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A Robotic Pill: An Innovative Technology in Drug Delivery

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ABSTRACT
To address the global issues in the healthcare system, robotic technologies are emerging in the pharmaceutical industry. The robotic pill avoids first-pass metabolism in order to protect itself against degradative enzymes. Robotic pills deliver a therapeutically appropriate dose, significantly boost systemic medication bioavailability, and don't cause any side effects when taken repeatedly. Using such formulations minimizes our need on injections with needles. Thus, patient acceptance rises and the difficulty associated with using needles falls. (1) The oral administration of proteins and peptides faces multiple significant difficulties, such as toxicity, cost, and quality. Oral dosage formulations could address a number of problems related to non-adherence, such as disruption of everyday activities, uneasiness, and injection pain. (2)

***Key words:** Robotic Pill, Rani Pill, Biotherapeutics, Biomarkers, Oral Doses of Insulin.*

INTRODUCTION
The new technologies concentrate on delivering macromolecules, especially recombinant proteins like heparins made from animal mucosal polysaccharides. [3]

A patient's ability to take therapy that ordinarily call for injections or infusions, such as those for diabetes, arthritis, and other conditions, was improved by taking the capsule.

Robotic oral ingestion drug delivery system that improves mixing, topically deposits the drug payload, and locally clears the mucus layer to increase drug absorption. The robotic pill accelerates the rate at which medication is distributed via the GI mucosal membrane while also protecting against degradative enzymes by avoiding first-pass metabolism. One could solve a number of problems related to non-adherence, such as disruption of daily routines, discomfort, and injection pain, by designing oral doses.

Although oral drug delivery for macromolecules like nucleic acids and proteins is the most popular, economical, and practical mode of drug administration, it is constrained by the gastrointestinal (GI) tract's deteriorative environment and poor absorption. To attain therapeutic bioavailability, drugs must pass through the viscous mucus barrier, penetrate through the harsh acidic environment of the stomach, dissolve in GI fluid, remain stable among the dynamic intestinal microbiota and degradative enzymes, and avoid efflux pumps.

The robotic pill has a little chamber within that contains the medication payload. The exterior has ridges, protrusions, and is covered in a gelatin that dissolves at a particular pH. The covering of the tablet is worn away as it enters the stomach after being taken. A motor inside the capsule then starts spinning the pill as a result of the small intestine's pH. This needle poke shouldn't hurt as much as a typical shot. Some sensations, like the sharp pain of a stomach ulcer, can be felt in the stomach. or the unpleasant sensation of being bloated.

However, those sensations are more tied to stretch receptors. Sharp aches, such those from an injection, are not sensed by the stomach's receptors.

RoboCap might be able to prevent patients from needing daily needles or from going to the hospital to get their meds. RoboCap is an innovative concept that aims to overcome the current difficulty in orally delivering many advanced and emerging therapies. (16)

Structure and Functions of Robotic Pill

The RP (Fig. 1a) is a mechanical device that can be swallowed that is housed inside an HPMC capsule that is the size of a 000. (ACG Worldwide). Figure 1b is an extended image that reveals the main parts of the RP, which are housed inside a specially made polyethylene balloon with dimensions of 752 mm in length and 21–25 mm in diameter. The drug payload is contained in a hollow, dissolvable polyethylene glycol needle that is housed inside a cylindrical polyethylene microsyringe that measures 14.5 by 8.5 millimetres (14.58.5 mm) and is linked to the balloon. This microsyringe holds the drug payload in solid form. Inside the balloon, a dissolvable reaction valve constructed of polyethylene oxide that easily dissolves when exposed to intestinal fluid separates two reactants (citric acid and potassium bicarbonate). A pH-sensitive polymer suspension of Eudragit L30-D55 (MW 320,000 g/mol) and 0.1-0.5% Plasacryl-HTP20 is applied to the capsule using a Caleva mini coater (agitation 8-15 Hz, pump 1.3- 15 rpm, and atomizing pressure 10-20 psi) (Evonik). The FDA has classified the components of the device as either food grade, food additives, active or inactive food ingredients, or GRAS (generally regarded as safe). (4)

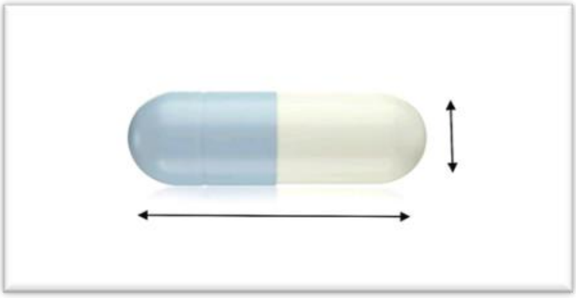


Fig. 1(a) RP design. a Fully assembled enteric-coated RP

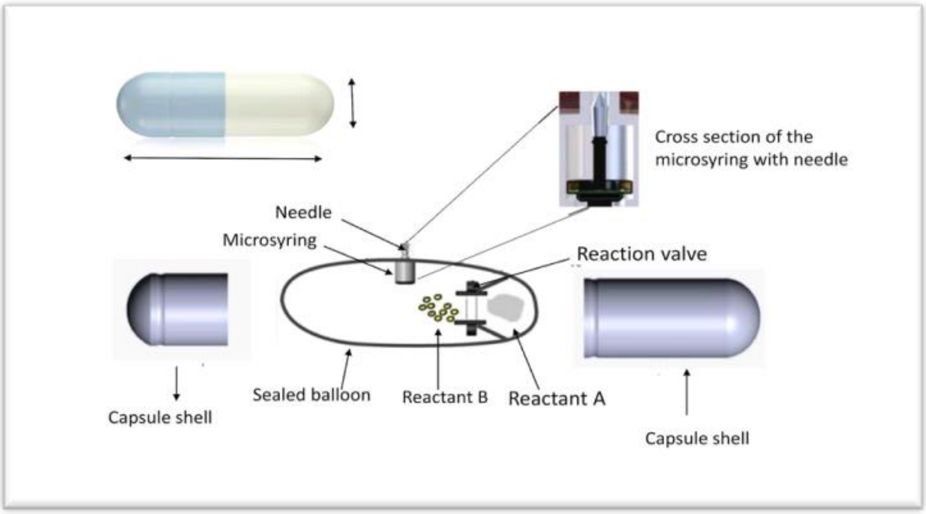


Fig. 1 (b). Schematic drawing showing various parts and components of the RP.

Inset shows the microsyringe containing the needle with the drug microtablet which gets injected into the jejunal wall. The microtablet and needle are aseptically manufactured in an isolator and hermetically sealed inside a drug chamber which is then inserted in the microsyringe

Advantages
1) The medication absorbs very quickly.
2) Remains of the medication are excreted within 1-4 days.
3) There are no metals, springs, or other components in the formulation.
4) Acceptable safety and tolerability standards.
5) The method is non-invasive.
6) Increased acceptability by the patient.
7) Suitable for injectable biologic drug oral administration.
8) Suitable for the treatment of certain disorders, such as acromegaly and diabetes. [5]

Drawbacks
1) It is inappropriate for medications that need a higher dosage than the capsule can hold.
2) Needs expertise.
3) Expensive.
4) Lack of control over drug release.
5) Limited drug storage capacity. [5]

Example -Rani Pill
Without insulin pumps, diabetes type I individuals inject insulin to their abdomens 700–1000 times annually with a needle. A painful injection into the muscles is given to someone with acromegaly once every month. A disease-slowing -interferon medication may be administered three times weekly in several injection sites to people with multiple sclerosis.

For the past seven years, Mr. Imran, founder, chairman, and CEO of Rani, has been developing a method to distribute large medicinal molecules. A "robotic" medication developed by Mr. Imran was recently tested on people. A "robotic pill" being developed by Rani Therapeutics claims to bypass the stomach and release more delicate medications directly into the bloodstream. The injection of big therapeutic molecules like peptides, proteins, and antibodies will be replaced with a robotic pill**.**

Due to the lack of pain receptors in the intestinal mucosa, taking the Rani Pill causes no pain. It has also demonstrated outstanding insulin bioavailability that is on equal with or better than subcutaneous injections. [6]

The Rani Pill capsules were tested on more than 100 animals, and it was found that they were 100% equivalent to injections.

Rani announced in February 2019, a human safety study was completed. [4,7,8,9]

Components of Rani Pill
The capsule contains a special enteric coated layer, sugar needles loaded with drug and which are attached to inflatable balloon structure. It contains chemical components like citric acid and sodium bicarbonate. (4,7,8,9)

Mechanism of Action of Rani Pill

Rani Pill capsule enters into the intestine

↓

When pH levels rise, the enteric coating of the capsule dissolves and a chemical reaction occurs (due to the mixer of citric acid and sodium bicarbonate)

↓

Inflates a balloon by the release of carbon dioxide gas

↓

The pressure in the balloon pushes the dissolvable micro needle filled with the drug into the intestinal wall

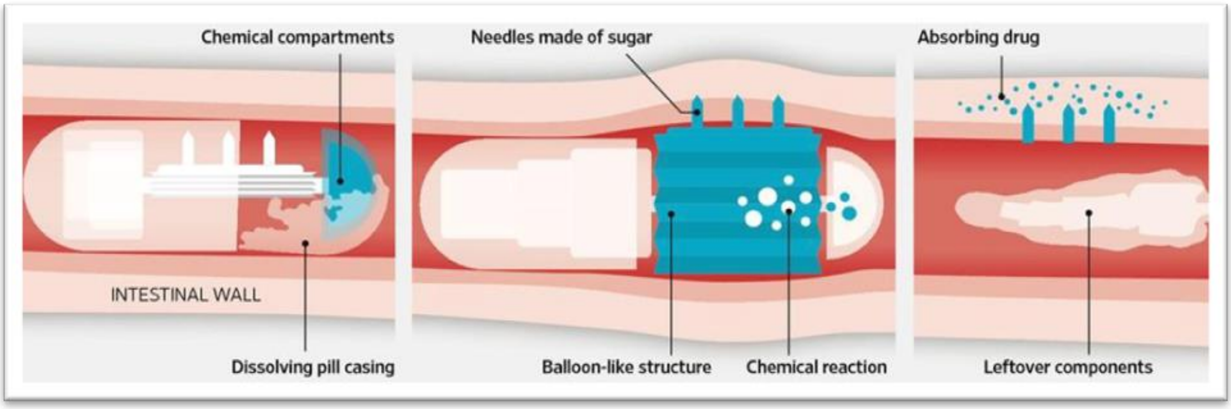


Figure 1 Mechanism action of rani pill.

APPLICATIONS

Pill for oral delivery of biotherapeutics

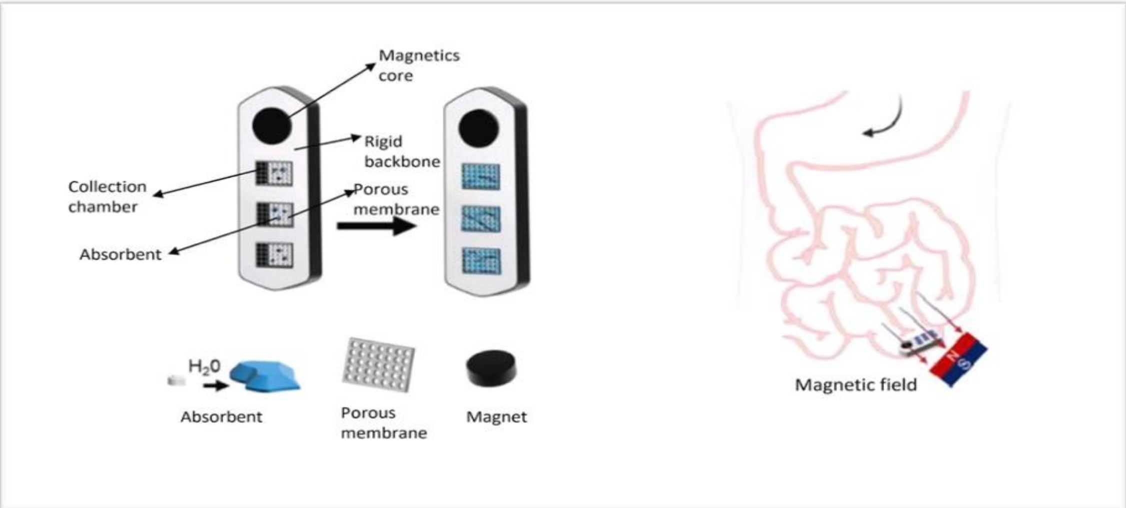
Biotherapeutics are very effective, yet poor patient compliance and ineffective disease management are caused by the discomfort and inconvenience of frequent injections. Due to their intestinal absorption problems and GI environment deterioration, oral biotherapeutic administration remains ineffective despite numerous attempts. We have created an oral robotic pill (RP) for medication administration that prevents the biotherapeutic drug payload from being digested in the GI tract.

These encouraging clinical outcomes imply that this adaptable, orally ingestible drug delivery platform may enable the safe and reliable delivery of biotherapeutics now supplied parenterally. (4)

Robotic Pill for Biomarker and Fluid Sampling in the Gastrointestinal Tract

The early detection of GI tract disorders may be enhanced by the development of on-site biomarker enrichment technologies. Circulating signatures or biomarkers, such as the secretome, extracellular vesicles, nucleic acids, bacteria, and other indicators, are coded with health-related information. Through repeated sampling, the collection and analysis of such signals can be used as an early indicator of the onset and progression of disease. Smart pill have been employed as a way to look into body cavities. For instance, finding GI polyps is frequently done with the PillCam, an ingestible capsule with an embedded camera.

The robotic pill is made up of three modular compartments, each of which is created for a specific function as shown in Figure 2 These three sampling modules allow the collection of various biomarkers in an absorbent trapping matrix while letting the biofluid pass through it, a porous membrane allows for the exclusion of larger objects (>5 m) in the collection chamber, and a magnetic core embedded in the structure aims to provide directed magnetic field. (10)



Oral Doses of Insulin

The invention of the Rani Pill and oral insulin dose capsules can solve the main issue with injectable dosage forms in type-I diabetes. For biologic hormone therapy to treat conditions like acromegaly, diarrhoea brought on by certain malignancies, etc., the rani pill and oral doses of insulin capsules are appropriate.

A medication capsule for delivering oral insulin dosages has been created by a team led by MIT (Massachusetts Institute of Technology). Insulin taken orally can lower blood sugar levels in type I diabetics who require injections. It can also be used to deliver protein-based medications, such as immune suppressants used to treat rheumatoid arthritis and inflammatory bowel disease. Patients with diabetes who have poor glycemic control, clinical problems, psychosocial comorbidities, or a poor mental state can benefit from oral insulin dosages. (11)

Based on in vivo research conducted that showed that more than half of insulin-dependent adults skip subcutaneous injections, which is linked to patient non-adherence, these investigations primarily focus on the self-orientation feature of macromolecules. Oral administration also eliminates the negative consequences of repeated injections and scarring.
Figure 4 shows how big a capsule of a blueberry is. It has an insulin-filled needle that is compressed and freeze-dried, and the needle is linked to a shaft that is biodegradable. (2,8,13,14)

Figure 2 Oral dose of insulin capsule.

Mechanism of Action: The mechanism action of oral doses of insulin described as follows

Similarly to the manufacturing process of tablet,needle tips are made with freeze-dried insulin that is 100% compressed.

↓

A sugar disk holds the shaft of an attached compressed spring.

↓

Once swallowed water in the stomach dissolves the sugar disk.

↓

Once the spring is released and the needle is injected into the stomach wall, the drug will be released.

The self-orienting millimeter-scale applicator (SOMA) is the mechanism that locates to the mucosa of the stomach and inserts the drug payload via the mucosa while orienting its injection mechanism toward the tissue wall. The medication disintegrates, and the appliance is eliminated from the body. The SOMA is stable in the stomach environment as soon as it is orientated in its optimal orientation.

RESULTS AND DISCUSSION

Robotic pills can replace needles, which is especially helpful for diabetic patients and children. The Rani Pill and oral insulin dose capsules are designed to replace injections of large drug molecules such peptides, proteins, and antibodies. These tools facilitate the administration of medications for conditions like diabetes, rheumatoid arthritis, inflammatory bowel illnesses, and other conditions that require injections or infusions.

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