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Devices for drug delivery in the gastrointestinal tract: A review of systems physically interacting with the mucosa for enhanced delivery

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ABSTRACT

The delivery of macromolecules via the gastrointestinal (GI) tract remains a significant challenge. A variety of technologies using physical modes of drug delivery have been developed and investigated to overcome the epithelial cell layer of the GI tract for local and systemic delivery. These technologies include direct injection, jetting, ultrasound, and iontophoresis, which have been largely adapted from transdermal drug delivery. Direct injection of agents using needles through endoscopy has been used clinically for over a century. Jetting, a needle-less method of drug delivery where a high-speed stream of fluid medication penetrates tissue, has been evaluated pre-clinically for delivery of agents into the buccal mucosa. Ultrasound has been shown to be beneficial in enhancing delivery of macromolecules, including nucleic acids, in pre-clinical animal models. The application of an electric field gradient to drive drugs into tissues through the technique of iontophoresis has been shown to deliver highly toxic chemotherapies into GI tissues. Here in, we provide an in-depth overview of these physical modes of drug delivery in the GI tract and their clinical and preclinical uses.

Contents

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1. Introduction

Physical modes of drug delivery in the gastrointestinal (GI) tract involve disruption or perturbation of the epithelial cell layer. The immense surface area of the GI tract provides a large target for drug delivery. The primary goals of these forms of drug delivery are to: (1) increase local or systemic drug levels not achievable through passive routes, (2) mitigate first-pass metabolism of drugs, (3) deliver macromolecules or highly sensitive pharmacologic agents that are challenging to deliver orally and rectally, (4) painless delivery, and (5) self-administration [1–6]. Herein, we explore different physical modes of delivery to the GI tract including needles, jetting, ultrasound, iontophoresis, and others (Fig. 1).

2. Physical modes in the GI tract

The GI tract is a series of hollow organs spanning the oral cavity to the anus. Each organ of the GI tract plays a role in digestion, absorption, or both. The oral cavity, esophagus, and stomach are primarily digestive in function, whereas the small intestine and large intestine function to absorb nutrients including fats, proteins, carbohydrates, and water. Absorption of orally delivered agents primarily occurs in the small intestine. Certain agents, especially macromolecules, are challenging to deliver orally because of the acidic pH of the stomach, digestive enzymes, and poor absorption across the GI epithelium [5,6]. Physical modes of drug delivery have been developed to overcome these challenges in the GI tract.

When developing physical modes of drug delivery to the GI tract, important considerations must be made with regards to safety, anatomical regions, and device design. Two major factors that dictate safety of physical drug delivery modes are the depth of perturbation of the GI tract wall and the size and shape of the device. Regarding depth of perturbation, physical modes of drug delivery must ensure that the wall of the GI tract is not perforated, which could constitute a medical emergency. Physical modes of drug delivery to the stomach provides a greater latitude for safety due to the 4–8 mm thick stomach wall compared to the 0.5–2 mm thick intestinal walls [1,2]. The high frequency of GI tract epithelial restitution also provides a rapid protective mechanism. Superficial injury in the stomach, duodenum, colon, and rectum is repaired within hours due to rapid migration of viable epithelial cells to denuded basal lamina [2]. Additionally, previous work in swine models indicates that ~4–5 mm is the maximum allowable penetration depth of the stomach wall, with wall thickness ranging from 4 to 8 mm depending on location [2]. Device size is a critical safety factor that must be accounted for in order to avoid any unwanted device retention or obstruction. Largely informed by the solid osmotic-controlled release oral delivery system (OROS) dosage forms, capsule-shaped devices with dimensions of 9 mm in diameter and 15 mm in length provide a safe benchmark for designing ingestible drug delivery systems, with only one significant GI adverse event occurring in approximately 76 million distributed tablets with these dimensions [3,4].

Significant variability exists between the different regions of the GI tract, especially with respect to pH and transit time (Fig. 2). Along the GI tract, the pH of the stomach is typically around 1–2, the pH in the duodenum of the small intestine is approximately 6, the pH then increases along the remainder of the small intestine to approximately 7.4 at the terminal ileum, where the pH then decreases to 5.7 in the cecum, and finally reaches 6.7 in the rectum [5,6]. The pH in a given location along the GI tract may inform what drugs can be delivered due to their stability [7,8]. Importantly, variation in transit time along the GI tract between patients is a critical consideration when designing drug delivery systems. Another aspect of the GI tract that is important to consider when evaluating physical modes of drug delivery in the GI tract includes the luminal macro- and microscopic architecture, including the gastric rugae, colonic haustra, and intestinal villi [2].

Triggers that activate drug release, both internal and external, are an important consideration for targeted drug delivery in the

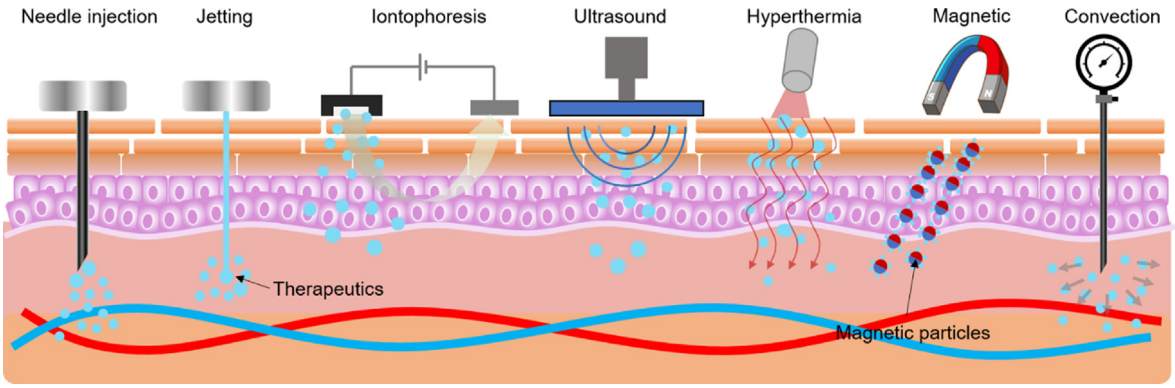


Fig. 1. Overview of physical modes of drug delivery to the GI tract including needle injection, jetting, iontophoresis, ultrasound, hyperthermia, magnetic, and convection.

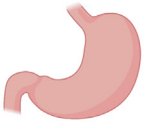
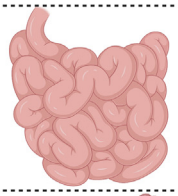
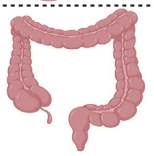
Section of GI tract	Wall thickness	pH	Transit times
	1.6-2.9 mm	7.4	4-8 seconds
	4.0-8.0 mm	1.0-2.0	4-5 hours
	0.1-2.0 mm	6.0-7.4	2.5-3.0 hours
	0.1-3.0 mm	5.7-6.7	30-40 hours

Fig. 2. Regions of the GI tract for physical modes of drug deliver [5–7]. Created with BioRender.com.

GI tract. Time-delayed or pH-responsive drug release mechanisms can leverage the variability of the different sections of the GI tract to induce drug release to a specific location [6,9–17]. Challenges may arise with pH responsive systems regarding variation in GI pH level due to diet or the use of proton pump inhibitors for treatment of acid-related GI disorders [18]. Additionally, variability in transit time between patients can complicate repeatability and reliability of time-delayed drug delivery devices. These challenges motivate the development of external triggers. Radiofrequency controlled pills are an alternative, non-passive options for physical drug delivery that allow for the physician or patient to deliver a drug at a specific instance when the device location is known [3,19–22]. However, these approaches are limited because the current size constraints of the electronics and batteries result in systems that pose an obstruction risk due to their large size [23].

Device functionality is a final critical consideration. Ideally, an ingestible drug delivery system would be able to simultaneously sense a given analyte or biomarker and respond accordingly via controlled drug delivery in a closed-loop system [24–26]. However, combining diagnostics and therapeutics into a single system still faces significant challenges in size, complexity, and reliability. Table 1 shows a summary of the physical modes of drug delivery to the GI tract.

Lastly, the physical modes of drug delivery to the GI tract have been largely adapted from transdermal drug delivery. The epidermal and dermal layers of the skin provide a significant barrier for transdermal delivery, and hypodermic needle injection, jetting, ultrasound, and iontophoresis have all been established for transdermal delivery of agents [3]. For use of these drug delivery techniques in the GI tract, there are a few considerations that must be acknowledged including needle path, method of injection, miniaturizing devices for placement in GI tract without obstruction, and power constraints [1–4,26].

3. Injection

3.1. Endoscopic needle injection

Endoscopic needle injection has become an important drug delivery technique for treating diseases of the GI tract since being described in 1911 [27]. To date, endoscopic needle injection of vasoactive agents, sclerosing agents, botulinum toxin, and tissue adhesives are routinely used to treat common GI diseases such as gastrointestinal bleeding, achalasia, and sphincter of Oddi dysfunction [28–40]. Endoscopic needle injection has become a mainstay therapeutic option in gastroenterology.

Endoscopic injection needles are relatively simple devices composed of a polymeric external catheter surrounding a metal needle connected to a handle with a Luer lock connection. The connection enables use of a syringe for delivery of drugs. There are multiple endoscopic injection needles currently available. One primary example is the Carr-Locke injection needle, which is widely used in endoscopy procedures for injecting medications during procedure. Carr-Locke needles are known to perform in the most tortuous conditions, including when the endoscope is in retroflexion or the elevator is engaged in a duodenoscope [35].

3.2. Capsule endoscopy and non-endoscopic GI tract perturbation techniques

A primary tool of gastroenterologists to evaluate the GI tract is the flexible endoscope. However, flexible endoscopy has major limitations including the invasiveness of the procedure, requirement of sedation, and the inability to visualize the entire GI tract. Techniques outside of the flexible endoscope have been developed for biopsy and monitoring, including the non-endoscopic tubes,

Table 1
Summary of physical modes of drug delivery to GI tract.

Physical mode	Specific technology	Anatomical region of delivery	Type of delivery	Drugs tested	Validation	References
Injection	Endoscopic injection needles	GI tract	Local	Vasoactive agents, sclerosing agents, botulinum toxin, tissue adhesives, paclitaxel	Preclinical and clinical	[28,29,31–34,36,38–40]
Injection	Capsule endoscopy and non-endoscopic biopsy	GI tract, specifically stomach, duodenum, jejunum, and colon	Local	Acetylsalicylic acid, ketorolac tromethamine	Preclinical and clinical	[54–56,69,70]
Injection	Microneedles and nanostraws	GI mucosa, buccal mucosa, tongue, palate, sublingual, and gastric wall	Systemic	Insulin, human growth hormone, octreotide, diltiazem	Preclinical and clinical	[1,2,50–52,74–76]
Jetting	Liquid jet devices	Various via intradermal, transdermal, subcutaneous, and intramuscular routes	Local	Insulin, antibiotics, local anesthetics, antivirals, hormones, vaccines, cancer therapeutics	Preclinical and clinical	[91,93,94,167–182]
Ultrasound	Focused ultrasound with microbubbles	Intravascular, transdermal, buccal mucosa, and CNS	Local	Liposomal doxorubicin, contrast agents	Preclinical and clinical	[114–117,125,126,140]
Ultrasound	Low frequency ultrasound	Transdermal and GI tract	Local	Macromolecules, hydrophilic compounds, vaccines, lipid polymeric nanoparticles, budesonide, glucose, insulin, mesalamine, hydrocortisone	Preclinical	[127–139]
Iontophoresis	Endoluminal and implantable	Intestinal lumen and mucosa, buccal mucosa, cervix, heart, and tumor tissues	Local	Gemcitabine, FOLFIRINOX	Preclinical	[4,6,7,142–145]
Iontophoresis	Mucoadhesive systems	Stomach and duodenum,		Insulin	Preclinical	[146,147]
Heat	Direct laser ablation	Various via transdermal route	Local	Human growth hormone, sulforhodamine B, and bovine serum albumin	Preclinical	[148–151]
Heat	Magnetic nanoparticles	GI tract	Local	Insulin, fluorophores, organic and inorganic polymeric particles	Preclinical	[152–155]
Heat	Near-infrared radiation	Various via transdermal, transmuscular, and intracellular routes	Local	Ligands, nanoparticles, fluorophores, doxorubicin	Preclinical	[156]
Magnetic	Magnetic nanoparticles	Various via transdermal, transmuscular, intracellular, and transvascular routes	Local	Chemotherapeutic agents, genetic material	Preclinical and clinical	[157–160]
Magnetic	Ferrogels	Various via intracellular route	Local	Chemotherapeutic agents	Preclinical	[161–164]
Electric fields	Electro-responsive hydrogels	Various via subcutaneous route	Systemic	Micro and macromolecules, both charged and uncharged (e.g. hydrocortisone, insulin	Preclinical	[165]
Convective-enhanced delivery	N/A	Interstitial spaces of CNS	Local	Chemotherapeutic agents	Preclinical and clinical	[166]

Crosby capsules, Video Capsule Endoscopy (VCE), and the Bravo system, among others [41]. Over time, capsule endoscopies have morphed into active devices with therapeutic applications, such as injection capability into the GI tract for drug delivery.

To provide a historical context for development of endoscopic drug delivery, we provide an overview of both non-endoscopic and endoscopic techniques that resulted in subsequent technologies capable of drug delivery. Prior to the development of capsule endoscopy, non-endoscopic GI interventions (e.g. obtaining gastric or small intestine biopsy) involved the use of flexible or rigid tubes that reached the stomach or duodenum. An initial concept used a Bowden cable without the aid of a gastroscope. Upon placement into the GI tract at the specific distance of interest, suction was applied pulling the tissue into the tube. A cylindrical knife was actuated with a wire, and a section of tissue was pulled into the tube [41,42]. The reproducibility of this technique came into question, as others attempted this biopsy suction technique without success [43–45]. To reach the duodenum, a longer (128 cm) wood suction tube was created [46,47]. The tube was weighted to enable passage through the pyloric sphincter, and it became known as the Quinton-Rubin tube [48]. Subsequently, the US army's Sprue team created the Crosby capsule that similarly used suction and a rotary knife to take biopsies within the GI tract [49]. A key aspect of the Crosby capsule was the flexibility and length of the capsule tether allowing for access to the jejunum. The perturbation techniques created by the Crosby capsule have provided precedence for many different physical modes of drug delivery in the stomach and small intestine [1,50–52].

The Crosby capsule has inspired many other capsule devices [53]. A robotic biopsy device concept consisting of tissue monitoring, anchoring and biopsy components enabled the device to obtain a biopsy when electronically activated. Magnetically-driven capsules that performed tissue biopsy and repair have been designed and tested in pre-clinical models [54,55]. Other capsules have been developed to collect additional data include the Medtronic Bravo, which is a catheter-less device for pH monitoring. The Bravo monitors esophageal pH by adhering to the esophageal mucosa using suction and a pin for physical immobilization. The entire monitoring procedure lasts 48 h but can be extended to 96 h [56].

Early-stage capsule endoscopy had several limitations, including the inability to orient, adhere to tissue, and deliver drugs. To address some of these shortcomings, magnetically activated and controlled systems, mechanical pistons, light-responsive materials, and microelectromechanical systems (MEMS) have been incorporated into capsules to enhance control over movement of the capsules and delivery of drugs [57–68]. For example, a capsule endoscopy system was developed for drug delivery and actuated

by an external magnetic field. The system was tested in a feasibility study in 13 healthy volunteers and shown to safely deliver acetylsalicylic acid without complication [69]. Other unique systems include an inchworm-like endoscopic robot that operated using magnetic field strength vectors and was shown to move up and down the GI tract, and a mechanochemical gripping robot that was able to maintain a long-residential time in the stomach due to the gripping arms [70].

3.3. Microneedles and nano straws

Nano- and micro-needle-based technology has increasingly become the subject of investigation since the mid-1990s when microfabrication technology started to grow globally [71–73]. Microneedle application had been mostly evaluated for delivery of drugs and vaccines to the skin and eye [50]. Transdermal delivery of a wide variety of agents, including small molecules, proteins, and vaccines, have been tested pre-clinically and clinically [50].

Incorporation of injection capability into ingestible devices such as capsule endoscopy, microdevices, and pills can provide a reliable means of drug delivery (*i.e.*, oral drug administration). Considering the small size of ingestible devices, potent solid drug formulations designed as nano-, micro-, and milli-meter sized needles are ideal for incorporation into these devices. However, there is growing interest in delivery of nano- and micro-needles into the mucosa of the GI tract given the large surface area for delivery [1–3,51,74].

Microdevices with planar, asymmetric geometries and nanostraw surface membranes were created to overcome the challenges of drug delivery in inflamed GI tissue. These devices consisted of materials from FDA-approved devices and were shown to have facile drug loading and tunable drug release, with their nanostructure enabling adhesion to GI mucosa and subsequent drug delivery. Furthermore, these devices prolonged drug release and reduced breakdown of drugs within the GI tract [74]. Other microdevices created through additive manufacturing techniques involving inkjet printing of Eudragit FS 30 D were created for oral delivery

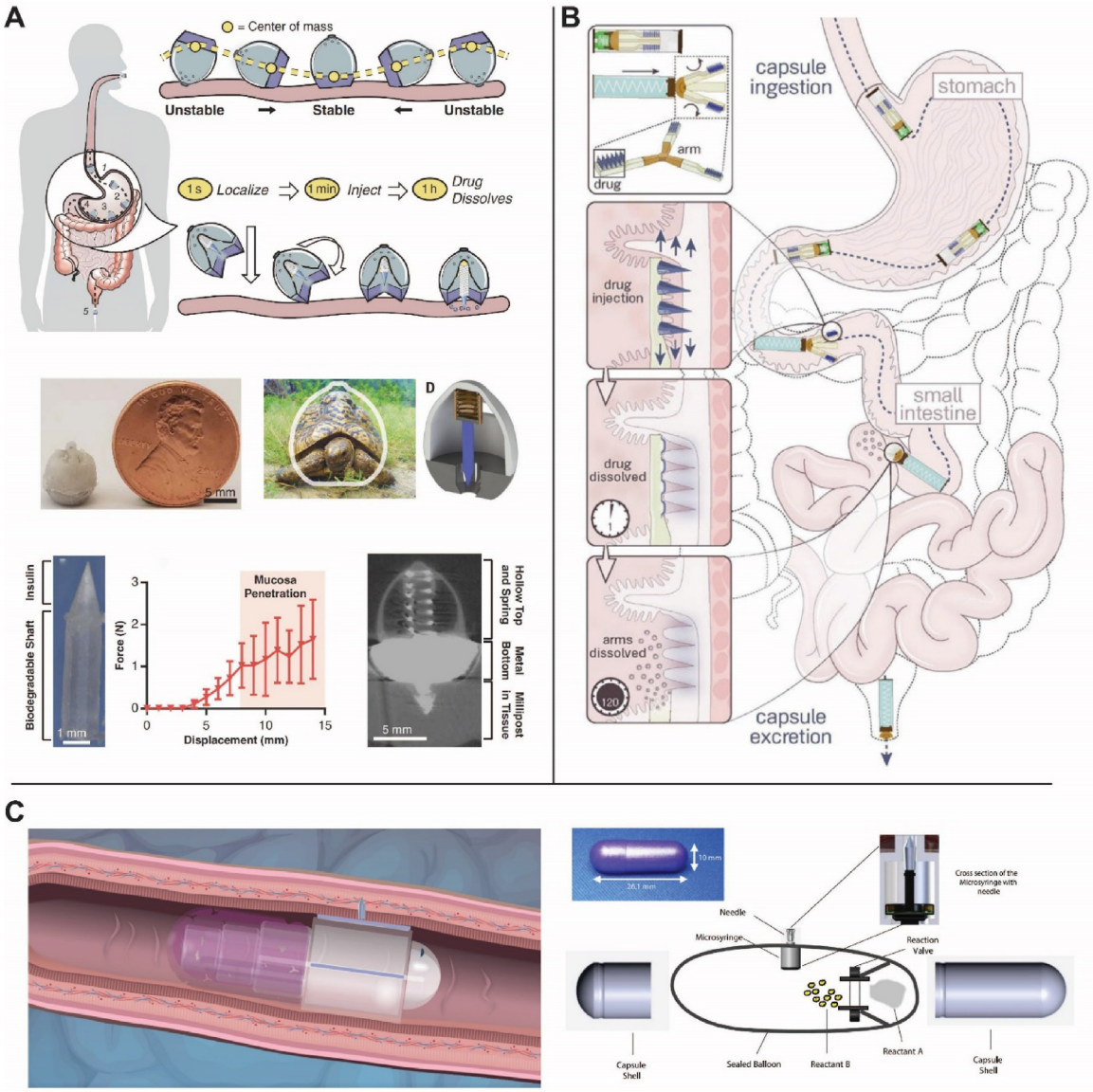


Fig. 3. Microinjectors for drug delivery through the gastric and intestinal walls. (A) SOMA device that localizes and injections an API into the gastric wall [1]. (Top) depiction of SOMA device positioning in gastric wall. (Middle) Design and size of the device. (Bottom) Design of solid API needle and force required for gastric wall insertion. (B) LUMI device that injects microneedles into small intestine and dissembles for excretion [51]. (C) RP device from Rani Therapeutics for injection of an API into small intestine [52]. (Left) Depiction of injection into intestinal wall. (Right) Design and size of RP device. Adapted with permission from AAAS and Springer Nature.

of highly sensitive macromolecular agents. Using insulin as a model drug, it was found that by capping the microdevices, the insulin maintained a high degree of stability and controlled release [50].

Microneedle systems directed for GI delivery have also been investigated to deliver at specific locations of interest. One such example was a microneedle-covered capsule that was shown to safely transit through the GI tract, including the stomach, duodenum, and colon. Additionally, GI injection of insulin demonstrated comparable and even more rapid hypoglycemia onset as compared to subcutaneous administration. It was proposed that a pH-responsive polymer could encapsulate the device and then dissolve at the appropriate anatomical location for delivery of macromolecules, whether through injection during peristalsis or release of the microneedles for delivery [75]. Another example is a microneedle patch designed for buccal administration of human insulin and human growth hormone. A thorough evaluation of the impact of anatomical location on microneedle application in buccal tissue was performed, including microneedle delivery to the tongue, palate, buccal cheek, and sublingual region. Pharmacokinetic analysis of the drugs after buccal administration demonstrated therapeutic levels of the drugs. Subsequently, an acceptability study of the buccal administration of the microneedles was performed in 100 healthy volunteers. Participant preferences for location of microneedle administration revealed that the palate was the preferred site of delivery [76].

Mechanical devices with micro- and milli-meter sized needles have been developed for macromolecular drug delivery to the GI tract (Fig. 3). One example is the self-orienting millimeter-scale applicator (SOMA) device that is capable of self-orientation to the gastric wall due to the center of mass and design similar to that of the leopard tortoise (Fig. 3**A**). A solid drug formulation of insulin was incorporated into the SOMA device and a mechanical spring was used to inject the solid drug needle into the gastric wall resulting in a drop in blood glucose in swine [1,2]. The gastric cavity offers several potential attributes including: an opportunity for minimization of variability due to the general rapid transit of material through the esophagus, a thick mucosal wall enabling deeper penetration with dosage forms and avoidance of the dependency on pH triggers which may be confounded in certain populations including those taking proton pump inhibitors. A limitation of this technique was the inability to control the actuation of the drug delivery [1]. Another novel microneedle-based mechanical device known as the Luminal Unfolding Microneedle Injection (LUMI) device was designed to open in the small intestine and deliver an active pharmaceutical ingredient directly into the intestinal wall (Fig. 3**B**) [51]. Using a compressed spring and pH responsive polymer coating, the system deployed upon exposure to pH 5.5 in the duodenum. After deployment of the drug, the LUMI device degraded to reduce the possibility of intestinal obstruction. In swine, the LUMI device delivered insulin into the intestinal wall and was able to achieve a significant reduction in blood glucose compared to administration of an insulin solution placed into the small intestine [51].

An ingestible robotic pill (RP) developed by Rani Therapeutics also has the unique capacity to deliver therapeutics directly into the intestinal wall (Fig. 3**C**). The system was designed with an enteric coating housing a balloon and microinjector. Upon reaching the small intestine, the enteric coating could dissolve and the device was then directly exposed to intestinal fluid resulting in a chemical reaction inflating a balloon. Once the balloon inflated, the microinjector punctured the intestinal wall delivering its drug cargo. A unique series of clinical trials were performed in healthy volunteers evaluating the success of drug delivery and pharmacokinetic analysis after deployment which demonstrated increasing successful drug delivery through iterative device design. Furthermore, the RP was able to effectively dose octreotide at therapeutically relevant levels in line with intravenous administration [52]. Another robotic platform capable of providing controlled release of a drug, monitoring GI transit times, and providing feedback on drug absorption is the IntelliCap. This platform was tested in a feasibility study in healthy volunteers and showed controlled delivery of diltiazem and excellent concordance with established pharmacokinetic profiles of the drug [77].

3.4. Safety of ingestion of sharp objects

Ingestion of sharp and foreign objects is a recognized clinical challenge often faced by gastroenterologists. A key challenge in these cases is determining the probability of morbidity and mortality from ingestion of the object. Guidelines have been established to address these scenarios that account for size and shape of the ingested object, as well as potential for complications [78]. It is known that a foreign object that passes into the stomach has a high likelihood of spontaneous elimination through the rectum, including sharp objects [79–81]. A case series of over 500 patients revealed that large size (>3 cm) determined the need to surgical remove the foreign object [82]. This size is much larger than the size range of needles typically being used in the ingestible devices. Furthermore, mortality rates among foreign object ingestion is very low. A review of case reports revealed that there were no deaths among 852 adult patients and 1 death among 2206 children [83–86]. In summary, based on prior studies and the size of needles, small capsules with microneedle drug delivery system are likely to be safe though further study will be required for successful translation.

4. Jetting

4.1. Historical development and applications

Jet injection is a needle-less method of drug delivery where a high-speed stream of fluid medication penetrates into a targeted tissue through a nozzle orifice and can provide enhanced or comparable immune response and excellent bioavailability compared with traditional needle and syringe injections [87,88]. The first example of jet injection was reported in the 19th century when a mechanic lost his finger due to accidental injection of fuel oil from a Diesel engine that later triggered the idea of using needle-free jet injection systems for medical application in the 1930s [89,90]. Since then, jet-injection mechanical devices have been in development and investigated for more than 80 years, with the goal of delivering vaccines and drugs across various length scales from small molecule and peptides [91] to macromolecule and proteins [92] and providing enhanced efficacy in the prevention, management and therapy of various bacterial diseases and cancers [93,94]. The jet injectors are typically made of a liquid drug reservoir that can be compressed by moving a piston to eject the pressurized (from 14 to 35 MPa) high-speed stream of drug solution (from 100 to 200 m/s) through a tiny orifice (from 0.05 to 0.36 mm, which is smaller than hypodermic needle, 0.81 mm for a 21G needle) that lasts about 1⁄3 to 1⁄2 of a second [95]. The jet stream punctures the skin to deliver a drug into the intradermal, subcutaneous, or intramuscular tissues. The penetration depth of the jet into a tissue is a function of the geometric features of injectors such as orifice diameter and shape, flow rate and viscosity of fluid jet stream, angle of injection, and the material properties and thickness of the targeted tissue [96,97].

Jet injectors are classified based on the mechanism of operation, which refers to the source of energy generation/storage to form and eject a high-pressure narrow stream of liquid drugs through a nozzle orifice. The examples are precompressed spring- or gas- [98], piezoelectric- [99], laser-, acoustic-, electric- [92], and electromagnetic- [100] powered jet injectors. For example, spring- or gas-powered injectors squirt the drug liquid using the sudden release of energy from a compressed spring or gas, such as CO_2 or N_2. Electrical power from batteries, hydraulic pressure, and manually applied mechanical force can be used to compress the spring. Piezoelectric transducers have been employed to develop miniaturized microjets that can drive liquid therapeutics through a micronozzle (50–100 μm diameter) into the skin. Such piezoelectric transducers have been shown to rapidly (~10 μs) expand to push a plunger that ejects and delivers a 10-nanoliter microjet of drug solution with a mean velocity of 127 m/s from a 100-μm diameter micronozzle [101]. Electromagnetic controllable jet injectors operate based on a linear Lorentz-force motor that can safely and precisely inject up to 250 μL into animal tissue up to a depth of 16 mm [102].

4.2. In vivo GI tract jetting

Jet injectors can be also classified based on the site of administration. The skin is a unique vaccination site due to its immune-rich milieu and its ability to induce humoral and cellular immunity [103]. The transdermal delivery of drugs and vaccines using jet injectors has been widely studied and demonstrated as an advantageous route compared to oral administration, topical application, and hypodermic needle injection [91,104,105]. Over the past 20 years, there has been an increased focus on developing jet-injection ingestible systems that can be self-deployed in the GI tract and locally deliver drugs and biologics, especially given the unique immune environment of the GI tract. The GI tract houses the largest number of immune cells in the body. The gastrointestinal associated lymphoid tissue (GALT), including areas of lymphoid follicles called Peyer's patches, provide rich sites that maintain immune homeostasis but can be harnessed for vaccine delivery [88].

Swallowable multi-nozzle dosing devices have been proposed in patent applications including designs for releasing medicines in the GI tract. The proposed devices are ingestible capsules filled with liquid medication that can be orally administrated and dispense the medication at/near tissue sites of interest in the gastrointestinal tract. They are comprised of a hollow shell as a reservoir to store medication, a piezoelectric droplet jet nozzle dispenser to eject medication through the shell wall, a dispensing axis, a closed-loop feedback regulator for delivery of the medication through the nozzle, a pressure sensor for sensing liquid pressure, and a power source. The capsule shape was designed to rotate and/or translate during release of a medication to homogeneously dispense the drug into the tissue sites of interest [106,107].

Recent technological advancements in digital fabrication and precise manufacturing have enabled the production of micro- and meso-systems and medical devices [108]. MucoJet is a 3D printed needle-free microjet immunization system that produces a high-pressure liquid jet for delivery of vaccines into the buccal tissue. Jet-spray systems provide a painless buccal alternative to the needle and are reported to deliver seven times the amount of ovalbumin into the bloodstream of rabbits compared to superficial placement on the buccal tissue [109]. Jetting of therapeutic agents into buccal tissue provides facile delivery in an immune cell rich environment for vaccine applications. A key challenge for transitioning into an orally delivered jet injector is the safety of gastric or intestinal wall penetration.

5. Ultrasound and low frequency sonophoresis

5.1. Background of ultrasound

Ultrasound (US) has been used in medicine since the end of the second World War [110,111]. Ultrasound involves the use of high-frequency longitudinal waves for diagnostic and therapeutic applications and is used daily in most hospitals across the world. As a non-radiation-based imaging technique, US can be applied to imaging of pregnant women and patients [112,113]. Ultrasound serves not only as a powerful diagnostic tool but also a unique method to facilitate delivery of therapeutic agents via a non-invasive manner. When combined with microbubbles, the high-frequency longitudinal waves can create cavitation and hyperthermia resulting in rapid and targeted delivery of drugs. Furthermore, ultrasound is often used in lithotripsy and tumor ablation, among other surgical applications [114–117].

5.2. Ultrasound with endogenous and exogenous microbubbles facilitates drug delivery

Ultrasound together with endogenous or exogenous microbubbles can permeabilize blood vessel walls and enable extravascular delivery of drugs into diseased tissue or areas of interest [118–120]. Exogenous microbubbles in the form of 1–4 μm gas-filled polymeric particles can concentrate acoustic energy more effectively than endogenous microbubbles and have a lower threshold for cavitation [121–124]. These microbubbles also act as intravenous contrast agents. Lastly, the collapse of these microbubbles can enable targeted drug delivery at the site of interest, such as a tumor or inflamed tissue.

Focused US with microbubbles has been demonstrated to reversibly disrupt the blood–brain barrier (BBB) for drug delivery into the central nervous system (CNS) [125]. In fact, magnetic resonance (MR)-guided focused ultrasound has been tested in clinicals trials for permeabilizing the BBB and validated this technique as a method of CNS drug delivery in humans [126]. The capability of using both diagnostic imaging and therapeutic US was proposed to remove the need for MR and generate a closed-loop targeted therapy. A dual transducer US system operating at a frequency of 274.3 kHzA was developed for stable cavitation without inertial cavitation behavior to facilitate drug delivery and monitoring in a rat glioma model [115].

5.3. Low frequency ultrasound mediated transdermal drug delivery

Low frequency US, also referred to as low frequency sonophoresis (LFS), has been demonstrated to be an excellent technique for transdermal drug delivery. Transient cavitation at low frequency ranges of 20 kHz to 100 kHz enhances drug delivery through localized transport regions. Drug penetration is improved within these transport regions [127,128]. Multiple teams have shown that the use of LFS can enable delivery of compounds that are challenging to deliver across the skin, including macromolecules, hydrophilic compounds, vaccines, and lipid and polymeric nanoparticles [127–136].

5.4. Ultrasound mediated drug delivery at the GI tract

The success in US-enhanced transdermal drug delivery has motivated researchers to evaluate US for delivery of large drug molecules through the GI tract. Patients with gastrointestinal disorders, such as inflammatory bowel disease, would benefit significantly from rapid US-based delivery of agents, especially in diseases where treatments include the local administration of

anti-inflammatory medication through enemas or other topical applications. Efforts in identifying optimal transport parameters and devices are underway to rapidly translate these systems to patients [131–136]. This is critical for ensuring safety of these systems.

To evaluate the utility of US in the GI tract, a hand-held system for LFS was developed and tested for delivery of macromolecules to the buccal mucosa of unsedated dogs. It was found that the treatment was well-tolerated, and there was no macroscopic change in buccal mucosa of the animal. They also showed that LFS can improve the delivery of budesonide in reducing the development of oral mucositis in hamsters [137]. Furthermore, the rectal US delivery of glucose, insulin (5 kDa), mesalamine, and hydrocortisone were successfully demonstrated in swine and found to have significantly higher concentrations after 1 min of US application compared to topical application without US [128]. The delivery of other macromolecules has also been investigated including small interfering RNA and messenger RNA and have shown successful delivery through fluorescence imaging and histologic markers [134].

To further enhance the efficiency of drug delivery in the GI tract, ultrasound-stimulated phase change contrast agents (PCCAs) have been created. When combined with US, the PCCAs have been shown to increase the transport of macromolecules through monolayers of Caco-2 cells. The use of PCCAs with ultrasound significantly increased the amount of a fluorophore-tagged dextran in the receiver compartment [138].

5.5. Engineering prototypes for targeted delivery of macromolecules at the GI tract via ultrasound integrated endoscopy technologies

The integration of US delivery of macromolecules through an endoscope provides an opportunity to deliver agents across the majority of the GI tract. A novel piezoelectric single crystal ultrasonic transducer incorporated onto an endoscope was shown to enable drug delivery in gastric mucosa [139]. In *ex vivo* tissue, the permeability of the gastric mucosa to albumin significantly increased (by ~5.6 times) in the presence of US treatment. Adjusting the duty cycle ratio of the ultrasound transducer enabled control over the permeability of the tissue. Furthermore, by taking advantage of the untethered feature of capsule endoscopy, a proof-of-concept capsule device was developed for combination imaging and drug delivery. In swine, this technique was shown to be able to deliver quantum dots into the mucosa of the small intestine using the combination of ultrasound and microbubbles [140].

6. Iontophoresis

6.1. Background of iontophoresis

Iontophoresis is the transport of dissolved drug molecules under an applied electric field. In the most simplistic form, iontophoresis involves driving a drug into tissue using a positive and negative electrode. Although predominantly a non-invasive method of drug delivery through the skin, this technique has been adapted for delivery of molecules through a variety of physiologic barriers, including cervix, heart, tumor, tongue, buccal mucosa, and others [4–6]. The first embodiment of this technique was described in the 18th century by Giovanni Francesco Pivati [3]. The field has significantly expanded over the next few centuries from the initial description, and a multitude of agents have been tested and delivered for therapeutic applications.

Important key criteria for iontophoretic drug delivery are drug and electrode characteristics. There are two major contributors to drug flux from iontophoretic drug delivery, including electromigration and electroosmosis. Electromigration is a charge-charge repulsion occurring at the electrode interface between the drug and the electrode. Electroosmosis is a fluid flux mechanism where there is volume flow induced by the current flow. For small, charged molecules, electromigration is the primary driver of drug transport. With increasing size and reduced polarity, the major contribution to drug flux becomes electroosmosis [141]. The balance of electromigration and electroosmosis can determine the amount of drug flux achieved. For active drug flux, there are different types of electrode materials used for iontophoretic drug delivery. These materials are traditionally classified as electrochemically reversible and inert. Reversible electrodes use materials that will recharge themselves upon reversing polarity, such as Ag/AgCl electrodes. In these electrodes, AgCl builds up on the Ag electrode as a cathode and then will release Cl^- upon reversing polarity. Inert electrodes, such as platinum, do not break down or change upon application of a voltage [142].

6.2. Endoluminal and implantable iontophoretic systems

Within the GI tract, there are opportunities to apply iontophoretic systems for the treatment of disease. One such example is the use of iontophoresis to treat cancer. Systemic chemotherapies impact both tumors and normal tissue, which results in side effects. To improve the therapeutic index of chemotherapies, implantable and endoluminal iontophoretic devices have been developed [142,143].

These devices were designed for discrete episodes of drug delivery through a reservoir-based electrode system, where a drug solution was infused into the device at a pre-specified rate to create a constant concentration around the electrode interface. The devices were initially tested on tumor tissue surrogates and *ex vivo* tumor tissue and found to enable significantly greater delivery of chemotherapies, including gemcitabine and FOLFIRINOX, through the device when an electric current was applied [143–145]. Furthermore, the amount of current applied was directly proportional to the amount of drug delivered. The devices were then tested in orthotopic patient-derived xenografts of pancreatic cancer. Single treatment pharmacokinetic studies revealed that the majority of drug was in the tumor with minimal systemic exposure. In efficacy studies, the devices were implanted for 8 weeks, with the first week allowing for device encapsulation within the abdominal cavity. Twice weekly 10-minute treatments with gemcitabine showed a significant reduction in tumor size compared to controls of intravenous (IV) gemcitabine, IV saline, and device saline. In addition, once weekly 20-minute treatments with FOLFIRINOX also demonstrated a significant reduction in tumor size compared to IV FOLFIRINOX, IV saline, and device saline controls. Furthermore, given the challenge of device implantation on pancreatic tumors, endoluminal deployment was also proposed for delivery to tumors on the head of the pancreas [143].

6.3. Mucoadhesive iontophoretic systems for intestinal delivery of biologics

The delivery of biologics through the GI tract remains a significant challenge due to the harsh environment of the stomach and duodenum. The use of an applied electric field to permeabilize the intestinal epithelium offers a unique way to enable cellular internalization of biological agents [146,147].

Proof of principle evaluation of this concept involved delivery of a FITC-insulin across a Caco-2 monolayer under a mild electric current, which revealed an increase in insulin transport. The tight junctions across the Caco-2 monolayers were also found to be disrupted by the applied electric current. Studies in small animals

were then performed using a laparotomy to expose the intestine and then place an insulin mucoadhesive patch on the luminal side of the intestine. A pulsed sequence of iontophoresis was subsequently performed, where current was applied for 1.5 min and then off for 3.5 min. This cycle was repeated 12 times, and the animals were closed. Blood glucose was trended, and the animals were found to have a significant drop in glucose compared to subcutaneous administration of insulin. Various currents were evaluated and found to not result in a significant drop in blood glucose level [146]. For clinical translation, there will need to be significant development of fully encapsulated systems to ensure no leakage of current or voltage.

7. Other modes of delivery

Various other drug delivery methods may provide opportunities for physical modes of drug delivery in the gastrointestinal tract. Heat has been demonstrated to significantly facilitate physical modes of drug delivery [148,149]. For transdermal application, the removal of the stratum corneum via direct laser ablation using localized microsecond heat pulses has been performed to create microchannels on the order of 10 μm to 100 μm in diameter in the skin [150,151]. Additionally, hyperthermia has been in use for many years as a cancer therapeutic [152], and more recently has been explored as a way to induce localized heating via magnetic nanoparticles in order to activate drug delivery [153]. Apart from the physical delivery of heat to tissue in order to induce or improve drug delivery, heat has also been explored as a triggering mechanism for controlled drug delivery in the GI tract [154,155]. In this method, drug delivery capsules were encapsulated in a nanoparticle-embedded wax to protect the capsules from the pH swings in the GI tract environment. Magnetic hyperthermia was used to melt the wax via nanoparticle motion to generate heat and expose the capsule to activate the drug delivery system. In addition to directly using heat via laser ablation or magnetic hyperthermia, near-infrared radiation (NIR) has been demonstrated as a useful method for triggering physical drug delivery [156]. NIR waves from 650 to 900 nm are able to penetrate tissue up to centimeters deep with very little in the tissue that absorbs these wavelengths, indicating potential for a safe and effective external triggering mechanism. The use of NIR-absorbing gold nanoparticles have been shown to play important roles into the drug delivery mechanism [156].

Magnetic methods of drug delivery have also been explored [157–159]. Typically, these approaches leverage a magnetic nanoparticle that serves as the core of the particle and is what moves or activates the system when put under the influence of an external magnetic field. This particle is then coated with some protective coating such as an organic coating or silica. From there, an organic linker molecule is attached to the surface of the protective coating at one end and to an active biomolecule at the other end. This method has demonstrated effectiveness at overcoming the challenges presented by hypoxic zones in cancer therapeutics [160]. Aside from nanoparticle delivery systems, magnetic hydrogels, termed "ferrogels," have been used as stimuli-responsive drug scaffolds that are manipulated in a magnetic field in order to create pressure gradients that release the therapeutic into the targeted area [161–163]. This method has the potential to enable unique drug delivery profiles that have been shown to be most effective against certain diseases. For example, pulsatile delivery profiles have been shown to be helpful in overcoming adaptive resistance exhibited by cancer cells exposed to therapeutics [164]. These ferrogels are fabricated by adding iron oxide powder to an alginate hydrogel before being cast into a monophasic material. Biphasic systems can be made by exposing the ferrogel to a magnetic field during the casting process in order to attract the iron oxide particles to one side [161].

Electric fields can also be used for physical methods of drug delivery [22]. Based on similar principles as the previously mentioned ferrogels, hydrogels can be synthesized that will de-swell under the influence of an electric field in order to create a pressure gradient that releases the therapeutic [165]. These materials in effect behave as soft actuators. With regards to opportunities for GI drug delivery, electric fields can be advantageous due to the ease of implementing systems that can deliver an electrical stimulus, especially in comparison to magnetic triggers that require significant external hardware in many cases.

A less explored mode of physical drug delivery that may have application in GI drug delivery is convective-enhanced delivery [166]. This process utilizes bulk flow driven by a pressure gradient across the drug-delivering catheter as opposed to diffusive flow driven by a concentration gradient. This method avoids the need for extremely high drug concentrations needed to drive diffusive flow into tissue. Additionally, convective-based flow is not dependent upon molecular weight, whereas in diffusive flow large molecules may take a long time to diffuse if at all. This method is currently used to deliver therapeutics into the central nervous system.

8. Key challenges for physical modes of drug delivery in the GI tract

Many technologies presented here have not been tested in clinical trials. There are several challenges that need to be addressed to progress these technologies into clinical use including safety and delivery consistency of the devices. The use of microneedle delivery and jetting systems in the GI tract may be consistency of dosing in the target area. If a device geared for delivery in the stomach deploys in the small intestine, there is the risk of perforation of the intestinal wall [1]. Major considerations for ultrasound delivery include optimizing conditions for creation of cavitation without causing significant damage to the luminal wall [136,137]. Iontophoretic devices include on-device electronics, which must be protected and limited. Other considerations for iontophoretic devices are depth of drug penetration and size of drug molecule delivered. The depth of drug penetration is limited for a single delivery episode; multiple episodes of delivery will be necessary. Lastly, drug transport using iontophoresis is limited by size of the drug molecule and favors smaller drug molecules for delivery [143].

9. Conclusions

There are many physical methods of drug delivery to the GI tract that currently provide significant therapeutic benefit to patients or appear promising through positive pre-clinical studies. Drug delivery through the GI tract is challenging due to the harsh environment of the GI tract. These modes of drug delivery include needle injection, jetting, ultrasound, and iontophoresis, among others. These technologies have been shown to deliver a variety of agents, including small molecules and macromolecules without significant metabolism or degradation. For clinical translation of these technologies, there will need to be a significant focus on safety and consistency of the systems.

Declaration of Competing Interest

The J.B., H-W. H., J.C.M., S.B. and G.T. report being co-inventors on multiple patents/patent applications describing systems which support physical modes of drug delivery via the GI tract. G.T. reports

receiving consulting fees and grants from Novo Nordisk and NIH which have supported in part development of systems enabling the delivery of drugs through physical modes of delivery. Complete details of all relationships for profit and not for profit for G.T. can be found at the following link: https://www.dropbox.com/sh/szi7vn-r4a2ajb56/AABs5N5i0q9AfT1IqIJAE-T5a?dl=0.

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