MS.ID-IJPBS-2675
International Journal of Pharmacy and Biological Sciences-IJPBSTM (2022) 12 (1): 16-24
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Biological Sciences | OA Journal | MCI Approved | Index Copernicus

Electronic Drug Delivery System-A Latter-Day Approach

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Received: 14 Oct 2021 / Accepted: 6 Nov 2021/ Published online: 01 Jan 2022
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Abstract
Aim: Electronic drug delivery system (EDDS) is a technological marvel which is going to revolutionize the way of drug delivery. This review illustrates about the various devices currently available in the market as well as critically analyses the advantages and disadvantages of electronic drug delivery system and also put forward future prospects. **Method:** This system is built upon the prime objective of patient compliance or rather patient comfort and accurate amount of drug delivery into the specific tissues or target sites. From the incredible microchips to sophisticated electronic capsules, all are galvanizing the portability, pro-activity, wireless connectivity of the drug delivery system. **Result:** These devices can deliver drugs with a great precision while simultaneously collecting various health data from the body so the drug delivery and its effects can be monitored in real time. This monitoring will increase the therapeutic efficacy as a whole. With the development in the field of artificial intelligence (AI) and we can delve into the synergy between AI and EDDS. This will pave the way for a more automated drug delivery system and in the near future we may develop a designer drug delivery system with customizable features according to individual needs.

Keywords
Microchip, Electronic capsule, transdermal patches, electronic pumps, Artificial intelligence

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INTRODUCTION:
Since the advent of civilization, mankind has sought to better its condition through technological innovations and electronically controlled delivery of drug is one such attempt. Drug delivery system is the method or process by which pharmaceutical compounds are administered to achieve therapeutic effect in humans and animals. Electronic drug delivery is a process through which certain drugs are delivered into human body by the help of devices having electronic components so that they can be controlled from outside of the body for accurate delivery of required amount of drug to a specific site[1]. Patient compliance or patient adherence is a modern-day problem with an increasing fatality due non-compliance behaviour shown by patients. A recent study conducted by a team of researchers on the rural population of Pondicherry, India showed that almost one-third of the study participants were non adherent to medications which can hinder the maintenance of drug concentration in blood leading to non-effective therapeutics [2]. Electronic drug delivery developed from the idea to build a more patient compliant medication delivery system. Electronic drug delivery system can reduce or rather eliminate the physical, emotional as well as cognitive burdens like forgetfulness, incomprehension and anxiety which paves the way for a healthy living.

Those of the Generation- Z may accept it more comfortably but others might find it difficult to adapt to these new technologies. Although electronics as an enabling technology in drug delivery has been evolving since the 1980s but still it is in its nascent stage of development due to various reasons. Electronic drug delivery is mention in (Fig. 1).

EVOLUTION OF DRUG DELIVERY SYSTEM:

Historically, drugs were delivered by capsules, ointments, eyedrops, and injections, all essentially descendants of ancient practices. The development of drug delivery system can be categorized into three following (Table.1) generations [3]. Electronic drug delivery system developed from the concept that the traditional drug delivery system has failed to mitigate the problem of different biological barriers as well as physiochemical barriers. This new system of drug delivery tries to overcome the problems posed by biological as well as physiochemical barriers.

Table.1: Development over the years

1st Generation	2nd Generation	3rd Generation
	YEARS	
1950-1980	1980-2010	2010 onwards
Controlled release is developed.	Smart Delivery systems are developed	Modulated Delivery systems are developed.
Physical properties like Dissolution, Diffusion, Osmosis, Ion-exchange are being used to achieve the controlled release.	Proteins, peptides, nanoparticles, smart polymers are used for smart drug delivery.	Self-regulated systems are developed for more patient compliant delivery of drugs.

DIFFERENT MODES OF ELECTRONIC DRUG DELIVERY SYSTEM:

Microchip Devices:

Last decade saw some great technological innovations specially in the areas of Micro-electromechanical systems (MEMS), Nano-electromechanical systems (NEMS), material sciences, polymer sciences, data management to name a few. The synergy of these technologies has paved the way for the development of miniaturized implantable devices for controlled and accurate delivery of therapeutic drugs from one or more reservoirs [4]. The EDDS outperforms the conventional drug delivery system in respect of therapeutic efficacy, safety, patient convenience etc. These implantable drug delivery devices permit target specific or rather local drug delivery by direct placement of the device at the site of treatment, delivery on demand (emergency administration), adjustable continuous dosing, pre-programmed dosing cycles, automated delivery of multiple drugs, and dosing in response to physiological parameters and diagnostic feedback. This innovative drug-medical device synergy may protect labile as well as delicate active ingredients within hermetically sealed reservoirs. This phenomenon of increased efficacy of delivery of certain drugs has revolutionized the way we deliver drugs into our body [5]. Experiments have shown that silicon microchips have the ability to store and release multiple chemicals on demand. Integration of active control electronics, such as microprocessors, remote control units, biosensors, could lead to the development of a 'smart' microchip implants that release drugs into the body automatically when needed. The specific drug containing microchip device is implanted on the target site inside the body and then whenever any physiological or external stimuli is being sensed by the device the specific reservoir's membrane melts and releases the drug on to the target site. As all the materials used including the battery can be degraded by the body, after the all the reservoirs become empty, it's going to be degraded by the body and eliminated in a safe way [6]. The component of microchip is given in (Fig.2). Human clinical trials began in Denmark during 2011 with successful results. The Micro-chips company has planned to develop implants with the capability to transport hundreds of drug doses per chip. Dosages will be scheduled in advance or triggered remotely by radio communication over a special frequency called Medical Implant Communication Service. Implantable microchip devices will provide real-time dose schedule tracking mention in (Fig.3) and as part of a network, physicians can remotely adjust treatment schedules as necessary.

Microchips' implantable device can provide 100% compliant delivery of parathyroid hormone for people who suffer from severe osteoporosis. These devices expand treatment options for addressing complex medical needs related to dosing [7]. Microchips' implantable device shown in (Fig.4). The designed microchip for drug delivery allows for storage and dependable controlled release of multiple drugs. This device is very much user friendly and works in a more target specific manner than traditional drug delivery systems. The microchip can be created by general micro-fabrication techniques and can also be self-contained, which reduces rather eliminates the need for patient or doctor intervention. The device can last over a year; however, the delivery abilities do depend on patient need.

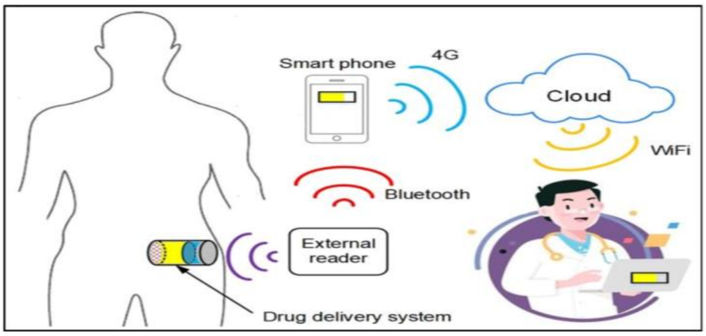

Fig. 1. Electronic drug delivery system.

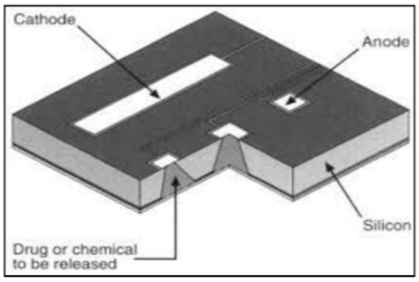

Fig. 2. Various components of microchip

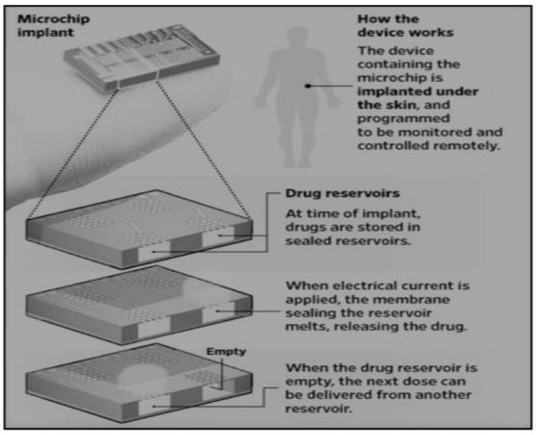

Fig. 3. Working of microchip devices

Electronic capsules:

Electronic capsules use the technology of different components such as drug reservoir, delivery pump, electronic microcontroller (MCU), wireless communication, batteries, and sensors [8]. These elements are combined in a way so as to retain small size, reliable manufacturing as well as safe to be used for medical purposes. The device containing (Fig. 5) these parts are built as a small, capsules-shaped, this is swallowed and passed through the gastro-intestinal tract. An electronic pill has a 16mm diameter, 55mm length and 5gm weight, and can be swallowed. It is covered by a chemically resistant polyether-terketone (PEEK) coating. As soon as the pill moves through the gastrointestinal track, it starts to detect diseases and abnormalities. The pill can easily reach areas such as small and large intestines and deliver real-time information to an external system. Data collected is then displayed on a monitor. It is a medical monitoring system, measuring parameters like temperature, pH, conductivity, and dissolved oxygen but its use has been extended to deliver drugs in our body. Use of an electronic capsule will empower patients to have a painless drug delivery having as well as liberate patients from having invasive methods such as catheters, endoscopic instruments, or radioisotopes for collecting information about the digestive tract [9]. Drug delivery using an electronic capsule will also be controlled with onboard electronics, enabling precise and adaptable delivery patterns, which are not yet possible by other means. An electronic capsule has multichannel sensors that will help towards in-depth and detailed investigation of diseases. In addition, its uses range from drug delivery to reaching specific regions of the human body to target different types of cancer, stimulate damaged tissues, and track gastric problems and measure biomarkers. To carry out these functions, the capsules is powered by an edible battery and equipped with highly efficient sensors. It is important to assure that the materials used to make an edible battery are not toxic to humans, as this can cause significant complications if it gets into the digestive tract. The capsule takes measurements of the local pH and temperature inside the body [10]. The working mechanism of this device is shown in (Fig. 6). These devices can also transmit information of pressure levels, or images of the oesophagus and intestines to the doctor's computer for analysis. Electronic capsules are also being used to measure muscle contraction, ease of passage and other factors of the body to reveal information that is very helpful for an effective diagnostic.

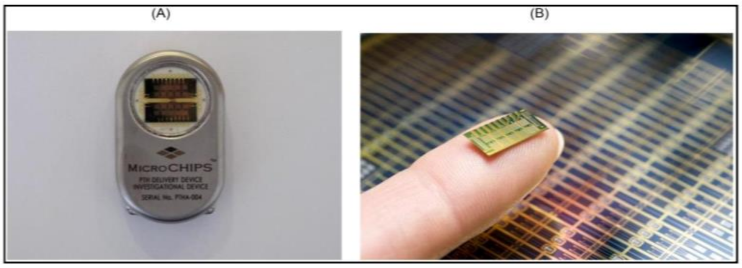

Fig. 4. (A) Microchip's implantable drug delivery system. (B) Microchip's array of reservoirs

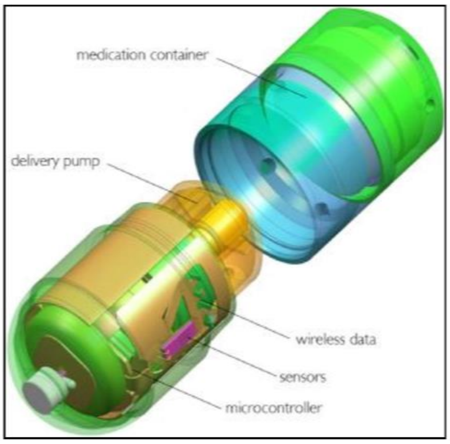

Fig. 5. Different components of electronic capsules

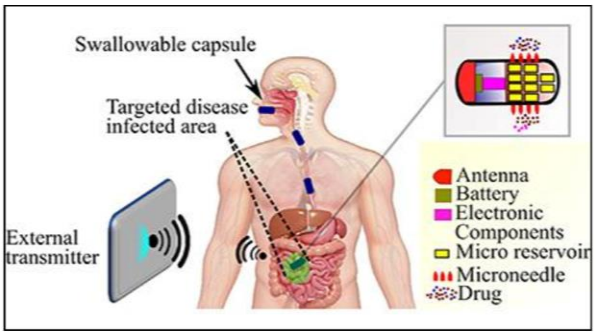

Fig. 6. Working of Electronic Capsules

Electronic Transdermal patches:

Traditionally we apply lotion on skin to deliver drug on the systemic circulation but not all kind of drug molecule can be formulated as a lotion so delivery of drug into systemic circulation at a pre-programmed rate using skin as a site of application is a recent method of drug delivery. Transdermal drug delivery provides many advantages over oral and intravenous administration. An ideal drug to be formulated for delivery as a transdermal drug should possess several specific physicochemical properties, such as short half-life, small molecular size, low dose to name a few.[11]The candidacy of many therapeutic compounds for topical administration is limited by the ability of the drugs to permeate the skin shown in (Fig. 7), in particular the rate-limiting barrier of the stratum corneum as well as solubility, lipophilicity, molecular weight or size, and hydrogen bonding ability of drug molecules. However, poor permeability and high amount dose are the two major hurdles in delivery across the skin. The number of drug molecules suitable for transdermal delivery would significantly increase with the use of chemical penetration enhancers like sulphoxides, saponins etc [12]. Transdermal delivery of drugs confers several advantages over traditional administration methods for example avoidance of hepatic first-pass metabolism, reduction in side effects (e.g., gastric irritation), better patient compliance, and enhanced therapeutic efficacy [13].

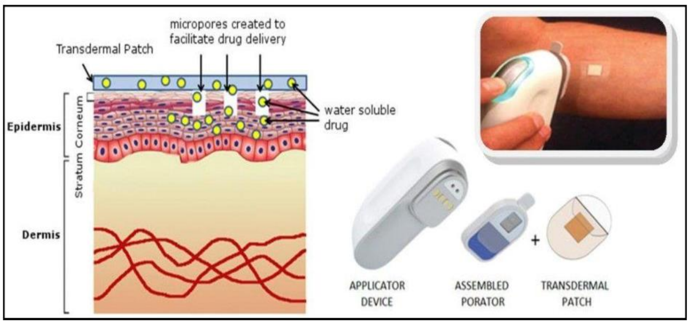

Fig. 7. Working of transdermal patches

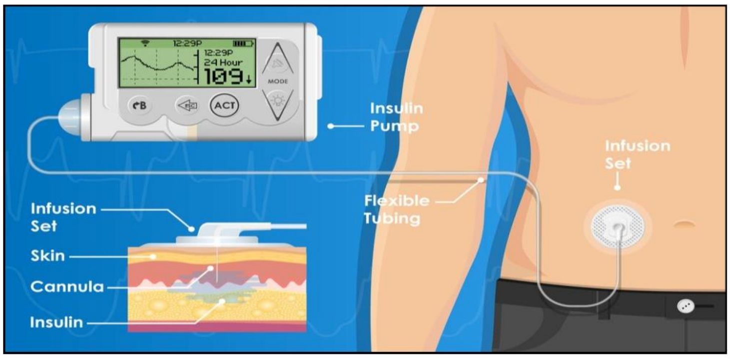

Fig. 8. Electronic pumps used by diabetic patient

Nowadays, numerous transdermal patches for active agents are available in the market (e.g., nitro-glycerine, nicotine, scopolamine, clonidine, fentanyl, oestradiol, testosterone, lidocaine, and oxybutynin). Depending on the activity and half-life, the time of delivery duration is generally from 1 to 7 days. A very important example of a successful system on the market is the oestradiol patch, which is used by more than a million patients worldwide per year. Moreover, transdermal clonidine, nitro-glycerine, and fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms. Nicotine patches have also played an important role in preventing smoking and prolonging life.

Although the technology of the electronic transdermal patches is still in nascent stage development most technologies use the principle of iontophoresis which is the application of electromotive force and low-level electric current for the delivery of charged and/or large drug molecules through the skin. In iontophoresis, electromigration and electroosmosis are the predominant mechanisms through which drug ions are driven across the skin into systemic circulation [14]. The pair of electrodes placed on the skin set up an electrical potential between the skin and the capillaries below. Positively charged drug molecules are driven away from the skin's surface toward the capillaries at the positive electrode, while negatively charged drug molecules are transported through the skin at the negative electrode. According to Faraday's law, flux is directly proportional to the applied current and therefore drug delivery increases as a function of applied current, however in practice the increase in delivery may plateau after a certain current. The experimental data suggests that the acceptable maximum value for current for in vivo applications is ~0.5 mA/cm^2[15]. Different design considerations are required like patch size for optimal drug delivery, type and size of the electrodes, control over the electronic circuit, appropriate selection of the battery technology since miniaturized electronics are required, and formulation factors affecting the state and ionization of the dissolved drug[16]. Research studies suggest that rate of drug release for electronic transdermal patches is constant during current application and the release rate drops as soon as the current is turned off[17]. These electronic patches can deliver multiple drugs at once and can also deliver proteins and peptides as well. It also allows for broader range of drugs to be administered with a greater control of delivery. This expands the potential for delivering drugs non-invasively and active transport of drug across and through the skin. The electronic transdermal patch is a painless alternative to injections and offers more immediate onset of action for relief.

Electronic Pumps:

There are several types of medical drug delivery pumps for example, an infusion pump is a medical device used to deliver fluids into a patient's body in a controlled manner. There are many different types of infusion pumps, which are used for in a variety of environments and for a variety of purposes. Infusion pumps can dispense fluids in large or small quantities and can be used to deliver nutrients or drugs such as insulin or other hormones, antibiotics, chemotherapy drugs, and pain relievers [18,19]. An insulin pump is a small electronic device, about 5.3cm wide and 9.6cm tall. The pump can help you mimic the way a healthy pancreas functions, replacing the need for frequent injections. The pump delivers accurate doses of rapid-acting insulin 24 hours a day, according to body's needs. It is an electromechanical device that provides drug delivery and glucose monitoring for intensive glycaemic management. The customized doses of insulin are individualized to match the patient's needs and the insulin pump delivers pre-set continuous basal insulin constantly over 24 hours as well as on demand bolus doses at mealtime. Insulin pumps offer an alternative delivery system to multiple daily injections in the management of insulin-dependent diabetes and for patients with frequent, severe or nocturnal hypoglycaemia.

A relatively new type of medical drug delivery pump is the piezoelectric micro pump. This type of pump offers a great alternative to standard pumps that have traditionally been used in precision-controlled drug delivery devices, such as infusion pumps, insulin pumps or nebulizers. Piezoelectric micro pumps offer the benefits of being small, lightweight, low power, low cost and accurate [20]. Micro pumps are now being used for applications such as transdermal insulin delivery [21]; antithrombogenic blood transportation, injection of glucose for diabetes patients, administration of neurotransmitters to neurons and for chemical/biological sensing.

DIFFERENT ASPECTS OF MATERIALS USED IN PRODUCTION OF ELECTRONIC DRUG DELIVERY DEVICES:

Biocompatibility [22]:

The above discussed various devices are going to interact with our body tissues directly so they must not be affected by our body's immune response i.e., their work of action should not get impeded by various adverse responses of our tissues. To mitigate these destructive issues biocompatible materials are used while producing these devices. Not all materials are equally biocompatible, in vitro studies according to the target site environment are conducted to evaluate the withstanding properties of the materials concerned. Some ideal characteristics of those materials are as follows: non-carcinogenic or not having cancer causing ability. Immunogenicity should be absent i.e.; recognition of an external factors should be absent which is capable of causing rejection. Teratogenicity should be absent i.e., birth defects causing capability Toxicity should be absent i.e., not having any inflammatory or toxic response in the body. Complete metabolization of medical implant is necessary after performing its function in the body. High mechanical properties. High corrosion resistance to resist the harsh body fluid environment.

Biosensors [23]:

Biosensors used in various devices that detect the presence or quantity of a bio analyte, such as biological products, metabolites, molecules ions or microorganisms, and generally comprises of an element that distinguishes the bio analyte and generates a signal, a signal transducer, and a readout as well as initiate a response to it. The biosensors employ conventional inorganic electrodes (e.g., platinum, platinum-iridium alloys, silicon) which are excellent electrical conductors, durable and chemically inert within the aqueous environments of the body and therefore do not interact with the surrounding tissues but such electrode/biological tissue interfaces can encounter major incongruities in terms of their chemistry or chemical interaction, electrical properties, and their mechanical properties. For example, stiff electrodes are unable to flex and stretch with the body which possess a major disadvantage as they can damage delicate tissues and initiate new stress dynamics to surrounding tissues. So, biosensors are designed in accordance with the physiologically relevant mechanical properties and display key characteristics, e.g., large electrochemically active surface areas, facile processing, and mixed electronic and ionic conductivity to enable interfacing with the ionic environment of the body. The electroactive biomaterials belong to an emerging generation of smart materials that transport charge carriers (i.e., ions and electrons) and are capable of transducing physicochemical signals of biological milieu into electrical signals and vice versa. This unique property has positioned electroactive biomaterials as superior electrodes for biosensing applications. These are specifically used in as an aiding component of microchips or electronic capsules, transdermal patches etc.

Edible batteries [24]:

All this electronic device requires power to operate. In general, electronic devices are powered by traditional batteries but in this case, it has become an obstacle as these will be used inside the human body. These batteries can increase the risk of toxicity. To mitigate this issue an edible battery is being used. In this battery melanin a natural pigment present in our skin is used as either the anode or cathode of the battery, with a second substance, such as the mineral manganese oxide or the benign metal magnesium forming the other terminal. All these melanin batteries are quite helpful in terms of its safety, but it has its limitations too like it can last only last up to 20 hours on the other hand lithium-ion batteries can last way more than that. With rapid technological innovation this will improve.

Advantages of Electronic Drug Delivery System:

1. Patients' adherence to drug dosages will increase which will ultimately increase the therapeutic efficacy.
2. Using electronic monitoring devices, the caregivers will be more accurate in their diagnosis.
3. Toxicity due to replication of dosages will be reduced drastically as the electronic devices will have the data for each dose already taken.
4. Patient compliance will increase through the use of digestible electronic capsules, transdermal patches etc.
5. Bioavailability of drugs can be increased through the use of electronic micropumps or transdermal patches as these routes are immune to hepatic fast pass effect.
6. By using electronic transdermal patches, the pain of getting injections can be reduced.
7. Through the use of ionophoresis we can use the transdermal method of drug delivery more effectively.
8. Microchips provide not only the remote drug delivery but also it provides real time data about the patients' health.
9. Digestible capsules can provide the drug delivery at specific location of digestive tract and at specific time without affecting the neighbouring tissues.
10. Electronic pumps help diabetic patients to manage their insulin dosing efficiently.

Disadvantages of Electronic Drug Delivery System:

1. Currently the technology associated with electronic drug delivery system is very expensive, so the devices are not produced in mass level which means the common people have a very little opportunity to use it.
2. Production of these devices requires special experts as well as specific machineries which requires a huge investment from the companies. This issue coupled with low monetary return is haunting the production of these devices.
3. Sometimes the materials used in implantable devices does not suit the individual which leads to compatibility issues and may show some adverse effects.
4. Electronics depends upon electromagnetic waves, circuits to work effectively which is prone to failure.
5. Remotely connected devices are prone to cyber-attacks which might endanger the life of individual who is using the device.
6. Implantable devices may trigger allergic reactions.
7. Sometimes invasive methods are required to put the device into patients' body.

FUTURE PROSPECTS:

The potential of electronic drug delivery system as a major mode of delivery is largely untapped. In the near future it can be the safest and most efficient mode of drug delivery with an absolute dominance over the healthcare system. All these devices will mitigate the limitations we have with the currently prevalent mode of drug delivery systems. Artificial Intelligence may be incorporated with those devices to make a customisable diagnostic data which can be used by caregivers for the most customised and efficacious mode of therapy. There is a great opportunity to build an individualized device having different drugs incorporated into it according to the need of the individual. This can be a revolutionizing step towards a more automated drug delivery. So electronic drug delivery system is indeed an optimistic mode of drug delivery which will lead to betterment of therapeutics.

CONCLUSION:

Currently, the issues of user adherence and self-management are key drivers in Electronic Drug Delivery System design. Ramifications of this technology can significantly improve human therapeutics. Drug delivery devices have transformed the course of therapeutic treatment in the medical field. They offer an advantage over systemic administration that performs sub optimally when a defined concentration of drugs is required for a prolonged duration. In a very short span of time, electronic drug delivery devices have provided promising therapeutic efficacy with minimal side effects. The recent advancements in Micro-electromechanical systems (MEMS) technology have played a pivotal role in miniaturizing the size of a drug delivery device by integrating components, such as batteries, electronics, processing unit, and tiny reservoirs within a compact space. And the components possess biocompatible, biodegradable properties which make these miniaturized electronic devices safest and most efficacious mode of drug delivery system. The story of implantable electronics has just begun, and a lot more is yet to come. Suffering patients look forward with great hopes and aspirations towards the emerging developments.

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