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An insight into gastrointestinal macromolecule delivery using physical oral devices

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Oral delivery is preferred over other routes of drug administration by both patients and physicians. The bioavailability of some therapeutics that are delivered via the oral route is restricted due to the protease- and bacteria-rich environment in the gastrointestinal tract, and by the pH variability along the delivery route. Given these harsh environments, the oral delivery of therapeutic macromolecules is complicated and remains challenging. Various formulation approaches, including the use of permeation enhancers and nanosized carriers, as well as chemical alteration of the drug structure, have been studied as ways to improve the oral absorption of macromolecular drugs. Nevertheless, the bioavailability of marketed oral peptide medicines is often relatively poor. This review highlights the most recent and promising physical methods for improving the oral bioavailability of macromolecules such as peptides. These methods include microneedle injections, high-speed stream injectors, magnetic drug targeting, expandable hydrogels, and iontophoresis. We highlight the potential and challenges of these new technologies, which may impact the future approaches used by pharmaceutical companies to create more efficient and safer orally administered macromolecules.

Keywords: Oral drug delivery; Macromolecules; Physical oral device; Bioavailability; Gastrointestinal tract

Introduction

The large surface area of the small intestinal tract makes it an attractive target for drug delivery. This benefit motivates physicians and drug developers to prepare oral physical devices that disrupt or perturb the gastrointestinal (GI) epithelial cell layer in order to promote the delivery of macromolecules. The main goals in developing these physical oral devices are to increase systemic drug concentration, to increase patient compliance and self-administration, and to enhance the efficiency of oral, buccal, and rectal delivery of sensitive therapeutics.[1–4] Various physical oral devices, such as microneedle injectors, high-speed stream injectors, magnetic devices, expandable hydrogels, and iontophoresis devices, are discussed in the following sections (Fig. 1).

Challenges associated with macromolecule absorption in the GI tract

For various reasons, the oral pathway has received more attention than any other route when it comes to drug delivery. This is due to its unique advantages, such as controlled and sustained delivery, easy administration, patient compliance, and the ability

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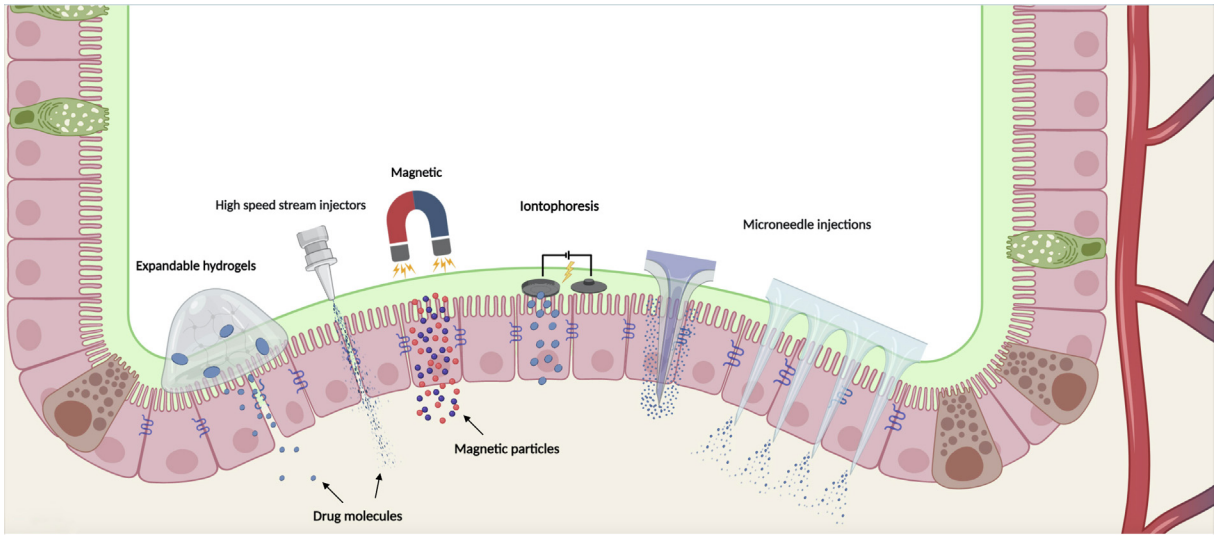

FIGURE 1

Overview of physical ingestible devices for gastrointestinal delivery of therapeutics. Created with BioRender.com.

to use solid formulations.[5] Furthermore, drugs can easily attach to and be absorbed by the large mucosal surface area of the GI tract. Mucus protects drug molecules from shear stresses caused by gastric juices flowing through the stomach.[6,7].

Because the small intestine contains a large number of enterocytes—particularly the microfold cells (M cells) covering the Peyer's patches and the lymphoid segment of the small intestine—the epithelium of the human intestine is very absorptive.[8] However, the absorption mechanism for oral drugs is more complex than that for drugs administered through other routes. Orally delivered drugs must be soluble in the gastric fluid so that they can be absorbed in the stomach, small intestine, or colon. Transcellular, paracellular, carrier-mediated transcellular, and facilitated transport are the four pathways by which drugs are absorbed after being taken orally. The transcellular pathway is the most important of these mechanisms. The barriers to drug absorption and efficacy are not limited to those encountered in the gut; challenges also arise after drugs enter the vessels beneath the intestinal epithelium.[9] Therefore, orally administered drugs are not suitable for emergencies because of their slow absorption and the multiple barriers that they must overcome. Even well-absorbed small molecules are rarely delivered by the oral route in emergencies.

In addition to physical obstacles, denaturation and chemical degradation in the stomach and intestine prevent the oral delivery of many macromolecules.[10,11] Most proteins are denatured in the GI tract, and enzymatic degradation begins in the stomach as the result of the acidic conditions (pH 1–2). A variety of proteases in bile salts further destabilize biologics in the small intestine by breaking them down into smaller pieces called oligopeptides and amino acids.[12] Bacterial fermentation can eventually decompose the remaining components in the colon.[13]

Only a few orally formulated peptide drugs for systemic delivery have entered clinical trials in recent decades, despite their efficacy in preclinical models. Only a couple of these have reached the market, such as semaglutide (Rybelsus®) and octreotide (Mycappsa®).[14] The oral bioavailability of peptides is typically around 1%, even when administered with the most common permeation enhancers tested in clinical trials, such as salcaprozate sodium (SNAC), sodium caprylate (C8), and sodium caprate (C10).[11] The formulations (e.g., Rybelsus® and Mycappsa®) also use permeation enhancers that are affected by the presence of food to a variable degree.[15] Physical delivery devices for oral drugs have been designed to overcome the GI obstacles by exploiting mechanisms beyond the traditional enhancement of chemical and biological permeation.

Reliability, stability, and design must be considered when designing physical oral devices for the GI tract. The wall disruption depth and the device dimensions are two important factors that determine the safety of ingestible physical devices. In terms of depth of perturbation, physical devices must not perforate the wall of the GI tract, as this could result in a medical emergency. The thickness of the stomach wall (4–8 mm) compared with that of intestinal walls (0.5–2 mm) makes it a safer target for physical drug delivery.[1,2,16]

The high rate of GI epithelial reparation also provides a rapid protective mechanism. Surface injuries in the GI tract heal within hours because of the rapid migration of viable epithelial cells to the denuded basal lamina.[17] Furthermore, research in animal models has suggested that the target depth to which the stomach wall can be penetrated is 4–5 mm, with wall thicknesses of 4–8 mm depending on the location.[7,18–24]

The size of the device is an important safety consideration that must be taken into account to avoid device interruption or cessation. Capsule-shaped devices of 9 mm in diameter and 15 mm in length set a safe standard for ingestible oral devices.[25,26]

Different parts of the GI tract vary significantly, especially in terms of pH and transit time. The pH of the stomach is usually between 1 and 2, whereas the pH of the duodenum is usually around 6, and the pH of the small intestine rises to around 7.4 at the terminal ileum. From here, the cecum pH declines to 5.7 and the rectum pH rises to 6.7.[19–21,27] In addition, the colon (30–40 hours) and the esophagus (4–8 seconds) have the longest and shortest residency times, respectively, in the GI tract. The residency times of the stomach (4–5 hours) and the small intestine (2.5–3 hours) make these locations ideal and appealing for targeting by physical oral devices.[22]

Both internal and external triggers that activate drug release must be considered when applying targeted drug delivery. Drug-release mechanisms that are time- or pH-dependent can take advantage of the variability of the GI tract to target drug release to a specific location. pH-responsive systems may face challenges as the result of changes in the pH of the GI tract caused by diet or the by use of proton pump inhibitors or H_2 blockers to treat acid-related GI disorders. Furthermore, patient-to-patient variability in transit time can make the performance of time-delayed drug delivery devices more inconsistent and less reliable.[28]

Various external triggers have been developed in response to these challenges. For example, radiofrequency-controlled pills provide a non-passive alternative to passive drug delivery that allows the physician or patient to deliver a drug at a specific time and at a known device location. Such approaches are limited, however, because current electronics and battery size constraints can cause obstructions.[29]

The functionality of the device is the final critical factor to consider. An oral ingestible drug delivery system could sense a specific analyte or biomarker while responding to it in closed-loop controlled drug delivery system.[30] On the other hand, combining diagnostics and therapeutics into a single system still poses significant challenges related to the size, complexity, and reliability of devices. Table 1 summarizes various physical oral drug delivery devices that are applied to the GI tract.

Finally, drug delivery devices for the GI tract that interact physically have mainly been adapted from devices for transdermal drug delivery. Transdermal delivery is hindered by the epidermal and dermal layers of the skin, which act as significant barriers, so microneedle injection, high-speed stream injectors, endoscopic needles, magnetic techniques, expandable hydrogels, and iontophoresis have been used for the transdermal delivery of macromolecules.[31,32]

There are a few considerations to be aware of when using physical oral devices in the GI tract, including needle path, injection method, and miniaturizing of devices to allow placement in the GI tract without obstructing it. The following sections describe the principles, benefits, and drawbacks of various physical oral drug delivery devices.

Microneedle injection

New mechanical approaches have recently been investigated to improve drug permeation. A notable example is the use of microneedles, which have been extensively investigated as a transdermal delivery method for a wide range of drugs and vaccines over the past two decades. Because of their low-invasive nature and high permeation enhancement effects, microneedles have been studied in many applications, including diabetes, pain management, and vaccinations.[42,57,58] Microneedles have also been tested for ocular, vaginal, and oral delivery. Since 2009, several patents have described the use of microneedles in the GI tract,[59] but some of these devices have not been tested in large animals or humans.

Gut patches

In many cases, patients refuse to receive injections or are unable to inject themselves. As a result, doctors are often reluctant to prescribe injectable medications if a pill-based alternative exists, even if it is less effective. For some macromolecules, however, injection is required instead of oral delivery.

Abramson *et al.*[33] described a new pill that ejects microneedle patches into the intestine. These structures, which are called a luminal unfolding microneedle injection (LUMI) devices (Fig. 2A), then deliver drugs across the intestinal epithelium and into the bloodstream without the use of hypodermic injections. The novel microneedle-based mechanical devices open in the small intestine and deliver an active pharmaceutical ingredient directly into the intestinal wall.

When the LUMI devices are exposed to a pH of 5.5 in the duodenum, the polymeric material that holds the spring dissolves, causing the LUMI to be pushed out of the capsule. The LUMI arms then open outward and press the microneedle patches against the intestinal wall, where they penetrate the epithelial barrier, dissolve, and release the encapsulated drug.[33,34] The LUMI devices degrade after the drug is deployed, allowing them to pass through the GI tract and be excreted in the stool, thereby reducing the risk of intestinal obstruction. When compared to the administration of an insulin solution into the small intestine, use of the LUMI device to deliver insulin into the intestinal wall achieved a significant reduction in blood glucose in pigs.[33] The LUMI can only hold 0.3 mg of a drug, so it is only suitable for high-potency drugs.

Microneedle injector devices

A robotic pill (RP) was introduced by Rani Therapeutics to deliver drugs directly into the intestinal wall (Fig. 2B). Dhalla *et al.*[36] used an enteric coating to enclose a balloon and microinjector in a system. The enteric coating could dissolve once it reached the small intestine, directly exposing the device to intestinal fluid and thus causing a chemical reaction that inflated a balloon. The microneedle pierced the intestinal wall after the balloon was sufficiently inflated, thus delivering the drug containers. Drug delivery and pharmacokinetic (PK) analysis were performed after deployment of this device in a series of clinical trials on healthy volunteers. PK analysis of successfully deployed RPs revealed that octreotide that was delivered by the RP had an absolute bioavailability of 65%, far exceeding the 1% achieved by previous approaches. The subjects experienced no pain or discomfort during RP deployment, showing that transient inflation and deflation of the balloon are insufficient to activate the intestinal stretch receptors. These studies also showed that food does not affect the dissolution of the enteric coating or the RP deployment time.[36] Despite the promising

TABLE 1

Summary of physical oral devices used for oral delivery of macromolecules.

Device name	Type	Fabrication method	Site of action in GI	Container size	Drugs	References
LUMI	Microneedle injection (Gut microneedle Patches)	3D printing of biodegradable polymers (PVP)	Small intestine	9 mm × 30 mm	Insulin	33,34
Needle-covered pill	Microneedle injection	Needles fitted manually into the surface orifices	Stomach, duodenum, and colon	10 mm × 20 mm	Insulin	35
Robotic Pill (RP)	Microneedle injection	A cylindrical microsyringe fitted into an enteric-coated capsule	Duodenum	10 mm × 26.1 mm	Octreotide	36
Carr-Locke injection needle	Microneedle injection (Endoscopic)	This device is composed of a polymeric external catheter that is wrapped around a metallic needle	The whole GI tract	2.5 mm × 2300 mm (Endoscopic device)	Vasoactive agents, sclerotherapy drugs, botulinum toxin, paclitaxel	37–40
SOMA	Microneedle injection	3D printing (SLA)	Stomach	10 mm × 15 mm	Insulin	1
L-SOMA	Microneedle injection	3D printing (SLA)	Stomach	12 mm × 15 mm	Adalimumab, insulin, semaglutide and epinephrine	41
Hookworm-like Theragripper robot	Microneedle injection (Endoscopic)	Using conventional metal-polymer microfabrication technique	Stomach, small intestine, and colon	250 μm	Ketorolac tromethamine	42
Generex Oral-Lyn	High-speed stream injectors	utilizing the RapidMist™ spray system	Buccal	–	Insulin	43,44
Magnetic tablet	Magnetic	Direct compression was used to create bilayer magnetic tablets with drug and ferrite layers and it was coated with a 15% chloroform solution of an insoluble polymer (ethylene-vinyl acetate copolymer) to keep it intact. The magnetic layer then adhered to the drug layer with cyanoacrylate adhesives.	Stomach	6 mm diameter	Acetaminophen and Acyclovir	45,46
Microparticle-micromagnet complexes	Magnetic	Embedded 0.25 T NdFeB micromagnets in PLGA microparticles along with 125I-labeled insulin (MW5808 g/mol).	Small intestine	3–5 μm diameter	Insulin	47
Magnetic pill	Magnetic	Freeze-dried calcium alginate sphere containing magnetic, radiopaque iron oxide loaded into size 9 gelatin capsules	Small intestine	2.70 mm × 8.5 mm	–	48
Magnetic Active Agent Release System (MAARS)	Magnetic	MAARS capsules filled with acetyl salicylic acid as a crystalline powder and then magnetized	Duodenum, jejunum and colon	7.7 mm × 18.2 mm	Acetylsalicylic acid	49
Ferrogels	Magnetic	Fabricated by adding iron oxide powder to an alginate hydrogel before casting	Various	–	Mitoxantrone, plasmid DNA	50–52
Superporous hydrogels	Expandable hydrogels	Hydrogels synthesizing by copolymerizing methods and then embedding the solid API dosages.	Small intestine	–	Insulin, octreotide, and buserelin	53–55
Mucoadhesive patches	Iontophoresis	Insulin mucoadhesive patches were prepared with Eudragit E PO, pectin, and SCMC. One side of the patch was completely covered with aluminum foil using a minimal amount of super glue placed at one corner of the foil. Wires with a small section of their protective insulation removed were then stuck on the aluminum foil using super glue	Small intestine	3 mm × 5 mm	Insulin	56

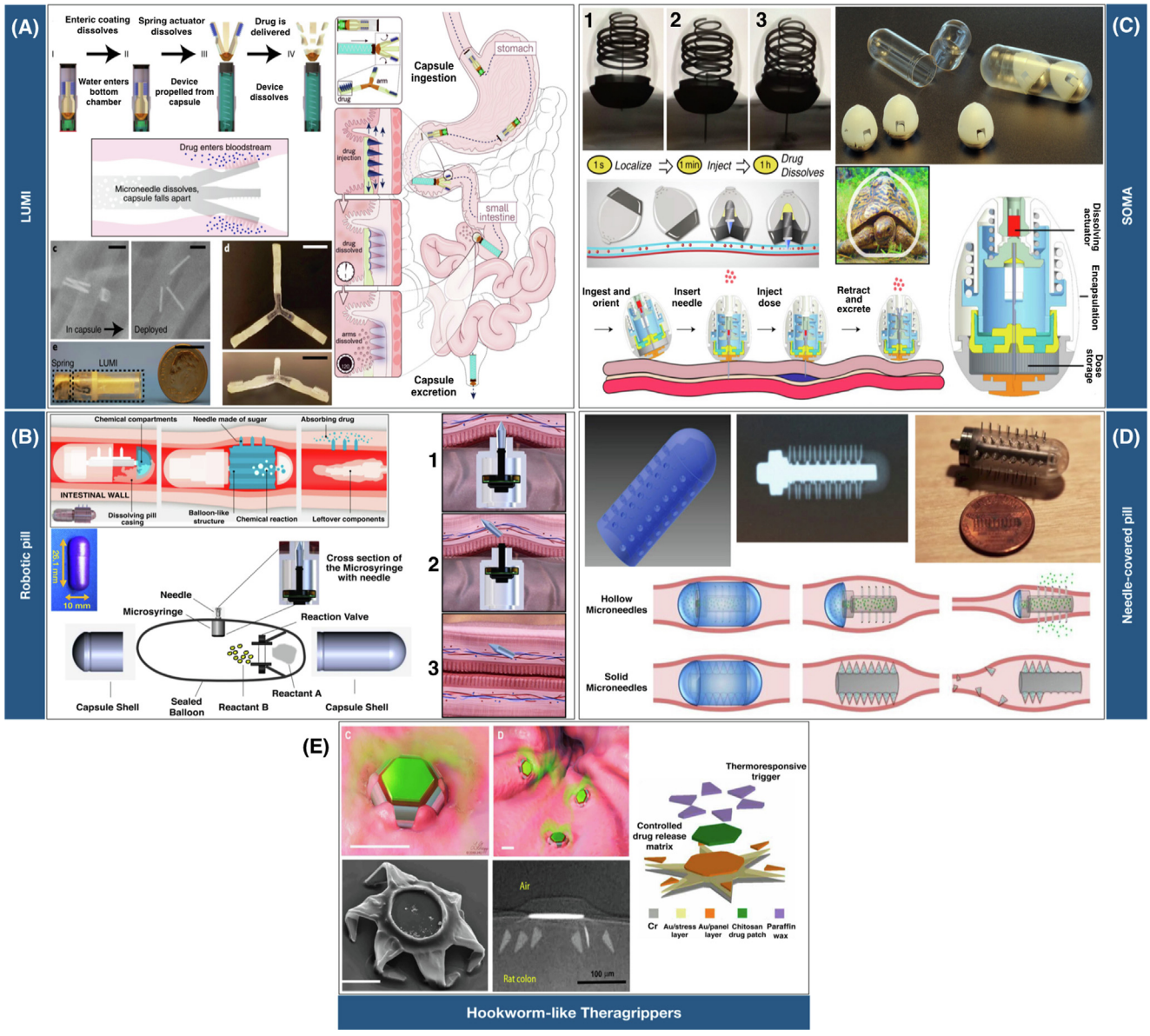

FIGURE 2

Microneedle injectors used to deliver drugs through the stomach and intestines. (A) Luminal unfolding microneedle injection (LUMI). (Right) Microneedles are injected into the small intestine by the LUMI device, which then disassembles for excretion. (Top left and middle) Design and action mechanism of the LUMI device. (Bottom left) Size of the device and overhead image of an unfolded LUMI.[33,34] **(B)** The design of the robotic pill (RP) device fabricated by Rani Therapeutics. (Top and right side) Illustration of an injection into the intestinal wall. (Bottom left) Design and size of RP device.[85] **(C)** Self-orienting millimeter-scale applicator (SOMA) device that localizes an active pharmaceutical ingredient in the stomach and injects it into the gastric wall. (Top and middle right) Design and size of the device. (Middle left and bottom) Depiction of SOMA device positioning in the gastric wall and mechanism of insertion.[1,41] **(D)** The design of a cylindrical needle-covered pill for the oral administration of biologic drugs. (Top) Size and structure of the device. (Bottom) Therapeutic use concept for the needle-covered pill. Both hollow and solid microneedles could be used. With hollow microneedles, peristalsis compresses the drug reservoir and releases it through the needles. Alternatively, the solid microneedles contain the drug and break off the pill to penetrate into the tissue, where they release the drug in a controlled manner.[35] **(E)** Shape-changing theragrippers as self-latching drug delivery devices. (Top left) Theragrippers attached to the mucosal tissue and releasing encapsulated drug (colored in green). (Bottom left) Image of the cross-section of a theragripper penetrating into the colon *ex vivo*. (Right) Micro-fabrication steps for an array of theragrippers.[42]

results of clinical studies, there are still some concerns that Rani Therapeutic should address, such as potential risks associated with frequent GI tract puncture, and infections that may arise as a result of increased exposure to food antigens, digestive fluids, and resident pathogens during chronic use. Furthermore, Dhalla *et al.*[36] did not specify the device failure rate. RP devices have two major limitations. First, because of the inherent variability in gastric residence times in humans, it is not possible to predict the exact time at which the RP technology will deliver the drug after oral ingestion. This may preclude the use of RP devices for temporally sensitive biotherapeutics such as mealtime insulin. Second, the maximum amount of drug payload that can be

retained by RP devices is determined by the needle's current capacity of 3.5 mg.

Another novel microneedle injector device, called the cylindrical needle-covered pill, was introduced by Traverso *et al.*[35] in 2015. These devices were made of clear acrylic, and the orifices were manually fitted with 25G needles that protruded 5 mm from the surface. The device had a length of 2 cm and a diameter of 1 cm. A metallic core was added to the device, making radiographic detection possible. There are two types of microneedle systems for these devices: hollow and solid microneedles (Fig. 2D). In both cases, the needles of the pill are covered with a pH-responsive coating to help with ingestion. The coating dissolves and reveals the microneedles when the pill reaches the desired location in the GI tract.

In the case of hollow microneedles, peristalsis compresses the drug reservoir, allowing the drug to be released through the needles. In the case of solid microneedles, the drug is formulated into the microneedles, and biocompatible polymers can be used to form drug-containing microneedles. These can be detached from the capsule and enter the GI tissue, where the drug is slowly released. Throughout the transit time of the device, no animals showed any clinical signs of obstruction. Furthermore, there was no indication of intestinal obstruction or perforation on radiographs. The long-term safety and tolerability of this device are promising and indicate the possibility of using derivatives of this device for extended-release oral formulations of macromolecules.[35]

Abramson *et al.*[1,2] developed an ingestible self-orienting millimeter-scale applicator (SOMA) that positions itself autonomously to interact with GI tissue before inserting a microneedle made of the active pharmaceutical ingredient (API) directly through the gastric mucosa without any perforation. The shape of the SOMA device, inspired by the leopard tortoise, allows it to orient itself quickly and stay stable in the stomach once it has reached its preferred orientation (Fig. 2C). In the research carried out by Abramson *et al.*,[1,2] the SOMA device contained a solid insulin drug needle that was injected into the gastric wall by a mechanical spring. Then, 0.3 mg of powdered insulin was compressed with poly (ethylene oxide) to make the microneedles. *In vivo* studies in rats and pigs have shown that SOMA delivers API plasma levels that are comparable to those obtained through subcutaneous needle administration. The loading of powdered insulin is an appealing feature of the SOMA.

Despite the many advantages of the SOMA, many key issues affect their performance. These include low pill dosing sizes, and delayed or zero-order kinetic drug delivery rates that limit absolute bioavailability to 10% or less during the first 3.5 hours after actuation. Another issue is the possibility that the drug formulation will contact GI fluid (which contains digestive enzymes) for a short period of time prior to injection, because the hydration-dependent actuator in the SOMA requires GI fluid to dissolve and actuate the barrier. The drug may in contact with GI fluid until the actuator vents dissolve to release a compressed spring. These limitations prevent SOMA devices from delivering drugs that need to be administered in large doses, such as monoclonal antibodies, or drugs that need to act quickly, such as mealtime insulin or epinephrine.

These problems led the SOMA design team from MIT to develop a new version, called the L-SOMA. Their new device can deliver drug doses in the microgram to milligram range, including doses of small molecules and monoclonal antibodies.[41] Furthermore, L-SOMA achieves a higher drug plasma concentration within 30 minutes than does standard subcutaneous injection, as well as an absolute bioavailability of up to 80% within hours.

Unlike SOMA, L-SOMA is loaded with liquid drugs. It is also larger and more accurate. The actuation mechanism for L-SOMA is located on the device's shell, removing the need for gastric fluid to enter the pill and contact the loaded drug before injection. When triggered, the L-SOMA plunges a needle into the tissue with excessive force to a specified depth. Subsequently, a second spring pushes down on a plunger, driving the liquid drug formulation through the needle and into the gastric submucosa. Because the needle is separated from the injection liquid, the device can deliver its entire dose to the tissue by penetrating it deeply rather than slowly dripping the liquid through the tissue. As a result, this staged injection system prevents any of the dose from being ejected into the gastric fluid, where it could be degraded.[33] Although promising results have been obtained with SOMA and L-SOMA devices, a number of issues must be addressed before these technologies can be scaled up. It is not clear whether commercial injectable systems would need to be sterilized. Sterile manufacturing or terminal sterilization may be difficult due to the complexity of assembling such devices. In addition, the manufacturing of these delicate devices is a complicated process. Needle carriers, trigger elements, and encapsulation materials are just some of the components that make up these devices. As a whole, these components make these devices more expensive and susceptible to failure than traditional oral formulations. SOMA and L-SOMA studies have revealed that the GI tissues are not severely harmed by these devices. Nevertheless, they did not discuss the possibility of painful bloating and distension, and these devices have not yet been tested in humans.[60] Moreover, the effect of gastric juice viscosity on the device orientation time in fast and fed conditions should be evaluated.

Endoscopic injectors

Endoscopic injection needles consist of a polymeric external catheter enclosing a metal needle and a Luer lock connection to a handle. The connection allows a syringe to be used for drug administration. Endoscopic injection needles currently exist in various shapes and sizes. The Carr-Locke injection needle is the most well-known, and it is commonly used in endoscopy to inject medications.[40,61,62] Carr-Locke needles are known to perform well in challenging situations, such as when the endoscope is in retroflection or when the elevator in a duodenoscope is engaged. Carr-Locke devices are widely used to inject vasoactive agents, sclerosing agents, botulinum toxin, and tissue adhesives to treat common GI diseases. They can also inject drugs throughout the GI tract.[39]

Ghosh *et al.*[42] recently developed a self-latching device comprising multiple layers of hydrogel with varying swelling ratios. After being hydrated, the device is morphed into a hookworm structure, allowing it to grip onto the intestinal mucosa and

improve mucoadhesion (Fig. 2E).[42] This device can stay in the GI tract for up to 24 hours because it latches on to mucosal tissue of the colon to enhance the efficacy of extended drug delivery. This hookworm-like theragripper is a metal-polymer hybrid, in which a shape-changing metallic pattern of segments and hinges made of gold and chromium carries a drug-eluting polymer patch that allows controlled drug release. A pressure-actuated microfluidic flow controller and endoscopy-assisted administration were used to administer the liquid containing the hookworm-like theragrippers through the rectum and stomach, respectively. This study showed that theragripper formulations of ketorolac were resident on colon mucosa for more than 24 hours, with a half-life of around 12 hours, which is considerably longer than those of many common GI drug delivery devices.[42]

High-speed stream injectors

High-speed stream injectors are a needle-free devices that allow a high-speed stream of liquid medication to penetrate a targeted tissue through a nozzle orifice. They are able to improve the bioavailability of drugs when compared to traditional needle and syringe injections.[63,64] Most injectors use a piston to compress a liquid drug solution. The compressed drug solution is then released in the form of a fast jet (100–200 m/s) through a tiny orifice.[65] The depth of the injection into the tissue is affected by the characteristics of the injection device, including the orifice diameter, flow rate, the viscosity of the fluid stream, and the angle of injection.[66]

Oral-lyn™ buccal spray, developed by Generex Biotechnology Corporation to administer insulin via the RapidMist™ spray device, is a well-known example of a high-speed stream injector.[44] This device delivers an aerosol into the oropharyngeal cavity at a high velocity (≈100 mph or 160 km/h) so that it is absorbed through the local buccal mucosa. Each Oral-lyn™ container holds 400 IU of regular human insulin. The liquid insulin is sprayed from the device as micelles, and the surfactant used for the micelles acts as a permeation enhancer. The micelles containing insulin are relatively large (>7 μm, with an average size of >10 μm), so they cannot get deep into the lungs.

Oral-lyn™ insulin was compared with subcutaneous injection of insulin in a study of patients with type 1 diabetes mellitus.[43] The results showed that Oral-lyn™ had a faster onset of action than subcutaneous injections. Nevertheless, owing to the many disadvantages of this device, such as its variable and low bioavailability and its low consumption compliance (12 puffs are required), it fails to meet the market approval requirements in many countries.[67]

Magnetic drug targeting

The use of magnetic fields outside the body is generally considered safe and is common in medical imaging techniques such as magnetic resonance imaging (MRI).[68] The use of magnetic force in oral drug delivery was one of the earliest methods in physical delivery systems. External magnetic fields can transport and activate ingested magnetic nanoparticles.[69] Protective silica or organic coating is applied to the magnetic nanoparticles. The protective coating is attached to one end of an organic linker molecule, and the active biomolecule is attached to the other end. This method may be effective in overcoming tumor hypoxia challenges in cancer therapy.[70]

To deliver certain proteins, such as insulin, some researchers have used magnetic retention in lipid-based microparticles, poly (D,L-lactic-co-glycolic acid) (PLGA) microparticles, and chitosan-alginate beads.[71,72] Insulin is currently the only protein drug that has been tested using this magnetic retention technique.

In a study by Teply *et al.*, ^{125}I-labeled insulin was encapsulated in negatively charged PLGA microparticles.[47] The microparticles were then combined with positively charged micromagnets (neodymium iron boron, 0.25 T) of a size that would prevent them from being absorbed. Electrostatic interaction produced a stable suspension. The suspension was then administered to the small intestines of fasted mice via gavage. After administration, a magnet belt kept the mice immobile for 90 minutes. The resulting reduction in blood glucose levels lasted 36 hours after commencing the administration of insulin in this way, with an absolute bioavailability of 5.11% (compared to 0.87% in the control group without the external magnet).[47] Toxicity and histological evaluations were carried out on different mice organs such as the small intestine, liver, spleen, and kidneys, which showed no signs of acute inflammation or magnetic microparticles. As a result, it was concluded that the encapsulated formulation offered improved performance when compared to magnetic particles because it generated greater forces and was resistant to GI mucosal uptake, such as Peyer's patches absorption.[47]

In another study, Fujimori *et al.*[45] investigated the effect of the gastric residence of acetaminophen magnetic tablets on the bioavailability of a drug by magnetically controlling the gastric emptying time in beagle dogs. The magnetic tablets were prepared by direct compression, with ferrite used as a magnetic agent. After administration, the stomachs of the dogs were exposed to a static magnetic field (0.2 T) for eight hours, resulting in a three-hour increase in gastric emptying time and a two-fold increase in acetaminophen bioavailability.

Similar results were observed in another study that used magnetic acyclovir tablets.[46] The same researchers also conducted a small clinical study on five male volunteers. After an external magnet was placed in the stomach region, the plasma concentrations of acyclovir were significantly extended from 1.25 to 12 h. Although clinical evidence supports the use of external magnets to extend gastric residence time, the effectiveness of peristaltic waves or inter-individual differences in GI motility should be considered before forming any conclusions because these factors may affect the rate at which the drug exits the stomach.[46]

Dietzel *et al.*[49] introduced a novel magnetic active agent release system (MAARS) that used a magnetic field-activated capsule endoscopy system for drug delivery. MAARS capsules were filled with crystalline powder of acetylsalicylic acid (ASA; aspirin) and were then magnetized. The effects of these capsules were examined in 13 healthy volunteers in whom the release procedure for ASA targeting the flexural duodenojejunal and the mid-part of the jejunum was monitored. The promising results showed adequate drug release from the MAARS, which was well-tolerated with no complications. Nevertheless, this system must undergo additional evaluations such as histopathological studies and verification of these results for liquid substances rather than powdered drugs.[49]

In addition to microparticles and solid oral dosages, magnetic hydrogels known as ferrogels have also been introduced (Fig. 3A).[50–52] These gels are modified in a magnetic field to create stimuli-responsive drug scaffolds that can release the therapeutics into the targeted area (Fig. 3B). This method enables pulsatile drug delivery, which might be the most effective treatment for overcoming adaptive resistance in chemotherapies. Ferrogel is made by mixing iron oxide powder with a mucoadhesive polymer-based hydrogel and then casting it into a monophasic material. The efficiency of ferrogels, when administered through the GI tract, is still under evaluation.

New instruments have been developed to quantify and better control *in situ* magnetic forces in order to prolong the GI retention of magnetic formulations. Laulicht *et al.*[48] developed a method for visualizing *in vivo* motion of such formulations using biplanar videofluoroscopy to localize magnetic pills. The distance between the external magnets in this system could be adjusted to change the magnetic force (Fig. 3C). The method was also tested on humans to observe how the oral magnetic pills affected their stomachs and to determine whether the system could be used in an outpatient settings. By allowing more precise local drug delivery, this method appeared to aid in the diagnosis of GI tract diseases such as gastric dysmotility disorder.[48]

Magnetic formulations may be more effective than mucoadhesive materials in prolonging drug retention in the GI tract because of their safety profile and adjustable external field. Control over the delivery sites and greater epithelium adhesion are two major advantages that magnetic systems have over mucoadhesive systems. There is, however, no known mechanism to explain how magnetic fields affect drug permeation pathways.[73,74] Moreover, because the magnetic force diminishes rapidly with distance, it is not practical to place external and sta-

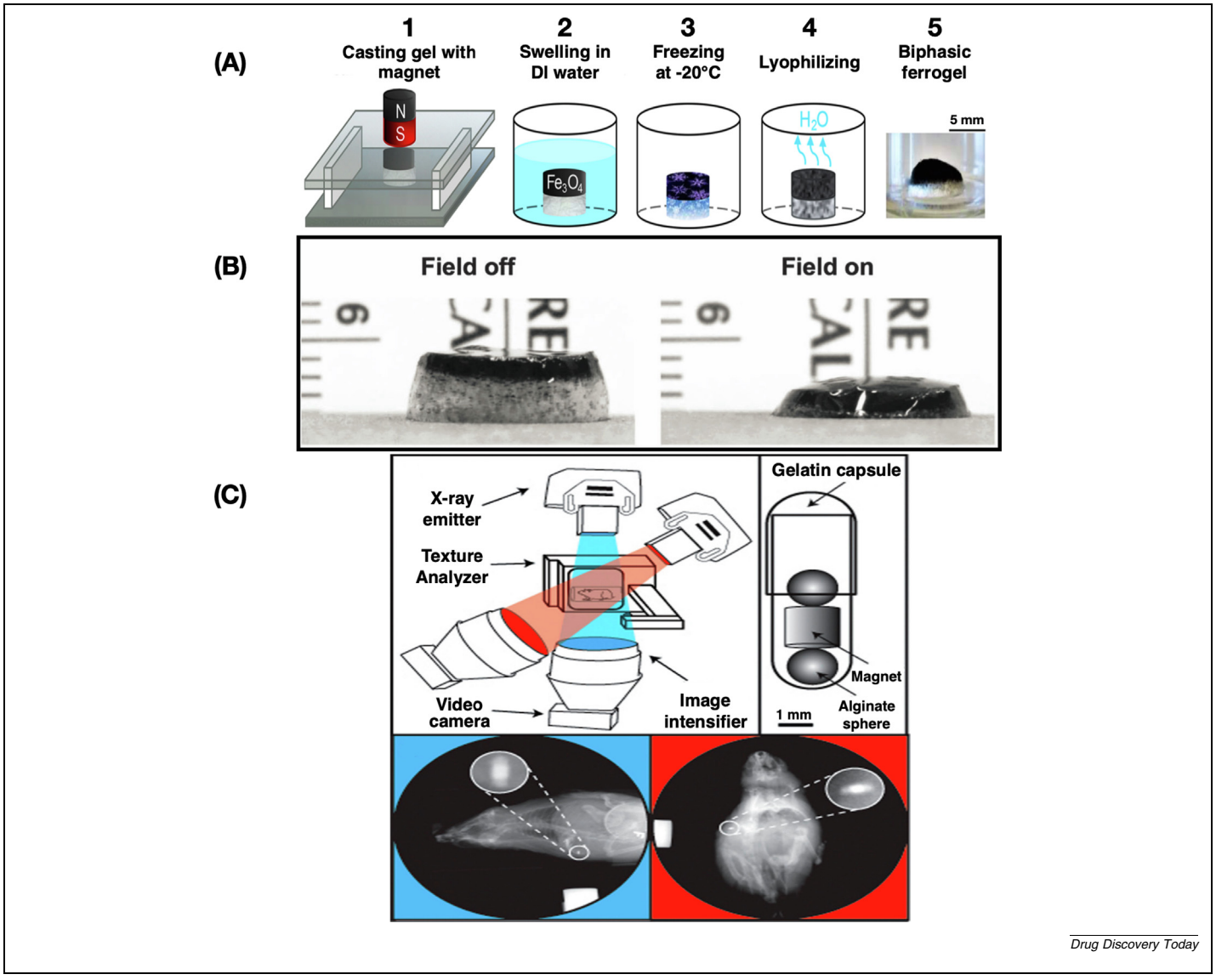

FIGURE 3

Delivery of therapeutics via the gastrointestinal tract by the magnetic method. (A) Biphasic ferrogel fabrication. Gels are formed between two glass plates with a magnet on top, swollen in deionized (DI) water after gel formation, frozen at –20 °C to form ice crystals, and lyophilized to evaporate the ice crystals and leave pores.[50] **(B)** Photographs of small iron oxide biphasic ferrogels in the presence of no magnetic field (field off) or a moderate vertical magnetic field gradient (field on).[86] **(C)** Using a biplanar video fluoroscopy system, researchers can see how the magnetic pill moves *in vivo*.[48]

tionary magnets to attract magnetic carriers close to the skin. As a result, the development of portable magnets to improve the efficiency of drug delivery is still a challenge.

Expandable hydrogels

This novel approach to achieve targeted drug delivery and local release was first introduced by Dorkoosh *et al.*[75,76] This drug delivery system relies on the use of superporous hydrogel (SPH) and SPH composites carrying solid oral dosages, such as small tablets. In the SPH synthesis process, the backbone chain of SPH is made up of acrylamide and acrylic acid monomers, which are then cross-linked with N,N′-methylenebis acrylamide. Sodium bicarbonate is added in the final step of the synthesis to generate CO_2, resulting in a large number of interconnecting pores within the polymer structure.[77] The large swelling capacity of this hydrogel facilitated the fixation of expanded formulation to the intestinal wall. *In vitro* and *ex vivo* studies showed that the opening of tight junctions occurred with the disruption of F-actin and occludin protein expression patterns.[76]

The oral bioavailability of insulin, octreotide, and buserelin administered via SPH composites was evaluated *in vivo* in a porcine model.[55,75,76] In these studies, two methods were employed for the drug loading of SPHs. In the first method, the dispersed drugs, melted in PEG 6000, were embedded into the hydrogel matrix. In the second method, mini-tablets were stuck to the outer surface of SPHs (Fig. 4A and B).[54] Both formulation types were obtained by inserting the SPH composite into Eudragit® S100-coated size 000 gelatin capsules and sealing the interior with biodegradable cyanoacrylate glue (Histoacryl®). This glue cover keeps the SPH from leaking out of the capsule. To ensure that the small capsule contents did not leak, the cap was also glued to the system's body with Histoacryl®.

When administered to pigs, by either the oral or the duodenal route, there was no significant difference in the bioavailability of the two formulations. The administration of SPHs containing insulin and subcutaneous insulin injections both showed bioavailability that was three times higher than that of an insulin control solution administered directly into the duodenum.[75]

Expandable hydrogels are attractive drug delivery approach because they combine several properties in one system, including local and targeted drug release, mucoadhesion, and permeation enhancement. The main issue with these formulations is that they may cause intestinal obstructions. As a result, researchers conducted a small clinical trial in which healthy volunteers

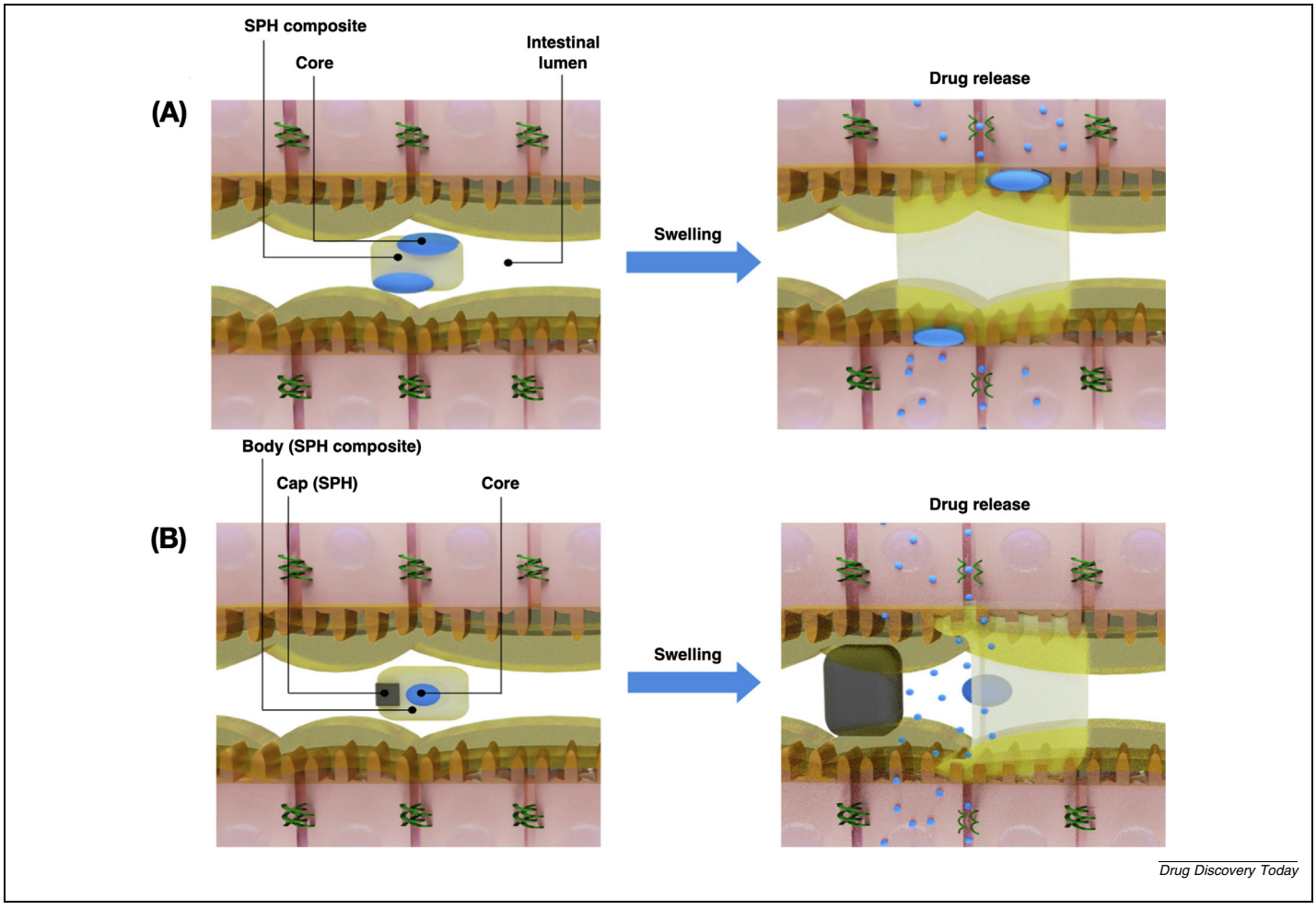

FIGURE 4

Superporous hydrogel (SPH) drug delivery formulation. (A) Drug molecules embedded in the hydrogel matrix are released from the core after the hydrogel has swelled. **(B)** Mini tablets adhere to the outer surface of the SPH, and the drug is released after the delivery system attaches to the intestinal wall. Reprinted from Luo *et al.*[87]

were given radiolabeled hydrogel formulations orally.[53] All formulations were loaded into enteric-coated capsules. After administration, the transition of the formulation along the GI tract was followed by scintigraphy imaging. The results were encouraging, but more research is needed to understand fully how these hydrogels behave in the highly dynamic GI environment. In addition, it is still not clear how food content can impact the performance of these swellable delivery systems.[53] Although the results on drug release from these studies were positive, there was no discussion of the effect of SPH on capsule shells, and there remains a possibility that SPH could affect the release profile or performance of the enteric-coated capsules. Future studies should evaluate the stability of hydrogels or macromolecules when they are loaded into gelatin capsules.

Iontophoresis

Iontophoresis is an efficacious technique for improving drug transportation across biological barriers. This non-invasive method can deliver drugs into tissue by using electrodes and an electric field, and it has been studied for the delivery of drugs to the skin, cervix, heart, tumors, tongue, buccal mucosa, and other tissues. Two decades ago, it was revealed that iontophoresis could also be used for drug delivery across intestinal tissue.[78] Although the FDA has approved iontophoretic devices for pharmaceutical and cosmetic applications, many have been withdrawn from the market due to safety concerns.[79]

Banerjee *et al.*[56] developed iontophoresis for the intestinal delivery of insulin via mucoadhesive patches. First, experiments on a formulation based on a Caco-2 cell monolayer support with a controlled electrical field were performed to study *in vitro* transport. The opening of tight junctions occurred, resulting in a three-fold increase in paracellular insulin transport when compared to control cells not exposed to an electric field. In the *in vivo* study, a mucoadhesive patch containing insulin and covered with aluminum foil was inserted directly into the small intestine of healthy rats for two hours. Without causing any damage to the intestinal tissue, iontophoresis produced a 63% drop in blood glucose in three hours.[56] The effectiveness of the treatment depended on the amount of insulin administered and the density of the electric field used.[56] These encouraging results suggest that orally administrable electric devices could be developed to allow clinical application of this approach in the future.[80]

Safety considerations and perspectives

For safety reasons, clinical trials have not been conducted on many of the devices mentioned here. Safety and device consistency are two of the most important concerns to be addressed before these technologies can be used in patients. The risk of GI obstruction and bleeding is a challenge that gastroenterologists frequently face when these devices are ingested.[1] Clinical guidelines have been established regarding the size and shape of drug delivery devices, and the potential complications that they might cause. The use of high-speed stream injectors and microneedle injectors in the GI tract may improve drug stability. Nevertheless, intestinal perforation can occur if a device designed for the stomach is placed in the small intestine instead. Fast transit of the small intestine may also be a problem for devices that need to be attached to the small intestine wall.[81]

Clinical studies have shown that oral ingestible devices larger than 3 cm require surgery to remove them from the GI tract.[82] This is, however, a much larger needle than is usually found in ingestible devices. Furthermore, clinical observations indicate that the ingestion of foreign objects has a low mortality rate.

The drug's penetration depth and molecule size are important factors for iontophoretic devices. A single delivery episode can reach only a certain drug penetration depth, meaning that multiple delivery episodes might be required for some macromolecules. Consequently, drug delivery by iontophoresis is confined by molecule size, with small molecules preferred.[83]

Prior research and the size of the objects used suggest that drug delivery devices that are ingested have the potential to demonstrate good results overall. However, additional research is required before it can be assumed that they are safe for successful translation. For example, numerous toxicology analyses have been carried out on some of these devices using methods such as IntelliCap and computational toxicology prediction, but these studies are still superficial.[84] In terms of macromolecule bioavailability, these devices outperform permeation enhancers and nanoparticles, and device-based concepts have entered the mainstream, but toxicology and scale-up may still be challenges.

Conclusions

Replacing injections with the oral delivery of macromolecules remains a challenge. Finding a solution for this challenge could improve patient care while lowering healthcare costs worldwide. Oral administration of GLP-1 agonist, semaglutide (Rybelsus®) and octreotide (Mycappsa®) are examples of primary goals, as the non-invasive chronic use of these drugs would provide undeniable therapeutic benefits. Progress in oral macromolecule delivery are expected to improve patient quality of life and safety. Material and fabrication advances have enabled formulators to consider alternative strategies that may overcome physiological barriers to the delivery of macromolecules via oral delivery. Physical oral devices have good potential to provide levels of bioavailability that are comparable to those achieved by parenteral routes. This line of research is critical for macromolecules such as peptides and proteins, which are poorly absorbed even with current permeation enhancers.

When compared to traditional methods, physical devices also allow for more precise drug release control by enhancing GI retention and improving localized and site-specific delivery. However, these methods are in the early stages of development although many of them have the potential to facilitate treatments. Numerous evaluations must be considered before their clinical application is permitted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

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