Reveal All

Electronics and digital technologies continue to play an important role in healthcare – not least of all in oral drug delivery, where smart pills promise better outcomes, cost-effectiveness and more efficient ways to manage both health and disease.

Electronic technologies have an ever-increasing impact on our lives in all areas of society and commerce. While adoption in the healthcare sector has been slower than in most other areas, momentum is growing. Adoption brings promise for improved outcomes, reduction of errors and lower costs. One aspect of the Affordable Care Act in the US is a mandate to use electronic medical records. This mandate illustrates the difficulty of adopting new technology in a historically conservative industry. While electronic medical records are widely regarded as beneficial, resistance is high due to the concerns and interests of many inter-related stakeholders.

There are several advantages of electronic systems and devices. Among those are the ability to acquire, process and move information, the possibility of networking with other devices and systems, and the potential for adaptive control of actions, personalised execution and interaction with patients. Despite the many advantages, application in the pharmaceutical space has been limited. This is starting to change. As the industry endeavours to transform business models, focus more on outcomes and move closer to the patient, the role of electronics and devices is gaining attention.

A straightforward approach is to use a device for drug delivery. That is, use a device to store and administer a drug in a manner that is difficult or impossible to achieve by other means. This falls into the category of a drug-device combination product. A combination product has special considerations in development and approvals as it aims to combine a drug action, a device action, and the interaction of both to achieve the intended effect.

Consider, say, a programmable insulin pump for diabetes care. Products include the Medtronic MiniMed, Insulet Omnipod and Animas OneTouch Ping. These systems combine elements of a drug reservoir, insulin pump, blood glucose monitor and handheld management device. Delivery of insulin is adapted to the patient’s current blood glucose level and may be delivered on demand by the patient – for example, at mealtimes. Additional drug-device combinations using electronics include implantable systems, transdermal systems, and pulmonary systems.

Despite being the preferred administration route, there are few examples of devices for oral drug delivery. While the concept has existed for decades, only recently has the technology advanced enough to make an oral smart drug delivery pill feasible. The most recent development is the IntelliCap system, which is used as a drug development tool to explore the properties of a drug when delivered precisely in the gastrointestinal (GI) tract. By quickly evaluating the behaviour in specific regions of the gut, development times and costs are reduced. This tool can be applied to modified-release products, oral delivery of peptides and biologics, and formulations for compounds with low solubility. The next step in the evolution is custom-designed electronic pills for novel therapies and unique functions.

Smart Pills

A recent report from MarketandMarkets analysed smart pills technology, where a smart pill is defined as an ingestible capsule with miniaturised micro-electronics (1). The report describes a fast-emerging cross-platform technology market growing from $442 million in 2012 to an estimated $965 million by 2017. Main market segments are capsule endoscopy, patient monitoring and drug delivery. The first of these is the oldest and largest. A capsule endoscope is a swallowed camera pill that captures images of the intestinal tract and transmits data wirelessly to a recorder for later review by a physician. Capsule endoscopy was introduced in 2001 with the PillCam by Given Imaging.
It was a breakthrough product allowing convenient and accurate visualisation of the small bowel for the first time.

The success of capsule endoscopy established a precedent for swallowed electronics and led to the development of other smart pill systems. Several research and product efforts are underway, moving from diagnostics to patient monitoring and drug delivery. One novel development bridging both the monitoring and drug markets is the Helius system from Proteus Digital Health. This system embeds a tiny ingestible sensor into an otherwise standard oral drug product. The sensor responds to body conditions and reports information to a data capture unit worn by the patient. A primary application is to monitor compliance or adherence to a prescribed drug regimen. The adherence pattern may be reported to and analysed by a physician, caregiver, patient or others. Non-adherence is a tremendous problem and will become increasingly scrutinised in the era of pay for performance and as cost-effectiveness demands rise among payers. A 2010 report from the Center for Health Transformation cites an annual cost in the US of $290 billion – and approximately 125,000 deaths – attributable to non-adherence (2).

Within the smart pill market, the emergence and rapid growth in drug delivery and monitoring devices is anticipated. Precise control of the dose and location of drug delivery in the GI tract has several advantages. The ability to combine drug delivery with monitoring, reporting and adaptive behaviour of the capsule creates more effective treatments, enables novel disease management solutions, and reduces healthcare costs.

Electronic Tools

The IntelliCap system is an electronic oral drug delivery device (3). Today, the product is applied as a unique development tool for the targeted delivery of drugs within the GI tract. The system is built for flexibility of operation, enabling a variety of tests to be completed quickly and efficiently. It is, therefore, a tool applied in a controlled R&D environment, as opposed to a drug-device combination product intended for a specified therapeutic benefit.

The IntelliCap capsule incorporates a microprocessor, battery, pH sensor, temperature sensor, radio frequency wireless transceiver, fluid pump and drug reservoir. Figure 1 illustrates the construction of the capsule in two main subunits: the electronics body and the drug reservoir. The capsule measures 11 mm by 27 mm – the same dimensions as the capsule endoscope with its established use and safety profile. The capsule communicates via a wireless transceiver to an external control unit worn by the test subject. Real-time wireless data recording, plus wireless remote control of dose delivery, gives researchers the ability to monitor the capsule’s progress through the GI tract and direct the delivery profile in situ.

The capsule measures pH and temperature nominally every 10 seconds. This data is used to monitor the environment of the capsule and determine its transit properties, thus providing location information. There is typically a sharp rise in pH as the capsule passes from the acidic environment of the stomach into the neutral environment of the duodenum. Subsequently, there is a fall in pH as the capsule passes from the small bowel into the colon. Armed with the pH and location data, targeted delivery and analysis of regional absorption can be effectively completed within a pharmacokinetic (PK) study.

The drug release profile is fully programmable and may be adapted to the individual GI transit properties.
The flexibility of the system has allowed a wide variety of studies to be designed and performed. Examples include:

- Delivery of a solution and a suspension to the colon
- Delivery of a large molecule drug to the ileum
- Mapping absorption throughout the entire GI tract with a single zero-order release profile
- Characterisation of the exposure from a complex release profile

**System Capabilities**

In a recent study, properties of an extended release profile in male participants were examined, with the PK profile from a reference product compared to that produced with the IntelliCap system. Release from the reference – diltiazem HCl ER 60mg – was measured in vitro with a dissolution apparatus. This 24-hour drug release profile was then quickly programmed into the IntelliCap capsule and matching of the *in vitro* release was achieved. The reference commercial formulation and IntelliCap release were then evaluated clinically in a small number of healthy volunteers within a pilot bioequivalence study (4).

Sample data from a representative subject is shown in Figure 2. From the pH data (red), location in the stomach, small bowel and colon is determined. The drug release profile (green) and plasma drug concentration (blue) are then analysed along with the position data to gain insight into the absorption behaviour of the drug throughout the entire GI tract. By incorporating the individual location data, a much clearer picture of absorption behaviour is created and confounding factors from variable individual transit are successfully accounted for.

A common application of this technology is for the development of oral modified-release products. In particular, colonic absorption of a compound must be present to allow extended release. The tool allows rapid evaluation before committing time and resources to development of the solid oral dosage form.
In particular, colonic absorption of a compound must be present to allow extended release. The tool allows rapid evaluation before committing time and resources to development of the solid oral dosage form. By bringing this knowledge into the early development process, risk of later failure is reduced, better performance is achieved, and resources are committed only when results show a good chance of success. This approach is effectively applied beyond modified-release products whenever the GI environment or location impacts results. Understanding the behaviour throughout the small bowel is important with formulations for low-solubility drugs and those showing high variability of bioavailability. Peptide or protein drugs for oral delivery are often formulated to target and modify the environment in specific areas of the small bowel in order to enhance their uptake.

**Drug-Device Combinations**

The next step in the evolution of smart oral drug delivery is the development of therapeutic products based on drug-device combinations. The basic building blocks of the IntelliCap system can be configured for specific applications. A smart drug delivery pill promises to bring unique capabilities to treat disease and manage care in a personalised way.

Targeted topical drug delivery has advantages for the treatment of locally active diseases of the gut such as inflammatory bowel disease, intestinal cancers and irritable bowel syndrome. Topical delivery to the region of involvement only may reduce toxicity from systemic exposure. The region of involvement can vary from patient to patient and even within a patient over time. The programmable nature of an electronic pill allows the target site and dose to be personalised. In addition to site-specific drug delivery, the electronic pill may also incorporate biomarker sensors and report measurements from within the gut. Sensor measurements may be transmitted wirelessly and data integrated automatically into the patient’s health record for reporting, diagnostics and management of long-term treatment.

Electronic oral drug delivery offers tremendous opportunities to pharma and device companies. Firms that embrace these possibilities and move early into the field will enjoy the advantages of defining the space and regulatory path. Pharma is well-positioned to lead as the primary mode of action is usually due to the drug. Partnering or acquisition of device expertise and future data services is a real challenge and beyond the scope of most pharma companies. Yet alongside the difficulties is the potential to open up new business models and move the industry from sales of pills to improvement of outcomes and establishing a direct relationship with patients.

**Conclusion**

Electronic-based drug delivery promises to be a large and important area as healthcare begins to embrace digital technologies and interconnected systems. There are relatively few examples of electronically enabled drug delivery today. Typically, they exist as stand-alone systems where unique benefits can be realised.

Oral drug delivery does present many challenges, although the market for smart pills is emerging. One approach to bring this segment forward would be the further growth of flexible electronic delivery and monitoring systems to aid in drug development. Continued evolution of drug-device combination products offers significant opportunities for improved therapies and the means for pharma to establish new business models, while moving ever-closer to the patient.

**References**

2. Bexley D et al, The 21st century intelligent pharmacy project: the importance of medication adherence, Center for Health Transformation white paper, 2010

Jeff Shimizu is a pioneer of the IntelliCap drug delivery system, and co-founder and Chief Technology Officer of Medimetrics. He has a background in physics and optics. Prior to Medimetrics, Jeff worked with Philips Research for over 20 years in systems research and development. Research into medical devices led to the development of IntelliCap, an electronic drug delivery capsule. Medimetrics was formed to bring this technology to the market. Email: jeff.shimizu@medimetrics.com