies include wearable smart patches for real-time illness treatment and implantable devices for long-term therapies. The examples of EDD devices from earlier research are categorized into three sections based on how they are intended to be used: ingestible, drugs and wearable. Each category highlights the particular illnesses or conditions that fall within that group (Guk *et al.,* 2019).

Wearable ECDD devices

Through the utilization of sophisticated materials and small electrical components, wearable present a novel approach to the targeted and accurate delivery of pharmaceuticals. Patients can conveniently wear ECDD devices on their bodies, thanks to the wearable part's portability and convenience, which is its main benefit. This makes it possible to provide medication continuously and individually without requiring invasive procedures or frequent trips to the hospital. They exhibit promise in the management of chronic conditions such as diabetes, in which prompt and precise insulin administration is essential. They can also be utilized to treat wound healing, neurological conditions, and even long-term illnesses like cancer, where customized dosage and accurate drug administration are essential. These gadgets are often used to enhance patient care because of their versatility (Domingo-Lopez *et al.,* 2022).

Diabetes

These devices are skin, and insulin administration can be facilitated through them, which reduces the pain that comes with the long infusion tubing of traditional pumps. In the field of wearable technology, patch pumps continue to be excellent options, even though their low insulin reservoir capacity and power consumption limit their durability.

A variety of mechanical patch pumps, such as the PAQ by CeQur and the V-Go made by Valeritas, are streamlined and intended for use in the administration of insulin. These gadgets are often distinguished by their disposability and low cost. As a result, more sophisticated equipment is required to guarantee that insulin is administered more effectively. Within this framework, wearable electronic continuous glucose monitoring devices (CGMDs) are highly configurable electromechanical systems that are combined with drug delivery systems, mechanical pump components, and electronic controllers. These devices are made to satisfy the specific requirements of people whose health is reliant on insulin (Ginsberg *et al.,* 2019).

Skin conditions

Owing to its broad surface area and exposure to the environment, the skin is an appealing target for wearable electrocutaneous drug delivery (ECDD) devices designed to treat a range of skin ailments and facilitate wound healing. Because wearable electronics can include medication delivery systems and sensors into flexible materials, they might revolutionize the way skin problems are treated. With the help of these gadgets, dermatological problems may be precisely monitored for factors like temperature, moisture content, and pH levels, which make diagnosis and individualized treatment easier. Furthermore, they minimize systemic adverse effects by delivering regulated drugs specifically to the afflicted skin regions, enabling tailored therapy (Patel *et al.,* 2022).

Cancer treatment

Globally, 18.1 million instances of cancer were recorded in 2020. There is great potential for wearable ECDD devices to change the way cancer treatment medications are administered. By continually monitoring certain cancer-related biomarkers or physiological parameters and modifying the delivery of anti-cancer drugs appropriately, these cutting-edge gadgets can provide tailored therapy. Their efficiency is further increased when integrated into remotely operated systems. Recent research, for instance, demonstrated the creation of an electrical device that is skin-attachable and flexible for remotely controlled wearable cancer therapy. The gadget was made out of a tiny battery and a soft electrical patch with a movable control circuit. This patch uses a flexible electro-resistive heater in conjunction with a nanotextile dressing to allow for the controlled release of the anticancer medication "doxorubicin" via electro-thermal actuation. Made of nanotextile, and a flexible electro-resistive heater that uses electro-thermal actuation to enable the controlled release of the anticancer medication "doxorubicin." Phase-change microcarriers are used in the nanotextile dressing, which is composed of biocompatible thermoplastic polyurethane materials, to control the distribution of doxorubicin. Stable and adjustable thermal actuation is achieved by the electro-resistive heater, which has a serpentine mesh and a liquid metal conductor. The usefulness of the patch in reducing tumor recurrence was established in in vivo tests. Its capacity to adapt to surgical incisions and operate remotely using a smartphone underscores its promise for cutting-edge wearable cancer treatment (Ma *et al.,* 2023).

Neurological disorders

For the administration of medications in a variety of neurological conditions, flexible wearable electronics provide a potential option. Movement disorders are frequently linked to neurological conditions such as epilepsy and Parkinson's disease. Parkinson's disease is characterized by tremors, stiffness, and slowness of movement, whereas epilepsy may also cause tremors, myoclonus, dystonia, and ataxia. While movement irregularities are the main symptom of Alzheimer's disease, they can also be present in Parkinson's and epilepsy patients, although they are usually less noticeable. By creating multipurpose wearable devices, one of the first wearable ECDD devices was created for the diagnosis and treatment of movement disorders. device combined top-down nanofilms and top-down nanoparticles to achieve optimal efficiency for data storage, diagnostics, and drug delivery. The portable system included strain sensors made of single-crystal silicon nanofilms, a temperature sensor, a resistive random-access memory (RRAM) system that used titanium dioxide nanomembranes integrated with gold nanoparticles, and electrical resistance heaters. These components were incorporated into an elastomeric hydrocolloid patch, ensuring mechanical compatibility with the skin. The system enabled continuous movement-related disturbances, data logging, and controlled transdermal drug delivery using thermal stimuli (Villarruel Mendoza *et al.,* 2020; Son *et al.,* 2014).

Conclusion

EDDS has a lot of benefits, but it also has several drawbacks that could prevent it from being used. The use of electronic drug devices aims to address a number of issues, one of which is adherence. However, there is an advantage to use this method of drug delivery over traditional therapy if the patient or the carer is able to follow the instructions for proper administration of the device.

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