Novel Aspects of Drug Delivery: Wireless Electronic Devices

Berina Tatlić, Lejla Šejto, Merima Sirbubalo, Amina Tucak, and Edina Vranić

Abstract

A novel system of delivery presents many advantages such as sustained delivery, higher bioavailability, improved medication compliance, and therapeutic outcomes, patient monitoring, and minor side effects. One of the improved ways of drug delivery is electronic capsules which can deliver drugs to a specific site in the gastrointestinal tract and can also be used for patient monitoring. Wireless transdermal patches are a novel electronic drug delivery system, which is portable, disposable and worn on the skin surface to deliver medications on the transdermal level. Electronic transdermal drug delivery has made a major contribution to clinical practice due to improving the efficiency of drug delivery over the conventional route. The improvement can provide a solution for getting rid of the bondage of batteries as well as the restrictions of inconvenient wires, on self-powered systems. The greatest achievement of wireless transdermal patches is the ability to further improve transdermal drug delivery for certain drugs that could not be administered using conventional transdermal patches. Electronic drug delivery systems such as capsules, on the other side, can be used not only to deliver drugs to a specific site in the gastrointestinal tract but can also record data and report the state of patients gastrointestinal tract, and after excretion, this information can be studied and used to present them graphically.

Keywords

Electronic drug systems • Transdermal delivery • Wireless • Patch • Pill

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1 Introduction

Electronic drug delivery systems (EDDS) have recently become highly popular as they are effective in administering drugs at an exact time and maintaining effective doses; however, as effective as they are, their uses are limited as EDDS can't be applied to every body part. This method of drug delivery is painless. When the drug formulation is applied to intact skin it will be delivered systemically. The research has been conducted on transdermal drug delivery system. A transdermal way is considered to be one of the most convenient forms of drug delivery. This novel system of drug delivery presents many advantages over traditional delivery systems such as sustained delivery, higher bioavailability, improved medication compliance, and therapeutic outcomes, patient monitoring and minor side effects caused by drugs. Electronic drug delivery systems can reduce side effects by delivering targeted drug particular sites in the parts of the body that are difficult to reach. This way of treating the disease can also be a noninvasive alternative to parenteral routes. Transdermal route suffers from limitations due to low permeability governed by the skin. Further in this paper we will discus more about novel electronic drug delivery systems, specifically wireless transdermal patches and electronic capsules, their working mechanisms and advantages over conventional drug delivery [1–5].

2 Smart Pills

An electronic capsule is a drug delivery system which can deliver one drug or several different types of drugs to a specific site in the gastrointestinal tract (GIT) where it may normally be difficult to do, and can also be used for patient monitoring. It is made from a durable material resistant to GIT secretions and contains a pump, drug reservoir, battery, pH and temperature sensors, a wireless receiver and a

microprocessor. Patient monitoring is achieved through constant measurements of pH levels and temperature [1, 6]. Since the capsule is made from materials resistant to GIT secretions, drug effects will be delayed until it reaches it's designated place in the GIT, where the dose will be fully released, which allows easier prediction of therapeutic effects. EDDS have certain other advantages compared to conventional pharmaceutical forms—they are portable, interactive and wirelessly controlled via a computer or a smart-phone which allows drug in question to be administered by the patient. There are, some disadvantages to these devices—their manufacturing is extremely pricey, there is difficulty in achieving necessary biocompatibility and there are certain dangers when it comes to devising failure while the device is in use [1].

2.1 IntelliCap®

The IntelliCap® capsule (Fig. 1), developed by Dieter Becker et al. and manufactured by Medimetrics, is an electronic wireless drug delivery system which can be administered orally and is capable of delivering real-time information on physiological conditions such as pH value and temperature. This allows the researchers to be able to locate the capsule at any point in time by the typical physiological pH profiles in humans. When using this device, certain individual patient factors such as body weight are used in combination with pharmacodynamics of the drug to develop the best release profile possible [1, 8, 9].

The capsule itself is, in fact, a pump (Fig. 2). The power source needs to be small but has a long-lasting power

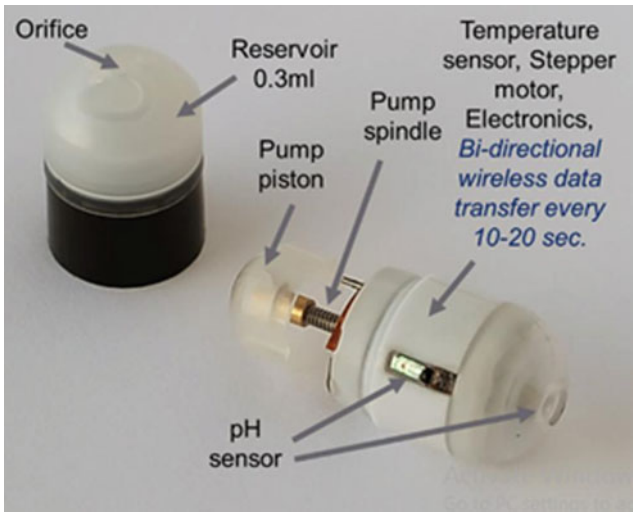

Fig. 1 Photograph of the IntelliCap® capsule (short version) [7]

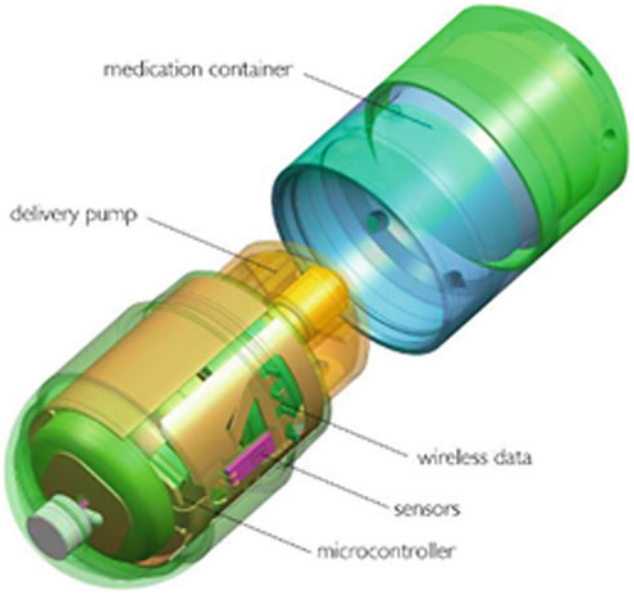

Fig. 2 IntelliCap® structure [1]

supply. Researchers from MIT have recently developed a device that when ingested, powers up using gastric acid, but since this device has been only tested on pigs, it has not yet been tested on humans or approved for human use. Sensors are used to collect environmental data of the capsule or device [7].

These can be pH sensors, pressure sensors, temperature sensors etc. and they must be made of biocompatible materials, so the device lasts as long as possible inside the body. Drug reservoirs are filled with a drug solution which flows through a system of channels modulated by valves and pumps. Electromagnetic propulsion technology with flow rates of 0.1–1000 ml/h supposedly improves the flow of drug solutions through and out of the device. The microprocessor is the most important part of this device. It is recommended to use processors with low power requirements in implantable and orally administered devices [7].

2.2 SmartPill®

SmartPill® is "an ingestible capsule that measures pressure, pH and temperature as it travels through the GI tract to assess GI motility" [1]. Other than assessing GIT motility, pH, and temperature, Smart-Pill can be used to determine a gastric emptying time, colonic transit time, total intestinal time and pressure. The capsule is minimally invasive and works via wireless technology. It should be ingested following a meal, after which measure values for pH, temperature and pressure

are transmitted to a receiver carried by the patient. This process is done until the capsule is excreted. Then the receiver is used to download recorded data to the SmartPill® software which expresses this information graphically and allows it to be used for diagnostic purposes [10].

2.3 Uses of SmartPill® and IntelliCap® So Far

The IntelliCap® system has been so far used in several studies as a tool to uncover the properties of drugs. In one of those studies, conducted in 2014 by Mauer et al., the IntelliCap® system was used to prove the ileocolonic release of ColoPulse® tablets.

The main goal was to prove in vivo that there was a connection between gastrointestinal pH and the release of the active substance in the ileocolonic area. Dual-label isotope strategy was used to study release from ColoPulse® tablets in 16 individuals who were healthy volunteers. They were each given a ColoPulse® specific-release tablet containing 13C-urea and a different, uncoated 15N2-urea tablet, which had an immediate release. After five minutes an IntelliCap® capsule was swallowed, followed by pH measurement until the elimination was completed (through the faecal route). It is important to note that release from ColoPulse® tablets occurred after a pH intestinal value of 7 was reached, regardless of how long it took the tablet to reach a said area, and this information was confirmed using the IntelliCap® system [8].

Also in 2014, two different studies used the IntelliCap® system in fasting human subjects with the goal of investigating pH and temperature profiles in the gastrointestinal tract. In this case, it was possible to measure gastric emptying time, intestinal transit time and how long it took the capsule to reach the colonic region, by measuring pH and temperature changes along the way. A high fluctuation of the pH values was discovered, ranging from pH 1.7 to pH 4.7. The values increased during the intestinal transit—to pH 5.9–6.3 in the proximal part and pH 7.4–7.8 in the distal parts of the small intestine. However, in the colonic region, those fluctuations were higher, varying from pH 5 to pH 8. These results can increase the comprehension of drug release from solid pharmaceutical forms taken orally while the patient is fasting [9].

The SmartPill® device has been approved for use by FDA since 2006 and has since been used in many studies and trials. In 2012, it was used to assess GIT function in patients with spinal cord injuries [1, 10]. In another study, it was used in combination with PillcamSB2 for patients suspected of having Crohn's disease [11].

3 Electronic Transdermal Patches

A novel electronic drug delivery system that is called electronic transdermal patches (Fig. 3) is portable, disposable and worn on the skin surface to deliver medications on the transdermal level. More functions are being integrated into devices that people can wear wherever they go. The main reason for developing such a delivery system is because convenient ways that need batteries can cause problems such as frequently charging as well as inconvenient to carry them. The improvement of self-powered systems provides a solution for wearable smart electronics to get rid of the bondage of batteries as well as the restrictions of inconvenient wires. These systems combine enhanced energy harvester and wireless transmission technology. The electronic transdermal patch usually contains sensors, memory, electronic circuits, and drug delivery components. They use data collected to determine when to deliver the drug which is stored within the patch. All of the stored data can be made available for downloading on the external source for patient monitoring and management [12, 13].

Design of the transdermal patches are usually contained of a reservoir where the drug is stored, that is enclosed on one side with an impermeable backing and has an adhesive that is in contact with skin on the other side. A reservoir can be liquid- or gel-based and the drug can be dissolved in those, which can simplify formulation and permit the use of liquid chemical enhancers such as ethanol. Hydrogel formulations are considered desirable because they can provide an electroconductive base with an added advantage of ease of application to adapt to the contours of the body.

Design of the transdermal patches characteristically is composed of four layers [13]:

- an impermeable backing membrane,
- a drug reservoir,

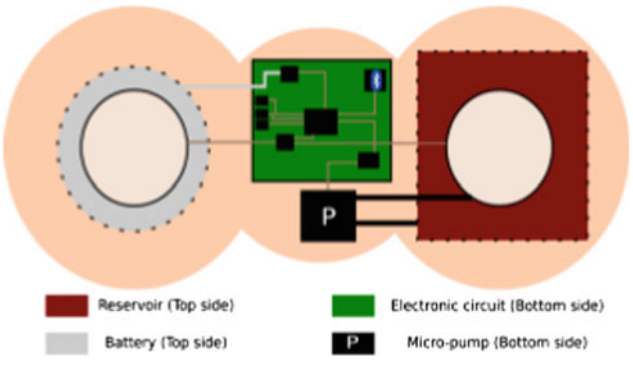

Fig. 3 Bottom view of the proposed patch (12 × 4 cm^2) [21]

- a semipermeable membrane (rate-limiting membrane) and
- an adhesive layer.

Other designs can incorporate drugs into a solid polymer matrix which simplifies manufacturing because matrix systems can have three layers by eliminating semipermeable membrane or just two layers if the drug is directly incorporated into the adhesive [13].

3.1 Physical Penetration Enhancement

The most of the transdermal patches that have been used in clinical are from:

- First generation of patches and in comparison with oral drug delivery, transdermal patches should be able to provide better bioavailability because of the need for not so frequent dosing of small, lipophilic, low-dose drugs.
- Second generation of transdermal delivery systems have some better preferences due to their ability to recognize that for the better expansion of drug is very important to enhance skin permeability. They have an advanced clinical practice. Because it has improved delivery of the small molecule [3, 4].

The ideal enhancer should increase the permeability of the skin is in the way that it would break the integrity of the *stratum corneum*. The enhancers that can be used are chemical, iontophoresis, and non-cavitational ultrasound [3].

- Third generation has made an impact on drug delivery because its effects are targeted directly to the *stratum corneum*. This can enable stronger disruption of its barrier and due to that a more efficient transdermal delivery of the macromolecules while still protecting other tissues with novel enhancers such as electroporation, cavitational ultrasound, and microneedles. And the main reason for enabling this advances to be made is that to make all aggressive approaches medically acceptable [15–20].

3.2 Active Methods for Drug Transport

There are certain technologies that are used to modify the barrier properties of the *stratum corneum*. The two major means of electrically-facilitated transdermal drug delivery systems are iontophoresis and electroporation. In electroporation, cells are temporarily exposed to high intensities of electric pulses that will lead to the formation of aqueous pores in the lipid bilayers of the *stratum corneum* which will allow the diffusion of drugs across the skin. On the other side, iontophoresis involves the application of physiologically acceptable electrical currents (0.1–1.0 mA/cm^2) to drive charged permeants into the skin through electrostatic effects and make ionic drugs pass into the body through the skin by its potential gradient. Iontophoresis has a minor effect on skin structure when compared to electroporation [14].

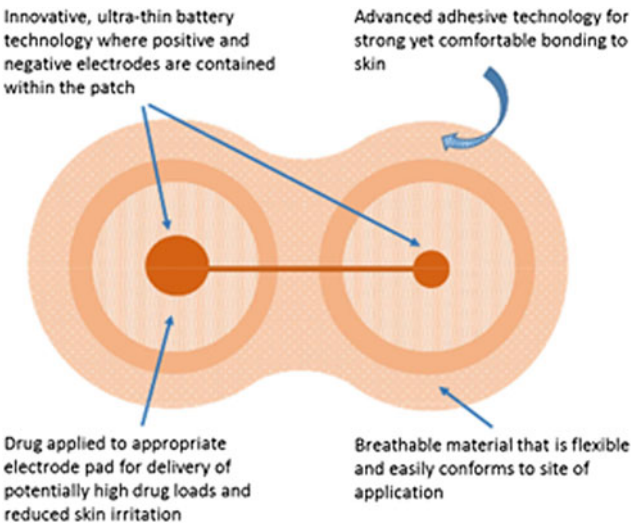

Fig. 4 WEDD® transdermal patch [1]

Ionsys® (Alza Corporation, Mountain View, CA, USA) was a second iontophoretic system that was approved by FDA in 2006. This was a fully integrated single-use iontophoretic system for the systemic delivery of fentanyl for fast relief of postoperative pain that is also patient controlled. But it was suspended by European Medicines Agency in 2009. Due to patch corrosion in one of the branches which could potentially lead to self-activation of the system with toxic over-dose [1, 13].

Wearable Electronic Disposable Drug (WEDD) (Fig. 4) is an example of noninvasive electronic transdermal drug delivery developed by Travanti Pharma a Teikoku Pharma Affiliate company and it is a portable and Disposable patch which uses low levels of currents to deliver medication transdermally. Combined with an ultrathin battery these electrodes are incorporated into the patch to give a single, self-contained disposable unit [1].

4 Conclusion

Over the past couple of decades, EDDS have become a highly popular way of administering drugs because of how efficient, reliable and simple to use they are. Wireless transdermal patches have the ability to further improve transdermal drug delivery by allowing for certain drugs to be administered that

could not be administered using traditional dermal patches. Their effect can further be improved by modifying the properties of the stratum corneum by using iontophoresis and electroporation. As opposed to patches, EDDS in the form of capsules or tablets can be used not only to deliver drugs to specific locations in the GIT, but also to record and report on the state of a patients' GIT (such as temperature, pH value, pressure etc.) and have recently seen a rise in development and production. Their advantage is the simplicity of usage upon ingestion, the device begins to send information to a wireless receiver. After excretion, this information can be gathered, presented graphically and studied.

Conflict of Interest Authors have no conflicts of interest to disclose.

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