Medtech Insight
Pharma intelligence

Market Intel: Robotic Pills And The Future Of Painless Drug Delivery

13 Sep 2018 I Analysis

By Bob Kronemyer

bkronemyer@frontier.com

Executive Summary

Robotic pill technology, which is already being used for diagnostic purposes, will likely be embraced for the oral delivery of biologic drugs as well. Biologic therapies currently require injections in most cases, but some are exploring specialized robotic pills as a pain-free approach that could increase convenience and compliance, and thus efficacy, of medicines. Several established companies and research centers are working on both diagnostic and biologic therapeutic applications of pill-based technologies.

The simple act of swallowing a pill or capsule is one of the most common ways by which people interact with the health-care system on a routine basis. Medtech innovators are looking to take advantage of that simplicity to improve how medical therapies and diagnostic assessments work.

By adding robotic or smart elements to a pill formulation, it offers the opportunity for less invasive therapies, better patient compliance and easier diagnosis for some conditions. Multiple companies and researchers are developing or already marketing robotic pill technologies designed to meet these goals.

RaniPill Seeks Oral Delivery Of Biologics

One person focused on this area is the prominent medtech inventor and entrepreneur Mir Imran, who has founded more than 20 life-sciences companies and is known for his pioneering contributions to the first US FDA-approved automatic implantable cardioverter defibrillator.

Imran runs the life-sciences venture funds InCube Ventures and Venture Health, and one of his latest projects to come out of the InCube Labs incubator is the San Jose, Calif.-based Rani Therapeutics LLC, which is working to develop robotic capsules to delivery biologics orally. Leveraging Imran's background and understanding of medical devices, Rani developed an ordinary-looking pill that is swallowed by the patient.

“The technology, to me, is secondary in importance to the overall goal of achieving oral delivery of biologic drugs,” said Imran, who is CEO of Rani Therapeutics. The company plans to start the first human study of the robotic *RaniPill* capsule next year. The study is designed to compare the RaniPill to standard subcutaneous injection of octreotide to treat acromegaly, a hormonal disorder that increases bone size by producing an excessive amount of growth factor.

“Biologic drugs are protein-based drugs like insulin and adalimumab (Humira) to treat chronic diseases," Imran told *Medtech Insight*. "Currently, patients have to inject themselves, as these drugs are not available to be taken orally. Achieving oral delivery of biologics is considered the holy grail of drug delivery.” Pharmaceutical companies have attempted to convert injectable drugs into pills without success for more than 50 years, Imran noted.

“Achieving oral delivery of biologics is considered the holy grail of drug delivery,” says Mir Imran, founder of Rani Therapeutics.

“We hope to show that absorption of the oral drug into the bloodstream is similar to or better than absorption by subcutaneous injection or an intravenous injection," he explained. Study results are expected to be released in the first half of 2019.

Once swallowed, the robotic pill travels through the stomach and enters the small intestines where it goes through a transformation and positions itself to inject the drug, via tiny needles made of sugar, into the intestinal wall. A major advantage of injecting a drug into the intestinal wall is that, unlike injecting through skin, patients don't feel pain.

“Because the intestinal wall lacks sharp pain receptors, the RaniPill capsule provides a completely pain-free injection,” Imran explained.

Pills can also significantly increase patient adherence to therapeutic regimens compared to injections, which are administered as frequently as twice daily to as

little as once every other week. Currently, some patients will skip their subcutaneous injections, because they do not like needles.

“Given the choice between pills and injections, patients will always choose pills,” Imran said. “We believe that for a number of biologic drugs, the pill form will be taken once a day.”

Generally, drug absorption from oral medication is actually slightly better than with a subcutaneous injection, Imran said. Further, he said, the oral drug is protected and not compromised by the digestive enzymes.

“In essence, the RaniPill capsule is a novel approach leveraging the anatomic and physiologic characteristics of the intestine,” Imran said. He believes that Rani’s technology can be used to deliver most of the current biologic drugs. The company has already shown that its robotic pill can deliver insulin for diabetes, Humira, and other similar biologics for rheumatoid arthritis, psoriasis and Crohn’s disease.

Over the past years, Rani has also been conducting pre-clinical studies of the RaniPill capsule using drugs from pharma partners including Novartis AG and Shire PLC. Rani is currently testing Shire’s Factor VIII, an injectable hemophilia drug, on its oral platform. Rani is also setting up a more automated manufacturing process for the RaniPill capsule, as it prepares for clinical trials.

Since Rani was founded in 2012, it has raised about $140m in funding to develop robotic pills. Key investors are InCube Ventures, Google Ventures, Novartis, AstraZeneca PLC and Shire, plus several unnamed private equity groups. Rani’s latest financing round was a $53m series D that closed earlier this year.

“If successful, robotic pills like the RaniPill capsule could positively impact hundreds of millions of people worldwide,” Imran said. “We are preparing for human studies with a number of molecules, and once approved, we expect that robotic pills will become the common way for patients to take some of these biologic medications.”

Jeremy Sohn, global head of Digital Business Development & Licensing for Novartis, said his company invests a meaningful percentage of its development operating budget to explore cutting-edge technologies like robotic pills.

“Our underlying objective is to develop the best drugs that we can for patients,” Sohn told Medical Insight. “And we believe that often times part of having the best drugs includes understanding the optimal delivery models for those drugs.” One of the major drivers for Novartis, which teamed up with Rani in 2015, is to make it easier for patients to take drugs, and allow patients to become more adherent, so they can receive the full value of the drug.

“We have a lot of optimism about our collaboration with Rani,” said Sohn. He declined to say which Novartis drugs will be incorporated into the RaniPill capsule. “If successful, this is more of a platform partnership as opposed to a specific indication," Sohn said.

Abilify MyCite And A New Era Of Pill Sensors

Novartis was also one of the first investors in and partners of Proteus Digital Health Inc. Last November, Proteus became the first company to receive FDA approval for digital ingestion tracking system incorporated with a drug, *Abilify MyCite*. ((Also see "Market Intel: Nanorobots, Digital Tracking, Dose Printing: Innovative Drug Delivery Systems Will Make Precise Drug Dosing A Reality" -

Medtech Insight, 18 Dec, 2017.)) The systems combines the antipsychotic drug aripiprazole, used to treat schizophrenia and other mental disorders, with a sensor.

“This is an example of technology embedded inside a pill to improve patient outcomes,” Sohn said. “Physicians and patients can make more appropriate treatment decisions, based on the sensor information.” The ability of robotic pill technologies to improve the biologic effect or the body’s response to a drug – for example, by being able to deliver a continuous dosing regimen – is an attractive proposition to Novartis.“These technologies may also allow us to more safely deliver more drug by always remaining in the optimal response range,” Sohn said.

Similar to glucose monitors and an artificial pancreas, robotic pills could measure the body’s current state in real time, and then provide a real-time dose based on that measurement, Sohn said. “That kind of continuous feedback loop might reduce adverse events and improve outcomes,” he said. “These novel drug delivery approaches could also reduce patient burden and improve the patient experience.”

Going forward, Sohn expects more investment in robotic pills and novel drug delivery technologies by drug companies, venture funds and, eventually, later-stage private equity funds as these technologies are further validated and people feel more comfortable with them.

Blockbuster Potential

Virtually all currently FDA-approved robotic pills are used to diagnose disease via capsule endoscopy, said Shailendra Gaikwad, a senior research analyst and team leader at San Francisco-based Grand View Research Inc.

The research firm expects worldwide robotic pills revenues to increase from $587.6m in 2017 to $1.98bn by 2024. Proteus' Abilify MyCite had sales of $185m in 2017, according to Grand View Research. In short, diagnostic robotic pills constituted 85.7% of the global market share in 2017, compared to only 14.3% for therapeutic robotic pills.

"Technology has been transforming the field of medicine with the largest changes being witnessed in diagnostic settings," Gaikwad told *Medtech Insight*. "The ability to detect and diagnose a disease in the least available time has become the norm."

The rising incidence of chronic diseases such as diabetes and cancer worldwide is the chief reason for the development of such cutting-edge devices, Gaikwad said.

"Early detection and prognosis aid in better treatment and management of diseases, facilitated through the use of these robotic pills," said senior research analyst for Grand View Research Shailendra Gaikwad.

Non-invasive capsule endoscopy systems can diagnose gastrointestinal (GI) diseases such as irritable bowel syndrome (IBS), Crohn's disease, obscure gastrointestinal bleeding (OGIB), abdominal pain, diarrhea, constipation, tumor detection and hyperproteinemia (high blood protein).

“Early detection and prognosis aid in better treatment and management of diseases, facilitated through the use of these robotic pills,” Gaikwad said. Likewise, for treatment, the advent of minimally invasive technologies allows many procedures to be performed with reduced scarring, bleeding, hospital stays and smaller incisions, coupled with minimal anesthesia.

“Technology is being used in collaboration with robotics to administer biologics for a wide range of diseases,” Gaikwad said. He added the rising incidence of diabetes, arthritis, psoriasis, cancer and mental illnesses, including depression, bipolar disorder and schizophrenia, "has been creating a huge demand for novel drug-delivery devices."

Monica Waghmare, senior research associate at Grand View Research, also underscored Imran's point that using robotic pills for treatment enhances patient compliance and adherence. They effectively administer biologics, “which are typically destroyed by gut enzymes, if delivered via typical oral therapeutics," she said. The RaniPill capsule could be a game-changer in the field of drug administration, by transforming how patients consume drugs, she said.

Similarly, Abilify MyCite “aids in mediation ingestion and records tracking data that helps individuals with mental illness to adhere to medication and monitor compliance,” she said. “Such technological innovations are anticipated to potentially change drug administration in the near future by being extremely patient-centric and offering utmost ease during drug administration."

An Origami Robot

Technologically, according to Daniela Rus, director of the Computer Science and Artificial Intelligence Laboratory (CSAIL) at Massachusetts Institute of Technology (MIT), there is a need for small, controllable, untethered robotic pill systems. To address this need, Rus' research team has developed an "origami" robot in pill form that unfolds in the body once it is released from a capsule.

“It is really difficult to control and place a robot inside the body if the robot is attached to a tether, and we wanted to find a way to get around this,” said Daniela Rus, director of Computer Science and Artificial Intelligence Laboratory at MIT.

“It is really difficult to control and place a robot inside the body, if the robot is attached to a tether, and we wanted to find a way to get around this,” she said.

Rus’ research team had to sufficiently compress the robot, made of biocompatible material, so it could fit inside the capsule swallowed by a patient. Similarly, when the capsule dissolves, the forces acting on the robot had to be strong enough to cause it to fully unfold. “Through a lot of trial and error, we created a rectangular robot with accordion folds perpendicular to its long axis, and pinched corners that act as points of traction,” Rus said.

Rus believes that removing foreign objects in the body and patching wounds are the two most promising applications for robotic pills. For example, every year, 3,500 swallowed button batteries are reported in the U.S. alone. “Frequently, the batteries are digested normally, but if they come into prolonged contact with the

tissue of the esophagus or stomach, they can cause an electric current that produces hydroxide, which burns the tissue," said Russ. For removing foreign objects, after the robot reaches the stomach it would unfold out of the capsule and be moved and steered by magnetic fields. "In laboratory tests, our robot was able to latch onto a button-battery with its own magnet, and then be guided toward the intestines to be excreted," Rus explained.

Before starting clinical trials, researchers need to assess the safety of the origami robot for long-term biodegradability and ensure that the body can remove the foreign object or discharge it. The investigators are also considering adding sensors to the robot and testing it in living animals. One drawback of the robot is that the magnet does not dissolve. In preliminary testing, a neodymium magnet with a low-to-moderate acute toxicity level was employed. In future work, Rus plans to use a specially treated biocompatible magnet in the robot.

Colorectal Cancer Screening Advances

Two important players in the diagnostics space for robotic pills are Israeli companies Check-Cap Ltd.. and Given Imaging Ltd., part of Medtronic.

Check-Cap is developing *C-Scan*, an ingestible capsule system for colorectal cancer screening. The device gained Israeli approval for colorectal cancer screening earlier this month. ((Also see "Global Device Approvals, Weekly Snapshot: Sept. 3-9, 2018" - Medtech Insight, 10 Sep, 2018.))

Check-Caps device employs innovative, ultra-low dose X-ray and wireless communication technologies. The capsule gleans information on the contours inside of the colon as it passes through the body. The information collected is

used to create a 3D map of the colon for detecting polyps and other abnormalities.

C-Scan could remove the the need for laxative bowel preparation and sedation, and is less invasive than standard screening techniques, Check-Cap says.

Given Imaging is a pioneer in video capsule technology with its *PillCam* system, which has been upgraded throughout the years. ((Also see "News Briefs: PillCam Colon Clearance; CGM For Pediatrics; SGR Reform Bill" - Medtech Insight, 10 Feb, 2014.)) The system embeds a camera inside a capsule that captures images at a frame rate of two to six frames per second, based on capsule speed as it travels through the small bowel.

David Zarrouk, an assistant professor and head of the bio-inspired and medical robotics department at Ben Gurion University of the Negev in Beer Sheva, Israel, who has no affiliation with Given, explains how the technology works. “PillCam allows internal photos of the small intestines, which is considered a dark area in the body,” said Zarrouk. “The capsule advances by the peristaltic motion of the intestines. As such, its voyage takes about eight to 10 hours, but it cannot stop at a desired position.”

“PillCam allows internal photos of the small intestines, which is considered a dark area in the body,” said researcher David Zarrouk.

Zarrouk is working to develop more advanced robotic camera pills. He said a robotic camera pill would allow a physician to control both the position and speed of the robot.

“The procedure would be performed in real time and takes between one and two hours,” Zarrouk said. “The physician can also stop the robot at specific places for further inspections and diagnostics.”

Ultrasound or X-ray will be able to pinpoint the position of the targeted area by stopping the robot at a specific location and finding it. A robotic pill could be used to perform simple procedures such as biopsies and targeted drug deliveries as well.

Zarrouk initially focused his research on understanding the mechanics of locomotion of miniature robotic systems crawling inside biological vessels. “This type of crawling is extremely challenging because vessel surface is very flexible and slippery,” he said. “Robots tend to slide a lot or stick in their place, without moving relative to the flexible surface.”

More recently, Zarrouk’s research team has focused on developing a snake-like bioinspired robotic system, which produces a wave motion. “As of now, we believe that the wave-like motion is the most promising of all for robotic pills,” he said. Zarrouk's research team is currently developing a miniature version of a wave-like robot, which will incorporate a camera.

“We have already shown a robot successfully crawling inside tube-like, highly flexible surfaces and have started performing ex vivo experiments on the intestines of a pig,” Zarrouk said.

“In preliminary experiments, the robot has succeeded in crawling inside the intestines. We are now learning more about its speed and reliability.”

Zarrouk hopes to raise enough funding to start a company to further miniaturize a robotic pill and perform more realistic experiments. But safety is key.

“Obviously, we must make sure that the robot is properly designed to avoid breakage inside the intestines; otherwise, surgery may be required to remove the robot,” he said.

NaviCam And The Cartwheeling Capsule

NaviCam, developed by Ankon Technologies Co. Ltd., stands out in that it uses sophisticated low-power magnetic control technology.

The company, with offices in Shanghai, China and California, developed a NaviCam capsule for the stomach that received a European CE mark in 2013 and is pending FDA clearance. After the patient swallows the capsule, the practitioner controls the capsule from a console next to the patient. A preset magnetic program activates a “shoot” button on the joystick, which causes the capsule to cartwheel proximally over the rugal folds to a selected proximal location.

A recent seven center, 350-patient study by Zhuan Liao, published in Clinical Gastroenterology and Hepatology, concluded that NaviCam detects focal lesions in the upper and lower stomach with comparable accuracy to conventional gastroscopy. The device is also preferred by almost all patients, compared with gastroscopy, and can be used to screen gastric diseases without sedation, according to Zhao-Then Li, director of the Department of Gastroenterology, Changhai Hospital, Secondary Medical University in Shanghai, China.

“The ability to add control to a device ingested by a patient holds infinite promise to enable less invasive methods to many existing procedures,” Kevin Rubey, chairman of Ankon’s advisory counsel, told Medtech Insight. “Our technology is very patient-friendly.”

Devices in general that are controlled from outside the body “open up a whole new arena for the diagnosis and treatment of many GI diseases in a way that is much more comfortable for many patients,” Rubey said. Ankon has other diagnostic capsules in various stages of development for small bowel, colon and constipation, among other indications. While the use of robotic pills is gaining increasing attention, they aren't without risk, noted Gaikwad.

Challenges Ahead

Novel devices always face the risk of low adoption rates and acceptance among patients,” Gaikwad cautioned. “But because these robotic pills are noninvasive in nature, they are receiving increased demand by acting as substitutes to invasive forms of disease diagnosis and treatment.”

For instance, a routine colonoscopy costs about $3,000 in the US, which compares to about $500 for a capsule endoscopy, she said.

“The only drawback associated with these robotic devices is the risk of capsule retention, abrasion or irritation in patients,” Gaikwad said. He added that while the concept of a robotic pill is relatively new, much research has been devoted to testing the efficacy of these devices in patients. And as for any specific regulatory hurdles, he said, there are none.

“The advent of robotic pills has had a substantially positive impact on the medical vertical with several advantages being offered by their usage,” Gaikwad said. “Early diagnosis offered by these devices is crucial in disease management. Drug administration through robotic pills is also expected to garner widespread attention, owing to its ease of biologics dosage.”