Smart Pills for Oral Drug Delivery

A smart pill is an ingestible capsule with miniaturised micro-electronics. A smart pill for drug delivery may be used in a wide range of applications from use as a smart tool in drug development to a key element in a smart connected care environment. This emerging technology presents significant opportunity for the pharma industry to exploit modern digital innovations and take a lead position in the future of healthcare.

Introduction

It seems that there are smart products of one sort or another everywhere we look, with new devices and models constantly being introduced. One industry that has seemingly resisted the pull of “smart” products is the pharmaceutical industry. To be fair, the industry is an extremely smart one with a very high level of technological prowess. Yet products based on smart digital devices or application interfaces are few and far between. For the most part, the industry thinks in production of white powders and innovation strictly means discovering and developing new chemical entities. With increasing competition, reimbursement concerns, and expiry of blockbuster patents comes great pressure on the pharma industry and expiry of blockbuster patents comes great pressure on the pharma industry to exploit modern digital technologies that are transforming society. Making smart use of modern digital innovations promises to bring a revolution in healthcare.

One direction that pharma has necessarily embraced is a shift in focus from pills to outcomes. That is a move from the goal of pushing a drug through the approval stage, to creating therapies that improve health and offer a clear improvement over current practice. In this move to improved outcomes, there is recognition of the role of the many factors beyond the direct action of the drug. Two areas to consider are devices and technology. Those companies that can successfully combine the elements of drug, device, and technology to bring about better outcomes will be rewarded (Figure 1). Trends also to be considered are personalisation of healthcare, greater ownership by the individual, digital management of data, and drive to reduce overall cost.

Examples of the integration of a drug with devices and technology are growing. An application area that illustrates well the merging of these elements is the 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. Similar is the emerging area of wearable bolus injection devices. These devices serve a need to enable delivery of an injectable drug while freeing an individual from the care setting and reducing the overall cost of administration. While the present use of digital electronics is modest, the path towards greater exploitation of digital technology solutions is clear.

A prime area for development is a smart pill. The oral route of administration is by far the most preferred and meshes well with the need to have greater ownership of health management in the hands of the individual at home. While the concept of smart pills has existed for decades, only recently has the technology advanced enough to make an oral smart drug delivery pill feasible. Due to the many technical, business, and human factor issues present, the development path for the smart pill is challenging. Early products may use only a small part of the potential of smart systems but this will grow with increased experience and familiarity with such devices. As the technology matures, we will see a move from the smart pill as a smart tool in drug development, to smart devices for novel therapies, to a smart connected healthcare environment.

Smart Pills

A smart pill can be defined as an ingestible capsule with miniaturised micro-electronics. This is an area that is old in concept, established in some areas, yet nascent. A report from marketsandmarkets gives an overview of the smart pills technology market. The report cites a fast emerging cross-platform technology market growing from $442 million in 2012 to an estimated $965 million by 2017. Capsule endoscopy is an established market for diagnosis of intestinal conditions. A capsule endoscope is a swallowed camera pill that captures images within the body and transmits data wirelessly to a recorder for later review by a physician. Capsule endoscopy was introduced into the market in 2001 with the PillCam by Given Imaging. This was a breakthrough product allowing for the first time convenient and accurate visualisation of the small bowel.

Entering into the drug arena, there are a number of early examples from parties ranging from university research groups to start-up companies and large established device or technology companies. One development bridging 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 the compliance or adherence of a patient to a prescribed drug regimen. The adherence pattern may be reported to and analysed by the physician, care giver, patient, or others.

Drug delivery directly from a smart pill brings many advantages...
and opportunities for improved drug effectiveness, personalisation, and better management of disease and health. Past examples are largely mechanically-based solutions or research prototypes exploring system construction. An example of an electronics-based product is the IntelliCap system from Medimetrics.

Smart Drug Development

A smart drug delivery pill is controlled by electronics and has great flexibility and precise control in delivery location, release rate, and dose. At the same time it can monitor the local GI environment, report measurements in real time, and be commanded by an operator to perform an action on demand. This type of performance is impossible with conventional oral drug forms. While there are myriad therapeutic implications, the system can also be viewed from the direction of a smart tool that can be employed to great advantage in drug development of more conventional oral drug products.

The IntelliCap system has the capability to house a drug formulation, protect it from the gut environment, and release it in a targeted location with a bolus release or extended release pattern. Such is essentially the target of modified release (MR) technology. With conventional formulation approaches, the performance in vivo often does not meet the desired target and is at the same time highly variable. This ends up in failed studies, re-formulation attempts, costly delays, and abandonment of projects. Often there is a lack of full understanding of the behaviour in specific regions of the GI tract and a lack of ability to release drug as desired. To address these difficulties we can apply the smart pill to act as a smart tool. This tool in turn is used to craft a smart drug development process, saving time, putting resources to more efficient use, and uncovering novel products. Since experiments can be designed and performed quickly, a more systematic approach may be employed, creating a deeper understanding of the drug properties. This is typically explored within a pharmacokinetic (PK) study where a delivery profile is designed to determine the bioavailability in specific regions. The resulting data leads to a better model, so that the delivery target and formulation may be improved, thus resulting in optimised performance.

One of the basic questions for extended release development is whether the compound has sufficient absorption in the colon. This can be quickly determined with a regional delivery study. The IntelliCap FR system may be used to house the drug, track transit until the capsule reaches the colon, and then release contents. An example from such a study is shown in Figure 3. The advantage of using the smart tool is that the release location in each subject is reliable despite a wide variation in GI transit time. Another common question is whether the drug has an absorption window. Or, related to this, what is the absorption throughout the entire GI tract. This may be determined with an absorption window mapping study. For example, the IntelliCap CR system may be used to create an extended zero-order delivery profile starting from the duodenum and extending throughout the small bowel and into the colon. The regional transit times from each subject are measured and this information is used to further analyse the data. PK and transit data are incorporated into a modelling program such as GastroPlus or SimCyp, to de-convolve the data and determine absorption at a finer level. An example is shown in Figure 4. The advantage of this approach is that the entire GI tract can be probed in a single study and a more sophisticated model created. Armed with knowledge of the regional absorption behaviour and a detailed simulation model, an optimised release profile is determined. In a process of rapid formulation prototyping, a smart pill system is used to program a desired release profile for testing in vivo before undertaking more lengthy formulation development.
It is clear that the use of enteric delivery has application beyond the traditional goal of modified release products intended to reduce dosing frequency. It has long been a goal to achieve oral delivery of larger molecule drugs such as proteins, peptides, antibodies, or vaccines. The oral route of administration is by far the most preferred due to convenience, cost, and patient acceptance. There are various strategies to enable oral delivery of macromolecules such as micro-particle formation, permeation enhancers, encapsulation, receptor targeting, and uptake by antigen sampling cells. The solutions are typically a combination of advanced formulation and location targeted delivery to the small bowel or colon. The smart pill provides a ready solution to test and prove concepts quickly through accurate and repeatable delivery of the test formulation to the target site in the intestinal tract. Thus delivery concepts can be validated early before undertaking more complex dosage form development. In a similar way, concepts to improve solubility of compounds may be tested and validated in vivo. A large fraction of compounds in development today face solubility problems and significant effort is applied to enhancing the bioavailability of these compounds. Typically the local pH and release concentration at the site of absorption are critical elements. Thus, it is just a matter of time before controlled release dosage forms for compounds requiring solubilisation become important.

**Smart Healthcare**

While the smart pill is put to effective use today as a tool for smart drug development, the full potential of the technology may be realised in creating innovative new therapies and as a key element in a smart connected care environment. The combination of functions available from a smart pill enables therapies not possible by conventional means. For example, targeted topical drug delivery has advantages for the treatment of locally active disease of the gut, such as inflammatory bowel disease (IBD), intestinal cancers, and irritable bowel syndrome. Topical delivery only to the region of involvement can reduce toxicity from systemic exposure. The region of involvement can vary from patient to patient, and within a patient over time. The programmable nature of an electronic pill allows the target site and dose to be personalised. Going beyond intestinal diseases, the unique features of an electronic delivery pill may be used more widely. Delivery based on time of day can be beneficial. For hypertension or Parkinson’s disease, there is benefit to establishing a base level in the morning, for example, by starting delivery one hour before waking. In areas such as pain or oncology, individual titration and delivery upon user demand can be put to effective use.

The combination of a drug with a device is by definition a combination product as viewed by regulatory authorities. A combination product must be considered separately as a drug, as a device, and in combination. The primary mode of action determines which area takes the lead in review and approval. While there are added difficulties in bringing a new combination product to market, the pioneer will enjoy a strategic advantage by defining the space and the regulatory path. Pharma, as opposed to the device industry, is well positioned to lead as the primary mode of action is usually due to the drug. Furthermore, a new combination product provides opportunities for extended patent protection of a compound as well as a creating a barrier to competitors that do not have access to the required device technology.

So far, we have focused primarily on the delivery capabilities of the pill itself. But a smart pill has the ability to perform much more broadly and become a key element of a larger connected care environment (Figure 5). Consider the use of on-board sensors for measurement of biomarker levels where data is transmitted wirelessly and integrated automatically into the patient’s health record for reporting, diagnostics, and management of long-term treatment. The innovative use of technology and connected devices promises to improve outcomes, empower the patient, and lower healthcare costs. As outlined well by Eric Topol, “The near future of health care will be revolutionized by two important critical factors, technology and consumerism”.

Pharma is well-positioned to become a key player and stands to benefit greatly by defining and executing a digital strategy in this emerging area. Herein lies an opportunity for the industry to move towards the centre of patient care and become a key interface to the patient. Let the era of smart healthcare begin.

**Figure 5**

![Figure 5](image)

**References**

3. van der Schaar, P.J. et al., Gastrointest Endosc 78(3), 520-528 (2013).

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