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News & Highlights

A Smart Pill for Insulin?

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Diabetes remains a substantial—and growing—public health problem, afflicting almost 10% of the US population (~30 million people) and a similar percentage in China (~110 million), with the latter number expected to increase to 150 million by 2040 [1,2]. Meanwhile, the basic treatment for diabetes has also largely remained unchanged, with most patients still facing the daunting ordeal of regular daily injections of insulin. Because of the significant burden this represents, and the clinical benefits that might be achieved with a more patient-friendly solution, finding a non-injectable alternative to deliver insulin has long been a holy grail for drug developers.

The oral route for drug delivery is preferred by patients and physicians, but it poses challenges for the effective delivery of drugs of large molecular size, including most of the proteins, like insulin, enzymes, and antibodies that make up an increasingly important share of the modern pharmacopeia. The human gastrointestinal (GI) tract, with its complex topography and brew of acids, enzymes, and bile, is inhospitable to many large molecules, which in unprotected forms are chemically destroyed or pass through the body unabsorbed. Anxious over the prospect of injections, diabetic patients can sometimes delay treatment by seven-to-eight years, said Giovanni Traverso, a research affiliate at the Massachusetts Institute of Technology (MIT) and an assistant professor at Harvard Medical School in Boston, Massachusetts, USA. Past and continuing efforts to develop non-injected insulin have focused mostly on nasal sprays and inhalers. None of these have yet proved entirely satisfactory, although the US Food and Drug Administration (FDA) approved the inhaled insulin Afrezza® in 2014. Developed with much anticipation by MannKind Corporation, the drug does not replace injected long-acting insulin and has had limited commercial success [3].

Now, groups led by Traverso and MIT Professor Robert Langer, winner of all three of engineering's big prizes, the Charles Stark Draper Prize, the Queen Elizabeth II Prize, and the Millennium Technology Prize, for his earlier work on drug delivery, have reported an innovative new pill design for the oral delivery of insulin [4]. Inspired by the self-orienting shell of the leopard tortoise, the team engineered a protective capsule composed of polycaprolactone and high-density stainless steel (Fig. 1). Like the tortoise shell, the capsule has a center of gravity that causes it to self-orient. Inside the capsule sits a small, stainless-steel-spring-loaded 7 mm-long tip, composed of insulin and polyethylene oxide, which is, in turn, connected to a biodegradable sugar shaft. Once swallowed, the capsule rights itself with respect to gravity and settles on the stomach lining. The shaft then biodegrades, causing the spring-loaded tip to plunge into the stomach wall, thereby injecting a dose of drug (this is painless, because there are no pain receptors in the stomach lining). Once the shaft completely dissolves, the pill releases from the stomach wall and continues through the gut to be eliminated with the feces. Study results showed the pill/device hybrid, which could potentially be used with other sensitive molecules besides insulin, worked well in pigs.

Fig. 1. Researchers at the MIT designed this prototype pill/device hybrid—inspired by the shell of a self-orienting turtle—to deliver insulin by the oral route by injecting it directly into the stomach wall. Credit: Felice Frankel, with permission.

While a promising development for diabetics worldwide, the use of such smart pills has precedents both good and not so good. Experience with other pill/device hybrids suggests that the road to the clinic could be long. Researchers have for decades explored gastroretentive pills intended to remain safely in the stomach and gradually release drugs over days or weeks using different methods including bioadhesives, pills that float on the surface of gastric juices, hydrogels, and expandable geometric shapes [5]. However, all of these approaches have yet to progress to the clinic, in large part because the animal models used—frequently pigs—have digestive systems that differ substantially from the human gut, with different fasting motilities, pHs, and geometries and folds, said Werner Weitchies, a professor of pharmacy at Greifswald University, Germany. In the last 30 years, researchers have

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designed capsules that expand into discs, rings, multi-armed stars, and other shapes that unfold in the stomach, and gradually release drugs over time. But while animal tests have shown some success, a human test of a tetrahedron-shaped device failed in the early 1990s [6]. Since then, efforts have been made to overcome the animal-to-human translation issues, including, for example, developing an elastic supramolecular polymer gel that safely disintegrates inside the stomach [7], and adjusting the gastric pH in animal models to more closely match that of humans. But to really move this technology forward, Weitschies said, researchers may need to design pill/device hybrid that can be safely and ethically tested in humans from the start. "The only model for a human is a human," he said.

On the other hand, one pill/device hybrid has proved quite successful, although no drug is involved. First approved by the US FDA in 2001, the PillCam® and related "capsule endoscopy" devices contain miniature cameras that capture images of a patient's gut as they travel from one end to the other (Fig. 2), enabling examination of areas not easily reached by conventional endoscopy of colonoscopy [8]. Powered by miniature batteries, microwave transmitters send images to an external receiver. Though scientists had envisioned swallowable cameras since the 1950s, it was not until 2000 that miniaturized charge-coupled device camera technology allowed electro-optical engineer Gavriel Iddan, then at Israel's Rafael Armament Development Authority, and gastroenterologist Paul Swain at the Royal London Hospital, to realize the concept.

Iddan founded the company Given Imaging to market the PillCam, since used in more than 1.7 million procedures [9] and now marketed by the global medical device company Medtronic, which purchased Given Imaging in 2015. Although PillCam remains the leading capsule endoscopy device with 95% of the market [9], other companies, including Chongqing Jinshan Science & Technology Co., Ltd., Olympus Corporation, CapsoVision, Inc., Medimetrics, and IntroMedic Co., Ltd., now also manufacture GI imaging capsules, which vary primarily in technical specifications involving data transmission and memory and image processing.

Medical engineers envision continuing to expand the capabilities of endoscopic capsule technology, with the goal of replacing even more GI invasive procedures, including possibly biopsies. For example, Piotr R. Slawinski, a graduate student in mechanical engineering and his colleagues at Vanderbilt University in Nashville, Tennessee, USA, are exploring the use of magnets to control the speed and direction of the capsule's path. Normally, peristalsis—the muscular contractions of the esophagus, stomach, and intestines—drives the capsules through the gut, but the movements of a magnetic capsule could potentially be controlled by an external magnet [9].

Progressing from the "smart capsule" to the "smart capsule + drug" is a real challenge, but one that might finally yield to an engineering solution. In any case, other intensive research efforts are on-going to develop improved monitoring and implantable or patch insulin pump technologies that can act as an "artificial pancreas" [10], as well as novel medical and genetic interventions that might address and possibly reverse the underlying autoimmunity thought to cause diabetes [11–13]. How insulin-delivering pills might fit into this bigger—and increasingly brighter looking—future picture for diabetics remains to be determined.

Fig. 2. The PillCam is one of many wireless endoscopy devices now available as an alternative to many conventional invasive GI procedures. The capsules contain tiny batteries and cameras that enable transmission of gut wall images to an external receiver as the device travels through the gut. Credit: Medtronic 2017.

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