MIT reveals new pill to deliver insulin

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By Dina Patel, freelance journalist

Taking inspiration from the leopard tortoise, an MIT research project sponsored by Novo Nordisk is aiming to deliver insulin orally with a pill that releases its medicine in the stomach lining, removing the need for injections. Dina Patel speaks to the lead author of the paper and MIT Chemical Engineering graduate student Alex Abramson and Ester Caffarel-Salvador, Postdoctoral Research Associate at MIT.

WHY DO WE NEED TO DELIVER INSULIN ORALLY WHEN WE CAN USE INJECTIONS ?

ALEX: This device enables the delivery of all biologic drugs, not just insulin. We expect it could be used for nucleic acid delivery, protein, peptide, and antibody delivery. It has the capacity to transform how we deliver all of these drugs. A lot of companies will kill projects that involve macro molecule drugs requiring injections because they only offer an incremental improvement over an existing small molecule drug. They know people won't want to take that injection over a pill that works almost as well, these macro molecule drugs which would have required an injection aren't suitable for the market. We expect a huge amount of the macro molecule drug projects currently being killed by pharmaceutical companies could really benefit from this new technology for oral delivery.

ESTER: We also anticipate that patients will not feel any pain from taking this pill. The gastrointestinal tract does not have pain receptors and, when tested in pigs, we didn't observe any evidence of discomfort. We've looked closely into this and the safety of the device.

WHAT HAVE BEEN THE CORE RESEARCH FINDINGS?

AA: When developing this pill, we created three new innovations. The first is the self-righting system.

I learned about a great mathematician in Hungary who had done a lot of research on the self-orienting nature of turtles and tortoises. We were inspired by the leopard tortoise – a tortoise found in eastern and southern Africa that can re-orient itself very easily based on its shape. It has a shell with a high, steep dome, allowing it to right itself when it rolls onto its back. Similarly, our pill has a shape close to the leopard tortoise shell and that makes it easy for it to re-orient itself if it lands in a direction that isn't facing the stomach tissue wall.

"The solid needle is made almost completely out of insulin"

The second breakthrough was the sugar-based trigger, which ensures the pill doesn't fire in the oesophagus when it's ingested, instead it always fires in the stomach. The trigger senses the humidity in the gastrointestinal tract and that starts a timer. The sugar begins to dissolve and after about five minutes, it releases a compressed spring which pushes the drug into the tissue.

The last finding is the solid needle made almost completely out of insulin and other biological drugs. It allows us to deliver a clinically relevant dose. If we weren't using a needle made almost completely out of drug, then we wouldn't be able to deliver enough of the insulin.

WHAT WAS YOUR ROLE IN THE PROJECT?

AA: This has been my main focus for the past couple of years. It's my thesis project and I helped coordinate the efforts between MIT and Novo Nordisk. My role consisted of developing the idea to make a self-orienting device and working on the amount of force necessary to inject the needle. I was also involved in making the sugar-based hydration mechanism and a solid dose of the needle.

ECS: The research began in August 2015. The lab is a very collaborative environment. We have a multidisciplinary team composed of technical assistants, professors, postdoctoral associates and many undergraduate students that visit for a term, the summer or even the whole year.

Alex and I have different areas of expertise. Alex is a chemical engineer and I am a bio-technologist and biochemist by training – our skills complement each other. I was involved in the formulation aspect of the prototype. I focused on tissue characterisation, on researching formulations and on the stability of the drugs. I tested the loading capacity of the device and optimised the analytical methods to quantify insulin. For example, I confirmed the insulin was still active when pressed into the device and ensured the properties didn't change considering that we are submitting the insulin and other biologics to a high pressure during the fabrication process. Initially, this was a three-year collaboration project, but, now that we have this prototype, we have extended the collaboration.

Image: Alex inspects the novel pill

WHY DOES THE PILL NEED TO BE ABLE TO TURN ITSELF?

AA: When I started working on the project, and was considering how to combine needles and pills, the first thing I did was place small needles around the entire pill. When we dropped that on the tissue, I realised only a quarter of those needles were making contact. The other 75% of the needles were just going to dissolve and not deliver the drug – or even worse, the pill would rotate and allow slightly more needles to enter the tissue causing variability in the dose amount.

This brought up the idea of only putting the needle on one side of the pill. To do that, we needed a pill that oriented in the direction of the tissue wall. This way, we could ensure the needles on one side of the pill were always in contact with the tissue wall. The idea of self-orienting came up and we wondered, what are some things in nature and in our environment that self-orient?

The leopard tortoise specifically has evolved over thousands of years to be great at self-orienting on land. We took the leopard tortoise shape and density distribution as an initial guess. Then, we plugged that into a mathematical model that looked at self-orienting in the stomach.

HOW DOES THE SELF-ORIENTING NEEDLE WORK?

AA: The needle itself is inside a slightly larger capsule – it's between the size of a pea and a blueberry. The bottom of the device is weighted and so the centre of mass is lowered, which makes one configuration of the device the only stable configuration. For example, if you think about a Weeble Wobble toy or one of those punching clowns, whenever you disturb it, it always comes back to its preferred configuration – which is upright.

The self-orienting device utilises a similar concept. It also has another key characteristic, a flat bottom, which ensures once a person takes it and the device has oriented itself towards the tissue wall, if the person were to lean over from side to side or their stomach was to growl, it would stay in the same position.

ECS: The needle is only expelled once triggered by the sugar mechanism. It is protected until the device reaches the desired configuration against the tissue wall of the stomach.

HOW LONG DOES IT TAKE FOR THE INSULIN TO BE FULLY RELEASED INTO THE BLOOD STREAM?

AA: This can vary depending on what excipient we add to the formulation. If it's made of 100% insulin, then it dissolves over the course of several hours. If you add another excipient that enhances or slows dissolution, the drug uptake profile can change dramatically. We've shown that we can use this to deliver insulin over the course of an entire day.

ECS: There are different types of insulin so there is a lot of room for optimisation.

WHAT ARE YOU PLANNING TO DO NEXT?

AA: Right now, the research is being tested on large animal models. The one thing we want to look at is the chronic effects of the injection in the gastrointestinal tract. What happens if humans or animals were to take these every day for six months? We want to continue doing a few large animal tests and once we've gauged that, we then hope to go to clinical trials with humans in the next three years.

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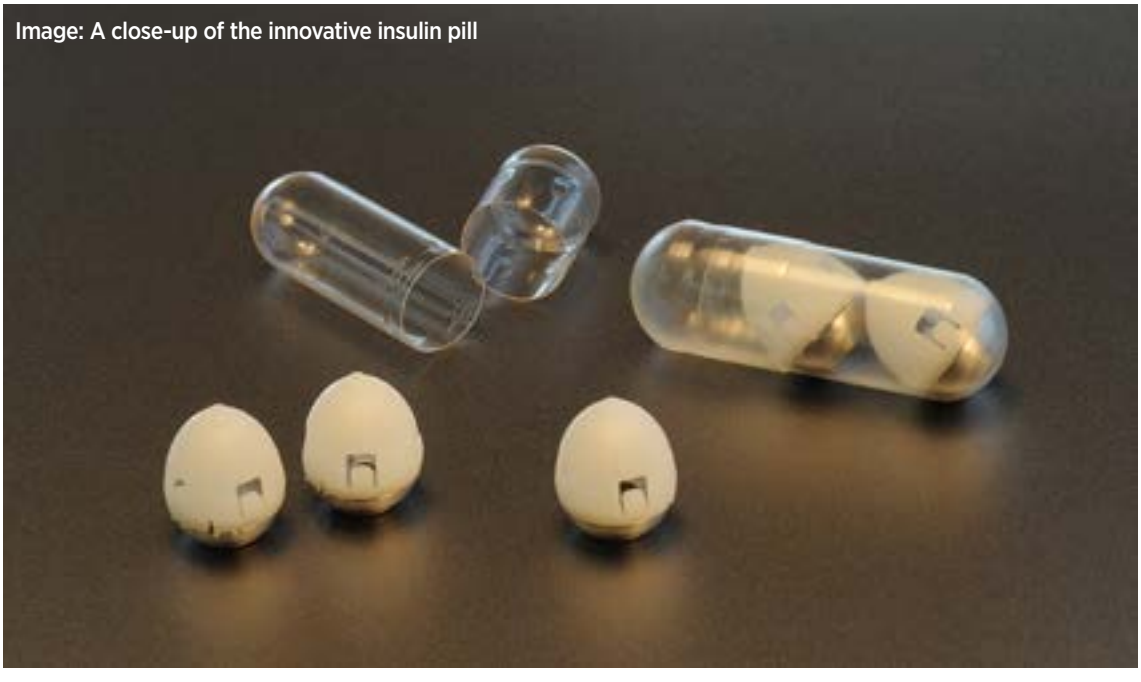

Image: A close-up of the innovative insulin pill