E-drug delivery: a futuristic approach

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Drug delivery systems are undergoing technology changes to enhance patient comfort and compliance. Electronic drug delivery (E-drug delivery) systems are being developed to regulate drug dose delivery by easy monitoring of doses, especially in chronic and age-related diseases. E-drug delivery can monitor the correct dose of anesthesia, could be used in GI tracking by E-capsules, in epilepsy, insulin drug delivery, cardiac ailments and cancer therapy. Wearable E-drug delivery systems and Smartphone apps are the new additions. In this review, the authors attempt to highlight how technology is changing for improved patient comfort and treatment. Personalized drug delivery systems will be the future treatment process in healthcare.

Introduction

Electronic drug delivery (E-drug delivery; E-DD) is the application of electronics and usage of technology for delivering drugs. The emergence of electronics in the past decade has been huge and has entered the field of medicine with diverse technologies. This has led to development of smarter, faster, smaller and wireless technology-based devices for treating and diagnosing diseases with affordable and enhanced care. The term 'smart' in the present context symbolizes the development from mechanical to electromechanical operations, smartly adding the electronic input to mechanics for a symbiotic electromechanical output. The application of medical electronics has developed innovatively designed devices, which has improved the health issues of society and patient comfort.

The use of E-DD empowers a wide array of smart and novel therapies, connecting these electronic devices to the human body. Molecular communication networks within the human body are composed of billions of cells [1]. Coming together, electronics and pharmaceuticals have enabled drug delivery devices to provide greater patient choice and improved adherence to therapy [2]. The success of 'electroceuticals' in drug delivery has been highlighted in the recent past owing to the proven role of electrical impulses within the human body [3,4]. Microelectromechanical systems (MEMS) technologies have a significant impact on advanced scaled-down devices with many medical applications [5]. The performance, safety and efficiency of new drug delivery systems has been significantly improved and controlled by automated technologies for a wide range of human applications [6]. The electronic factor (E-factor) is technically useful to provide the scientific information related to the drug information or the time of next dose to the patient. How this E-factor leads to a perfect platform with varied applications for the precise delivery of drugs is portrayed in Fig. 1.

An automated drug delivery system is a preprogrammed dosing concept that has minimized human medical intervention in drug administration. Dosing is achieved through the use of electronic and/or mechanical instrumentation such as microprocessors, which adjusts dose rate as per the required targets: drug concentrations, clinical response, plasma drug concentration, among others. The pH sensitivity of poly(ethylene glycol)-diacrylate/laponite was utilized as microfabricated electrodes and used in the electronic circuitry for improved wound healing [7]. Application of E-DD with a controlled release will take this concept to newer heights of how sustained release can be used to achieve

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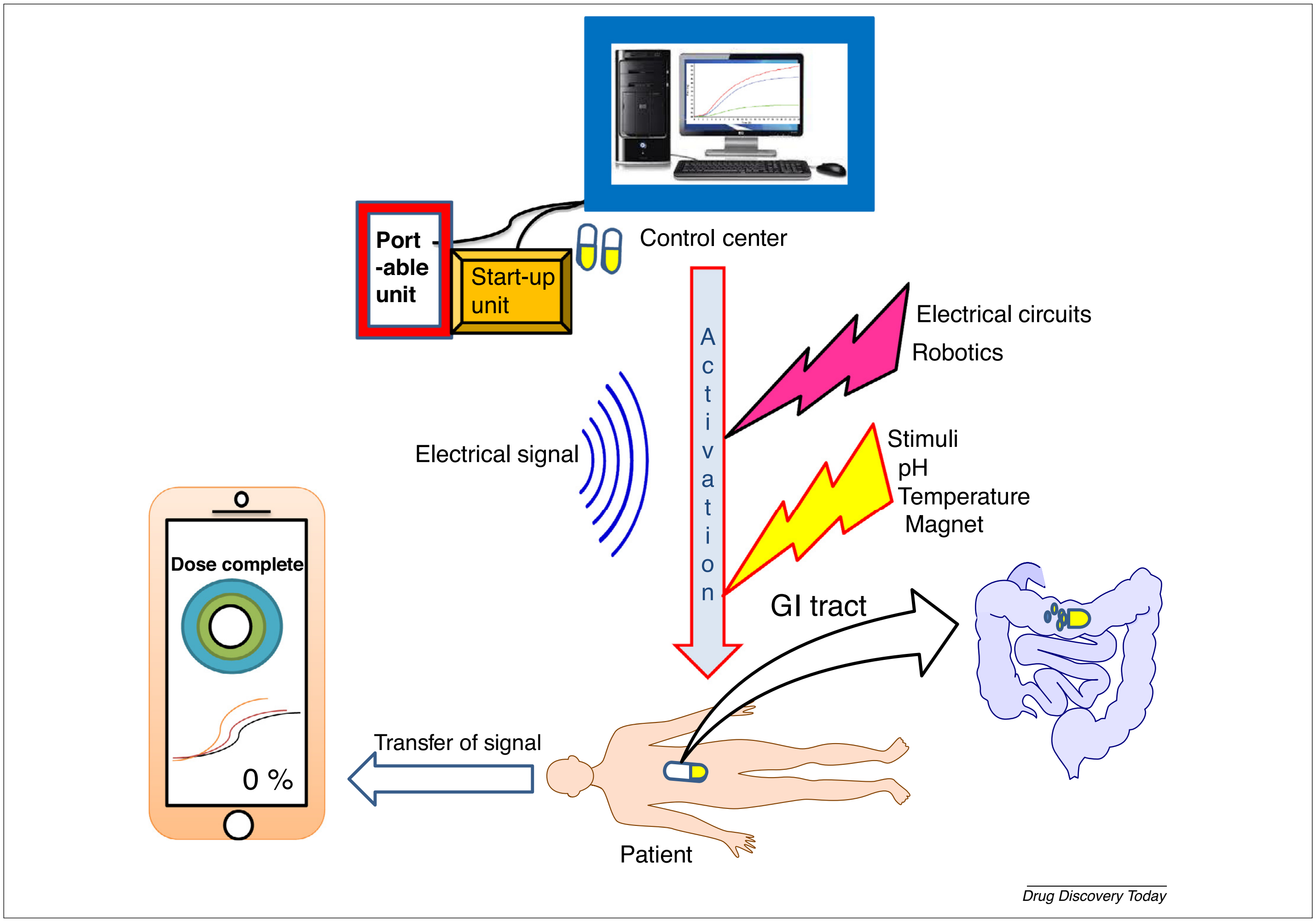

FIGURE 1

Electronic drug delivery (E-DD) strategy. This illustration shows an E-capsule that consists of a drug diagnostic sensor and a programmable microprocessor with start-up and portable units. Capsules are programmed to monitor pH and temperature control. Any physiological stimuli are used to expel the drug *in vivo*. All data received by portable units are downloaded onto a PC and real-time analysis is sent to the control center.

constant release of a drug over a prolonged period of time and for constant monitoring of the dose, especially in geriatrics. Here, the authors have compiled the wide applications of E-DD in management of diabetes, administration of anesthesia, oral drug delivery, epilepsy, cardiac attack, cancer, wearable E-DD devices and use of Smartphone apps.

E-DD as a solution for nonadherence

Medication adherence is defined by the WHO as 'the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider' [8]. Adherence to medical treatment is becoming difficult, especially in cases of chronic diseases where patients fail to stick to the prescribed treatment regimen. Nonadherence statistics reveal that only 50% of the prescribed medication is taken as the regimen. Such nonadherence is not only increasing their chances of hospitalization but also a greater number of deaths per year are reported [9]. Reasons for nonadherence to medications and major therapeutic areas where E-DD is needed are listed in brief in Fig. 2.

E-DD for management of diabetes

Worldwide, ~250 million people have been diagnosed with diabetes mellitus [10]. Patients with diabetes mellitus must periodically monitor their blood glucose levels and minimize the risk of hypoglycemia. High patient noncompliance is seen and large individual variations in insulin sensitivity in diabetes is a concern. However, such systems are at preclinical and early clinical developmental stages and, according to the FDA, the first premarket approval application for a fully automated closed loop system could be 5 years away. Noninvasive smart microneedle-based microfluidic components and MEMS have glucose sensors and are used as insulin delivery units [11]. The Medtronic MiniMed™ external physiological insulin delivery (ePID) system comprises an external pump and a sensor with a variable insulin infusion rate algorithm designed to simulate the physiological characteristics of a human β cell. Insulin injection pens were developed with an intention to improve the delivery of insulin by decreasing the medication errors leading to hospitalization of the diabetic patients. Other benefits that are reported are accuracy in dosing,

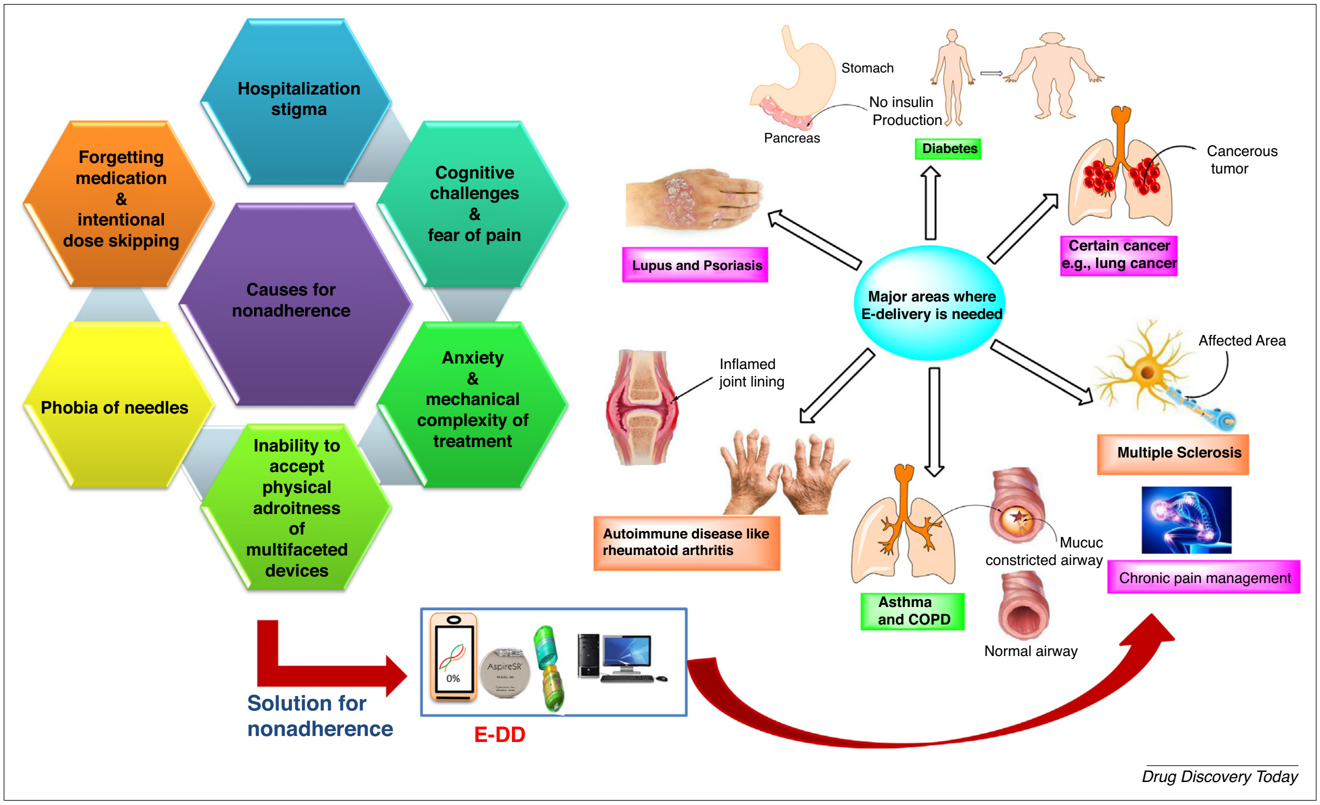

FIGURE 2

Major areas where electronic drug delivery (E-DD) is needed with causes for nonadherence. The diagram is a pictorial representation linking two things. One is the listing of some of the causes for nonadherence and the other is major areas where E-DD is needed. The link between the two is application of E-DD. Some of the causes of nonadherence include: hospitalization stigma, fear of pain, phobia of needles, anxiety of long-term treatment, mechanical complexity of treatment, inability to accept physical adroitness of multifaceted devices, cognitive challenges, forgetting medication and intentional skipping of doses. The major areas where E-DD would be most beneficial include: diabetes, autoimmune diseases (rheumatoid arthritis, lupus and psoriasis), cancer, asthma and COPD, chronic pain management and multiple sclerosis.

clinical efficacy and improved adherence rates [12]. Overall, the device has an improved quality of life (QoL) for diabetic patients. Many companies have come up with their versions of insulin pens. They differ in make, durability (reusable or with a replacement cartridges) and disposable forms. The NovoPen Echo® by Novo Nordisk, with electronic memory features, keeps track of dosage time and size, as a built-in feature [13]. Other insulin pens include the HumaPen Luxura® and InPen system. OmniPod®, a wearable device that has a tag line of 'fit and forget', ensures consistent drug delivery over a longer period of time. The first wearable insulin pump was AutoSyringe AS6C, which could continuously release insulin subcutaneously [2].

Timesulin™ smart cap

Timesulin™ is a Bluetooth-enabled technology capturing dose data. Timesulin™ is a smart replacement for the insulin pens which provides information, for example when the insulin was last taken. Having to remember the dosing schedule leads to anxiety among patients [14]. Timesulin™ automatically tracks the timings of the last injection and helps in maintaining the dose. One Timesulin™ cap lasts for 12 months.

E-DD in controlling and administration of anesthesia

Anesthesia has a high number of parameters that need to be monitored and it requires rapid onset of action with continuous administration of drugs to maintain normal cardiorespiratory activity during surgery with simultaneous management of side-effects. Regulation of anesthesia through automated systems can overcome issues of under-dosing or overdosing of anesthesia in patients, maintaining the adequacy of an anesthetic regimen and balance between anesthetic-induced depression and surgery-induced stimulation. The components of anesthesia control the hypnotic, analgesic and paralytic states (H, A and P), as depicted in Fig. 3 [15]. The closed-loop systems in anesthesia consist of three elements:

(i) Brain – a central operating system with built-in algorithms.
(ii) Effect – a target-controlled variable.
(iii) Actuator – a drug delivery system.

All these elements are connected by a feedback system that allows the automated control of drug delivery to maintain a pre-set target value of the control variable without any manual input [16]. Agrawal *et al.* quantified the amount of isoflurane to be delivered for maintenance of desired anesthetic depth in patients using a fuzzy proportional-integral-derivative (fuzzy PID)-based control system [17]. Soltesz *et al.* reported an individualized closed-loop control approach for propofol anesthesia where the individualization of the controller is at the end of the induction phase of anesthesia [18]. Automated anesthesia drug delivery systems thus offer improved patient safety, low drug consumption, reduced therapy cost, better postoperative recovery and optimal performance over manual

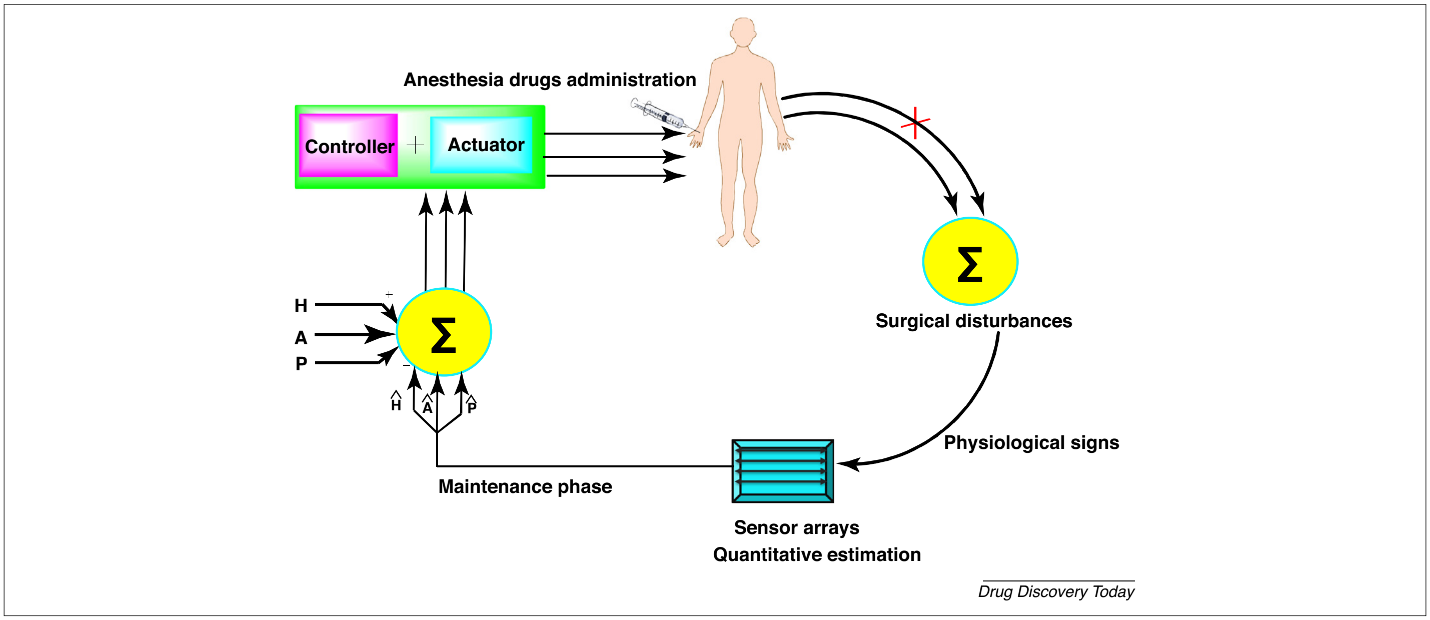

FIGURE 3

Components of an anesthesia control system. The illustration shows the way a control system and actuator system are used in sequence for controlling hypnotic (H), analgesic (A) and paralytic (P) states based on set points. Redrawn from Ref [15].

methods of anesthesia. However, most of these systems are still under development and the safety, efficacy, reliability and utility of such closed-loop anesthesia systems need to be extensively established for successful clinical applications.

Targeted delivery in the GI tract using E-DD

New types of drugs can be delivered exactly to the required place in the body. Medimetrics is a pioneer in biotech and pharmaceutical products, along with Philips, and have designed the world's first intelligent electronic oral drug delivery and technology capsule: IntelliCap®, for targeted delivery of drugs into the gastrointestinal (GI) tract. IntelliCap® is a novel, oral, compact, single-use, ingestible, built-in intelligence electronic capsule with pH and temperature sensors and wireless RF (Radio Frequency) connectivity. It is a minimally invasive drug delivery platform for targeted delivery to the GI tract monitored 'on the fly' via a PC, enabling personalized delivery of drugs in required doses at a specific place and time, all clearly monitored by this device [19].

IntelliCap® is based on five technologies and combines the functions of electronically controlled drug release, drug-release measurements, sensors for navigation through GI tract, radiofrequency connectivity for two-way real-time communication and an operating system (Fig. 4a). IntelliCap® is a small capsule (11×26 mm) with a drug reservoir consisting of fluids such as solids, liquids, powders, pastes or suspensions and a microfluidic pump-controlled integrated microprocessor for pumping these fluids and an electronic body that houses a pH and temperature sensor, microprocessor, wireless transceiver and actuator for drug dispensing. It is powered by an onboard battery and its electronics are fully sealed to ensure biocompatibility.

Two IntelliCap® versions are available: IntelliCap® CR and IntelliCap® FR, which have the same electronic systems but a different drug reservoir and delivery pattern. IntelliCap® CR dispenses the drug in small increments under microprocessor control and allows any delivery profile, whereas IntelliCap® FR consists of powder, particles, solid fluids and dispenses drug in a single fast-release pattern. Drug absorption in the colon is essential for sustained-release formulations to maintain plasma levels for $\sim$24 h. Better colonic absorption has been reported by using IntelliCap® compared with marketed sustained-release coated beads [19] and a low gastric pH was ensured in beagles with IntelliCap®. It is a medical device and has been successfully used in preclinical and clinical studies in Europe and the USA owing to their rigidity, design manufacturability, easy production, cost-effectiveness and affordability.

E-DD in the treatment of epilepsy

Neurological disorders such as epilepsy are characterized by spontaneous seizures. The standard medication therapy and surgery fail to control the seizures in the majority of those affected and globally the number has risen to 50 million. Lack of control of seizures with oral therapy of antiepileptic drug(s) (AED) has led researchers to focus on new ways to deliver AEDs directly to the seizure foci in the brain to achieve more-effective high doses to reduce the seizure foci and minimize side effects. Thus, there has been a growing interest in neuroresponsive intracerebral local treatments of seizures such as focal drug delivery, focal cooling, electrical stimulation and implantable devices to predict, detect, prevent and abort seizures as newer options for treatment of drug-resistant epilepsy. The implantable devices are neuroengineered products, driving engineering technology toward investigating and treating neurological diseases. Ultra-low-power implantable devices comprising an intracerebral electroencephalographic acquisition system, seizure detector, brain stimulator and wireless system have been developed for treatment of medically intractable epilepsy. The fully integrated automatic implantable device

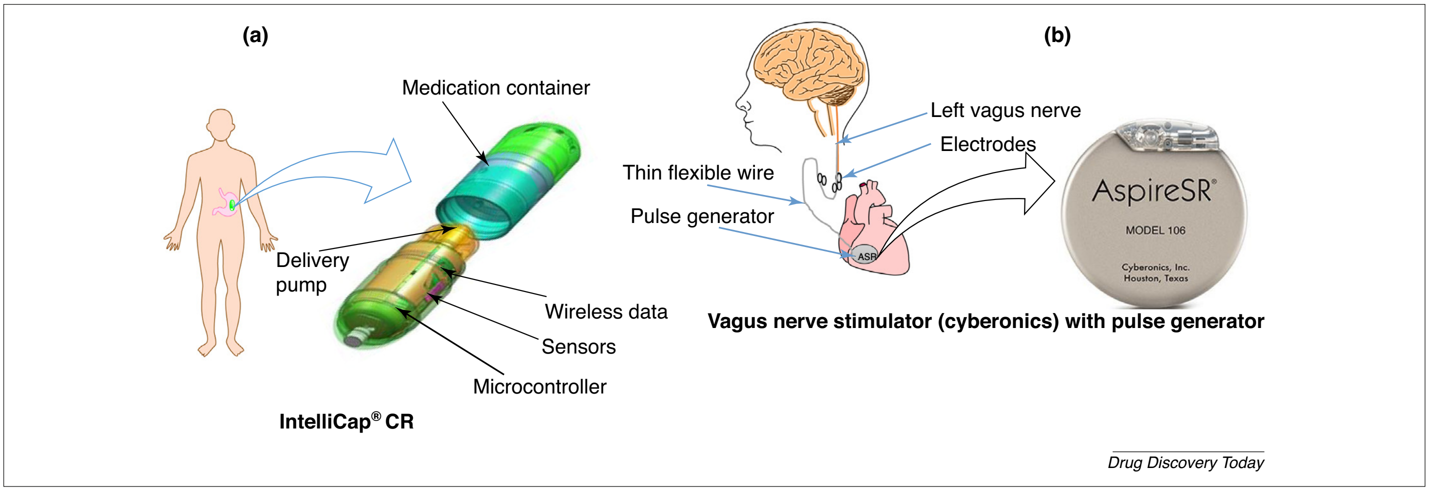

FIGURE 4

(a) IntelliCap®: schematic illustration of the novel oral capsule. This E-DD device can used to track the entire gastrointestinal (GI) tract. **(b)** Vagus nerve stimulator with pulse generator. This is a schematic diagram of an E-DD implantable system with two main components. The first one is the lead with electrodes and an anchor enveloped around the cervical vagus nerve. The second is the pulse generator which is positioned at a subcutaneous pocket in the chest wall.

detects low-voltage fast activity and triggers focal treatment to disrupt seizure progression [20].

Seizure treatment with open-loop devices

The vagus nerve stimulator (VNS; Cyberonics, Houston, TX) (Fig. 4b) and deep brain stimulation (DBS) of the anterior thalamus for partial epilepsy are devices based on open-loop technology and have been approved for use by the FDA in the USA and EMA in Europe, respectively. The VNS is a simple and effective open-loop antiepileptic device that stimulates the central nervous system (CNS) through a cranial nerve in a repetitive cycle, where the physician programs the stimulation parameters. The VNS has been reported to cause a reduction in the number of seizures in an individual by an average of 30–40%, <10% patients were seizure-free.

Kinetra® neurostimulator (Medtronic) is another open-loop device currently tested in the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial. This device is used in the treatment of partial-onset epilepsy where it stimulates the anterior nucleus of the thalamus [21]. Responsive neurostimulation recently completed a successful multicenter trial, whereas transcutaneous magnetic stimulation (TMS) provides a noninvasive method to stimulate the cortex. Other techniques include optogenetics which controls excitability of neurons with light [22].

Seizure treatment with closed-loop devices

Closed-loop devices are based on the principle of recording and converting real-time biological signals to detect seizure onset, triggering an intervention. The first-generation closed-loop device in clinical trials is the Responsive Neurostimulator (RNS®) system (NeuroPace, Mountain View, CA). The RNS® is an implantable device that comprises an electrode that records, processes and transmits the intracranial electroencephalographic signals as an input algorithm, determining the seizure onset and triggering focal electrical stimulation to stop seizures [23]. Salam *et al.* have reported an implantable closed-loop device for intracerebral electroencephalography (icEEG) data acquisition and real-time epileptic seizure detection with simultaneous focal antiepileptic drug injection feedback. The device includes a neural signal amplifier, an asynchronous seizure detector, a drug delivery system, a micropump and a hybrid subdural electrode [24].

E-DD in cardiac ailments

Congestive heart failure (CHF) and hypertension are the most common diseases affecting >1 million people every year. CHF is a condition where the heart fails to pump sufficient blood to meet body tissue requirements. Thus, hemodynamic variables such as mean arterial pressure and cardiac output need to be maintained within normal ranges by systemic administration of cardiac drugs. The high inter-patient response variability in controlling systemic arterial pressure (PA), cardiac output (CO) and left arterial pressure (P_{LA}) in acute heart failure after myocardial infarction or cardiac surgery on administration of cardiovascular agents such as inotropes and/or vasodilators have initiated researchers to develop closed-loop systems to facilitate automatic drug administration. Karar *et al.* have reported an automated drug delivery system comprising a fuzzy neural network (FNN) with two subcontrollers to manage CO and mean arterial pressure (MAP) through infusion of vasodilators and inotropic agents in patients with hypertension and CHF. The FNN control system is based on the direct adaptive control strategy of the neural networks using an online back-propagation learning algorithm and can significantly improve the performance of a cardiac drug infusion system [25].

In this section, the Holter device needs a mention. It is a portable device that is used to measure the electrical activity or the electrocardiography (ECG) of the heart. Monitoring cardiac events in patients is crucial especially where occasional cardiac arrhythmias are seen. The Holter is battery operated and is usually worn using a waist belt or suspended around the neck with at least two electrodes on the skin to keep track of ECG [26]. The Holter device stores data and gives information when the software analyzes the recorded signals. However, the future holds true for smaller devices that are soft in nature with flexible or stretchable circuit boards [27]. Such devices have utility of soft and conformal biosensors and are predicted to transmit data by wireless modes.

E-DD in cancer therapy

Cancer treatment possibilities consist of chemotherapy, use of radiation, surgery or a combination thereof. Use of anticancer drugs is associated with severe drawbacks of being nonselective and destroying healthy cells. In addition, many side effects such as nausea or loss of appetite damage the QoL of patients. Smart or intelligent delivery systems and the biomaterial devices can respond to environmental stimuli. This stimuli responsiveness has become the advanced technology that is used in the treatment of cancer, having a powerful impact. Some of the stimuli that need a mention include pH, temperature, pressure, biological signals, electrical signals, light, magnetic field, enzymes and pathological changes [28]. These electrical signals are used as the stimuli for release of the active drug to exert its response. There are two types of devices in this situation. First, the electronic devices which can either be worn or implanted inside the body and have been discussed in the previous sections. The second type of device are those that utilize polymers triggering the electric stimuli via conductive polymeric bulk materials [29].

The MEMS devices can be tailored according to the individual needs and have been reported as one of the first to be used in cancer therapy. Song *et al.* demonstrated a MEMS-based device made up of polydimethylsiloxane and loaded with doxorubicin, with a significant impact on pancreatic cancer cell lines [30]. Such devices can be an answer to automatic personalized delivery of drugs as well as improving individualized disease treatment in the near future.

E-DD using Smartphone apps

E-DD using Smartphone apps was inevitable for three vital reasons. First, Smartphones are omnipresent and, second, self-administration and self-monitoring of drugs by the patient are necessary. Third, and the most important reason, is the possibility of multi-device integration, which makes this technology useful in drug delivery. The Smartphones available are empowered by applications like Android, iOS and windows, which allow easy installation of apps and wireless connectivity using Bluetooth, making it possible to keep track of medical needs. Other features associated with Smartphones that instinctively give analysis of the samples studied, for example in-built user interfaces, storage space and backup of data in a cloud, have made it easier for the patient to think about self-administration of drugs.

Kenzen's smart patch

Kenzen's smart patch applied on the body can be connected to Smartphones by Bluetooth and sync data to the Kenzen devices. This enables taking care of any symptoms and signs related to injury or changes in physiological functions. This patch can mend and monitor the way recovery would be set up for the diseased condition by continuously checking progress. In our fast-paced world, apps fitted with mobile applications enable people to know about the biofeedback of their physiology, such as monitoring of stress [31]. Most of the Smartphone-app-based drug delivery systems are wearable (e.g., SmartDose® electronic wearable injector).

Medopad Apple watch chemotherapy app

Digital healthcare is a futuristic approach for treating many diseases including cancer. Medopad reported one of the firsts apps for cancer chemotherapy [32]. This app was linked to the Apple watch and worn by patients receiving chemotherapy to save time and reduce errors. The Apple watch app ensures that the patients take the medication on time. The physicians will be able to monitor the patients and, hence, a better treatment modality is expected where even symptoms can be traced.

Wearable E-DD systems

The drug delivery systems that can be worn for treatment for an extended period of time could play an important part in chronic disease therapies. In such cases, the device to be worn is adhered to the body, which subsequently allows delivery of the drug for an extended period for hours to days. These advanced devices are ergonomically designed with easy to use features and reduce the overall difficulties faced by conventional systems such as traditional syringes and needle devices. These devices are a great boon to patients with cognitive or dexterity challenges.

The Wearable Electronic Disposable Drug (WEDD®) delivery technology is a remarkable platform for drug delivery. WEDD® is an electronically enabled handy device that is based on iontophorosis for the transdermal delivery of drugs. It has characteristic features of being a single-use device that is disposable. The Pushtronex™ system is a wearable device reported for delivery of Repatha® (evolocumab) in the treatment of high cholesterol. 'Promising more and delivering less' fits the working principle of this device because the desired dose in this case is very small (3.5 ml) and expectations are high on performance or therapeutics [33]. The E-factor would further provide information on disposing of the device after delivering the drug. Wearable devices for detecting sugar based on enzyme sensing are reported that put forth the alternative for avoiding the presently used invasive methods [34]. With biologically sensitive (to detect and respond to physiological signals) wearable devices, the transdermal route could also be well utilized for providing drug delivery for personalized medicine [35].

SmartDose® electronic wearable injector

The electronically enabled wearable injector SmartDose® stands out as a device that adheres to the patient's body (Fig. 5). This is a polymer-based device that is pre-programmed to deliver drugs. Benefits of single use, ease of use, getting notification of dose and self-administration make this device patient friendly. It also enables the use of viscous liquids, sensitive drugs and larger amounts of drug to be administered. The comfort level to the patient is high because some patients might not like themselves to be seen using medicines and this device is discrete. The cons of wearable devices in gathering of biometric-data-based information come with the risk of bigger data getting leaked, where safeguarding the personal health and medical data can become an issue.

Concluding remarks

The healthcare system is undergoing a major paradigm shift where patients want to know about their health and their physiological parameters on a regular basis. Hence, this has created a need for more technology-based prevention of diseases, early diagnosis and comfortable chronic treatment. All this has paved the way

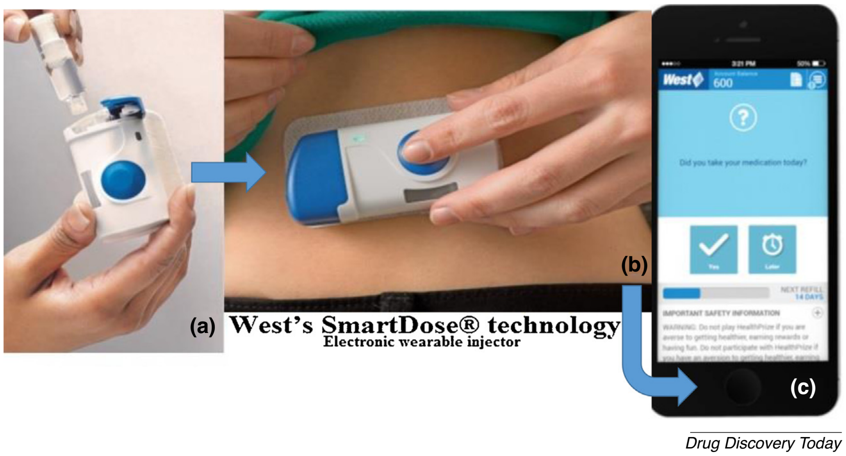

FIGURE 5

West's SmartDose® technology. **(a)** Cartridge is made ready to deliver a specified dose. **(b)** Device is worn on the skin. **(c)** Monitoring using an app on a Smartphone.

for E-DD systems that are patient-centric and 'friendly'. Some of the foremost examples of development in this field have been the use of E-DD in biological therapies where the number of doses of drug required has been reduced.

Every technology comes with pros and cons and, at the outset, it is important to understand both so that the disadvantages do not necessarily obscure the advantages. E-DD would have the ability to not only monitor the therapy but also keep a track on its progress. These devices being portable have benefits of being either implanted or worn easily and have the medical information stored. However, the inability to measure the correct data or sending false readings for an inappropriate dose would be the major disadvantages associated with E-DD. Because these devices are battery operated their short battery life and wireless operations could be another drawback. Despite many advantages and applications, E-DD also faces challenges that need to be understood. A major challenge is the use of electronics day to day, especially when these devices are worn. Patient privacy could be at stake in development of a cloud system owing to wireless connectivity. Because these devices store patient information, concerns with maintaining and sharing such data would be significant.

E-DD systems can reduce the cognitive, emotional and physical burden that mainly comprise patient adherence and compliance. Technology can be developed for newer medical drug delivery devices for drug delivery in different diseases and can be delivered by this method. Scientists and medical device manufacturers are working toward this direction and comfort of patients looks bright in the coming years. These E-DD devices can be rightly termed as 'onboard electronics' that are useful in giving information on time for dosage delivery as well as when to remove the device. The latest technology and gadgets in healthcare will change the perception of patients taking medicine and the frequency of taking drugs can be reduced. This technology will also be of huge benefit to the geriatric population and people who live alone, where drugs and dosage can be monitored. One of the biggest achievements of E-DD would be the adherence to prescription owing to less frequent dosing. In the modern world the mindset of a chronic therapy necessitating a daily dose would change to a weekly or monthly dosing under regulatory compliance and the future looks bright in this field.

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