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Orally ingestible medical devices for gut engineering

Nikolaj Kofoed Mandsberg, Juliane Fjelrad Christfort, Khorshid Kamguyan, Anja Boisen, Sarvesh Kumar Srivastava *

Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Health Technology, Technical University of Denmark, Denmark

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ABSTRACT

Orally ingestible medical devices provide significant advancement for diagnosis and treatment of gastrointestinal (GI) tract-related conditions. From micro- to macroscale devices, with designs ranging from very simple to complex, these medical devices can be used for site-directed drug delivery in the GI tract, real-time imaging and sensing of gut biomarkers. Equipped with uni-direction release, or self-propulsion, or origami design, these microdevices are breaking the barriers associated with drug delivery, including biologics, across the GI tract. Further, on-board microelectronics allow imaging and sensing of gut tissue and biomarkers, providing a more comprehensive understanding of underlying pathophysiological conditions. We provide an overview of recent advances in orally ingestible medical devices towards drug delivery, imaging and sensing. Challenges associated with gut microenvironment, together with various activation/actuation modalities of medical devices for micromanipulation of the gut are discussed. We have critically examined the relationship between materials–device design–pharmacological responses with respect to existing regulatory guidelines and provided a clear roadmap for the future.

Contents

1. Introduction: Orally Ingestible Microdevices and the GI microenvironment

History of medicine has taught us that complex biological problems need not necessarily have to have a complex biological solution – a simple engineering device can do. Medical devices, both with and without electronic interfaces, have already revolutionized the diagnosis and treatment of many diseases. From hip and cochlear implants [1,2], to cardiac stents and pacemakers [3,4], to vestibular prosthesis and insulin pumps [5,6], all highlight tremendous engineering efforts for translating basic science into relevant patient-care technologies [7]. Also, miniaturization of technology has triggered development of non-invasive microdevices, including microrobots for cellular surgery and regeneration [8,9], orally ingestible devices for insulin delivery, and microsensors for *in vivo* imaging and biopsy [10–12]. This has ushered a new era of medical devices to 'explore and manipulate' complex biological microenvironment, which was otherwise restricted owing to bulky device size and poor biocompatibility. For instance, the first insulin pump invented in 1974, *The Biostar,* was the size of a microwave oven, thereby, limiting its usage to treatment of diabetic ketoacidosis [13,14]. Nonetheless, the concept of ingestible microdevices for monitoring did exist as

* Corresponding author.
E-mail address: sksr@dtu.dk (S.K. Srivastava).

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early as the 1950s and was termed endoradiosonde. Mackay and Jacobsen "produced a small capsule that a person can swallow, and which contains the sensing transducer and the radio transmitter" and the "device successfully operated in the gastro-intestinal tract" [15]. This review focuses on the design of such engineered ingestible microdevices for applications in sensing, drug delivery and gut microsampling (Fig. 1A). We chose 'device size' as an important distinction criteria as we noticed a strong correlation between size scale and associated biological application as shown in Fig. 1B.

Despite advances in polymer engineering, leading to 'sustained release formulations', several challenges remain with contemporary oral capsules [16]. For instance, a) many therapeutics are not absorbed in some or all parts of the gastrointestinal (GI) tract; b) drug absorption is limited by GI transit time; and c) any biological response is dependent on chemical stability of the formulation in the harsh GI environment.

These challenges get amplified many folds in case of oral delivery of biologics, including proteins, peptides, hormones and nucleic acids [17,18]. Biologics are relatively sensitive to external factors, including pH and temperature, ionic concentrations and denaturing conditions, like high acidity and proteases – conditions that are present in abundance in the GI tract [19]. If biologics would somehow survive all of the above, the presence of a 40–450 μm thick mucus layer acts as a negatively-charged barrier, thereby, preventing the entry of biologics into the underlying GI epithelium [20]. Here, Orally-ingestible microdevices (OIMs) are designed to protect the drug molecule and minimize the distance between the site of release and the epithelium. This prevents drug release in the intestinal lumen and limit exposure to above mentioned *rate limiting* factors (pH, microbes, continuous mucus secretion *etc.*). Note that the term 'microdevice' is used irrespective of the size scale *i.e.* normally referring to both microscale (μm) and macroscale (mm), unless otherwise specified.

2. Oral drug delivery challenges: How can oral medical devices bridge the gap?

At this point, it is important to understand how an orally administered drug interacts with the body. Once ingested, the drug is dissolved in the intestinal fluids and can then be absorbed by: **i**) the transcellular pathway *i.e.* drug transport across the cells mainly *via* passive diffusion and carrier-mediated transport; or **ii**) the paracellular pathway *i.e.* drug transport between the cells through passive diffusion [21,22]. Most oral drugs are absorbed by passive transport *via* the transcellular pathway [23]. Fig. 2 presents an overview of challenges faced by a microdevice after oral ingestion. Apart from the shared conventional oral drug delivery challenges (like pH, transit time, and enzymes), microdevices are strongly impacted by their size. Therefore, minimizing accidental retention is of paramount importance. In a way, device size and shape determine its safe passage from the esophagus all the way to the colon – the GI section with the highest residence time of 1–2 days [24]. But the journey in-between is also perilous – including low pH in the stomach, risking an unwanted leaching of material, and various enzymes in the different sections of the GI tract (Fig. 2). Additional challenges include tissue wall localization due to constant motility and peristalsis in the GI tract. Evidently, both device size and associated design play a key

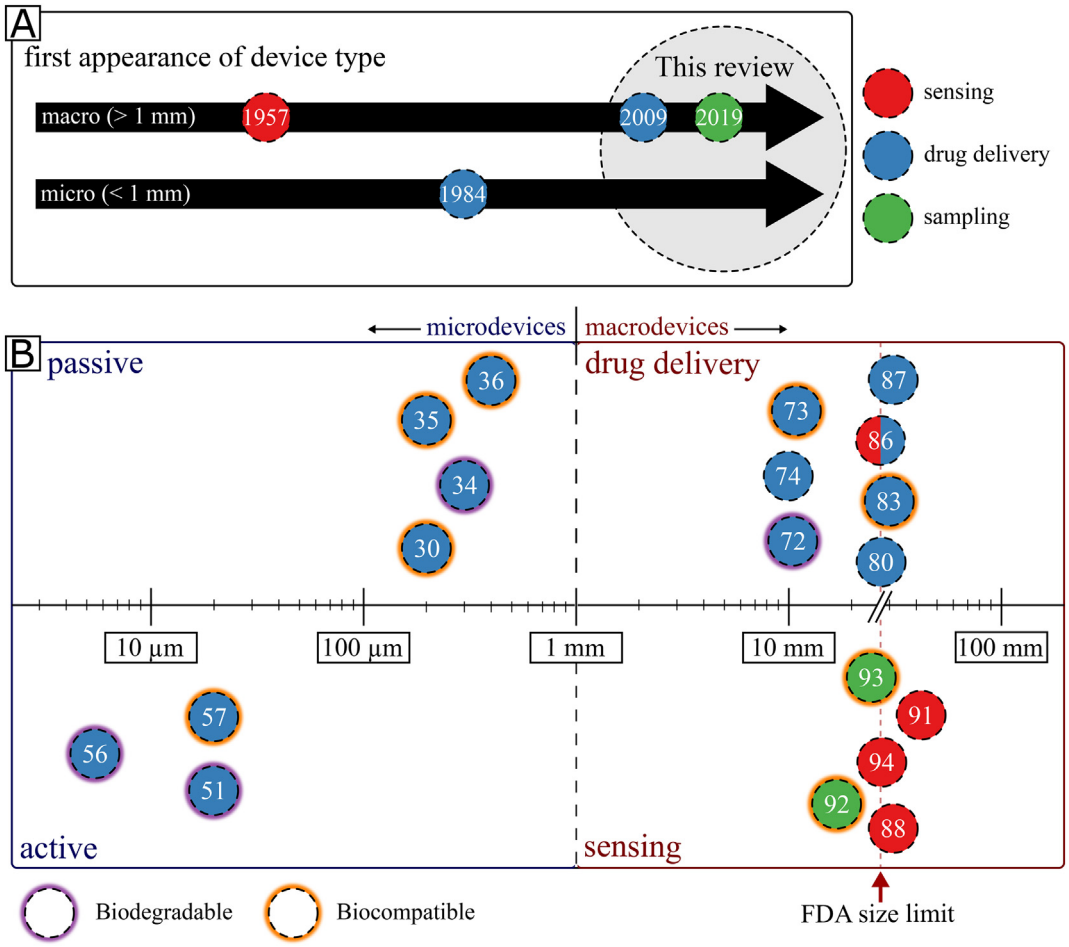

Fig. 1. Orally ingestible microdevices: 1A) Timeline depicting the first appearance of multi-compartment sensing, drug delivery, and sampling devices to illustrate technological progression and the focus of our review; 1B) Size scale as a selection criteria for oral device application in sensing, drug delivery and gut microsampling.

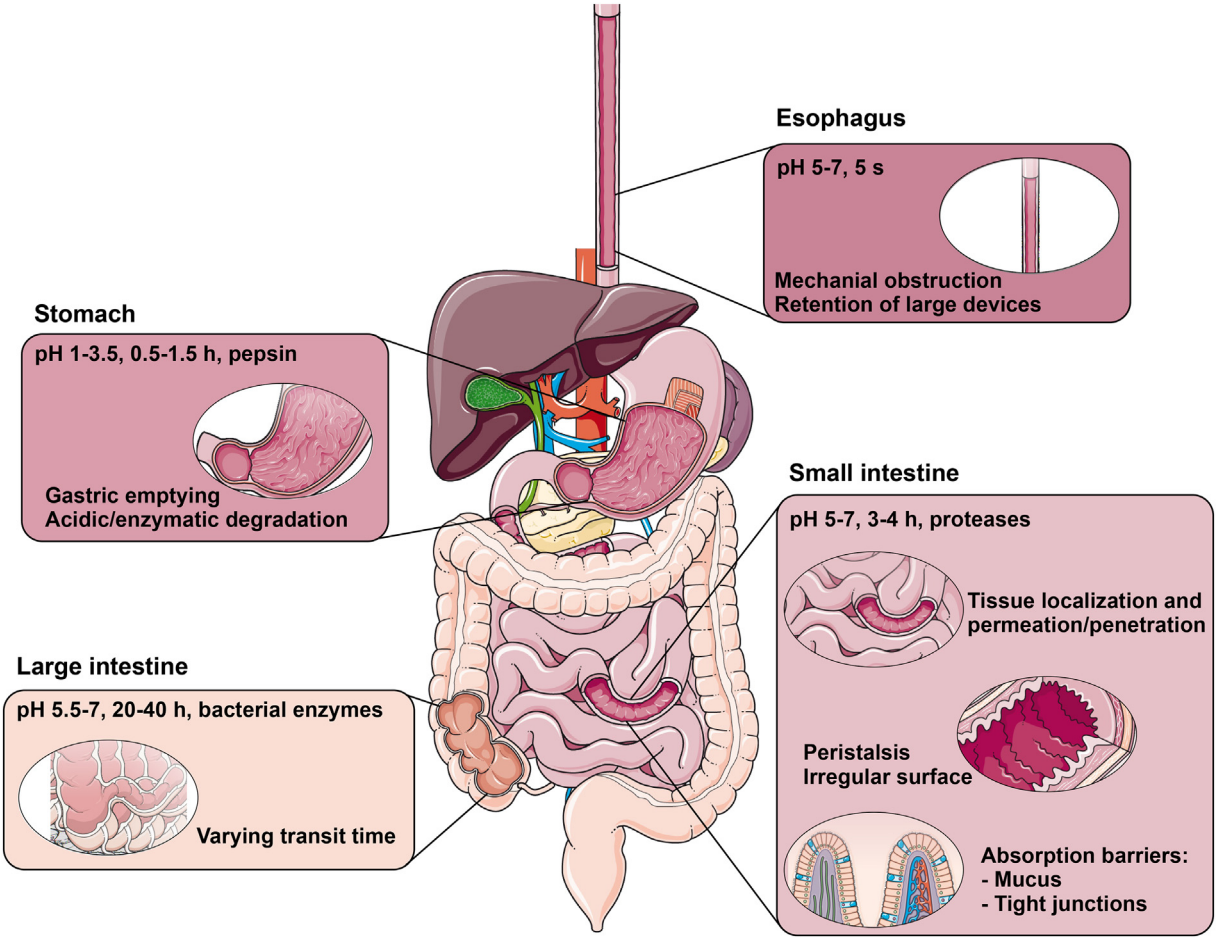

Fig. 2. Schematic of the gastrointestinal (GI) tract with site-specific pH ranges, average transit times and predominant enzymes [24–26]. Additional challenges faced by orally ingested microdevices traversing through the GI tract have been highlighted. Images adapted from Servier Medical Art by Servier and licensed under a Creative Commons Attribution 3.0 Unported License.

role in governing safety profile and therapeutic efficacy of any orally ingestible device.

The current generation of OIMs are of considerable interest with direct application in: (**1**) Understanding of metabolic and pathophysiological conditions linked to the GI tract; (**2**) *Re-designing* gut microbiota in modulating autoimmune diseases, like Coeliac and Crohn's disease; and (**3**) Oral delivery of biologics, like vaccines and hormones, which are otherwise administered *via* injections. This becomes important since escaping the gut metabolism does not guarantee high bioavailability as the absorbed drug is subjected to first-pass effect (with exception to those absorbed in terminal rectum) [27].

Clearly, to overcome above challenges, we need multidisciplinary fundamentals rooted in materials/polymer engineering, device design and integrated microelectronics, and robust assessment of pharmacological response in pre-clinical studies. In this regard, oral delivery of microdevices has emerged as a superior method for gut engineering, with a potential for high patient compliance, and the ability to combine multi-modalities onto a single-ingestible device – all pointing towards a successful clinical translation. This article encompasses all the above multidisciplinary elements and provides an up-to-date assessment of orally-ingestible GI microdevices *in vivo*. We have taken this opportunity to not only discuss key-developments but also provide inputs on potential research areas more suitable for certain device types. Both scientific publications and industrial patents are discussed to highlight key-elements necessary for a successful clinical translation. We have made a conscious effort in selecting state-of-the-art OIM technologies, assessed their design-material-bioactivity relationship, and provided an in-depth discussion on the regulatory framework of U.S. Food and Drug Administration (FDA) and Communautés Européennes (CE) associated with the regulation of such oral microdevices.

2.1. Passive microdevices for oral drug delivery: opportunities and challenges

The idea of uni-directional drug release, similar to a transdermal patch, has influenced the development of OIMs. The concept of patches and microcontainers filled with drugs *i.e.* "*reservoir containing a plurality of tiny pills*" dates back to the 1970s – thanks to Alejandro Zaffaroni, the founder of Alza Corp, who was one of the major early pioneers in the field of controlled drug delivery systems [28,29]. Microfabricated drug devices incorporate planar geometries with low aspect ratio, together with uni-directional release, as most are sealed from one end (*i.e* reservoir-like geometry). Therefore, they offer drug protection and minimal shear stress induced by constant peristalsis and mucosal fluid gradients, resulting in higher drug bioavailability due to increased intestinal retention [30].

Chirra et al. developed planar microdevices (Fig. 3A inset), where a poorly permeable drug (acyclovir) was loaded in a PEG-PMMA hydrogel to improve the oral bioavailability in wild-type C57BL/6 mice [30]. The area under the curve (AUC), which represents the total drug exposure across time, was found to be approx. 4.5 times larger for the microdevices than for an oral solution with the same dose (Fig. 3A). To this end, we have also actively investigated oral delivery of drugs with another type of a passive microdevice, namely microcontainers

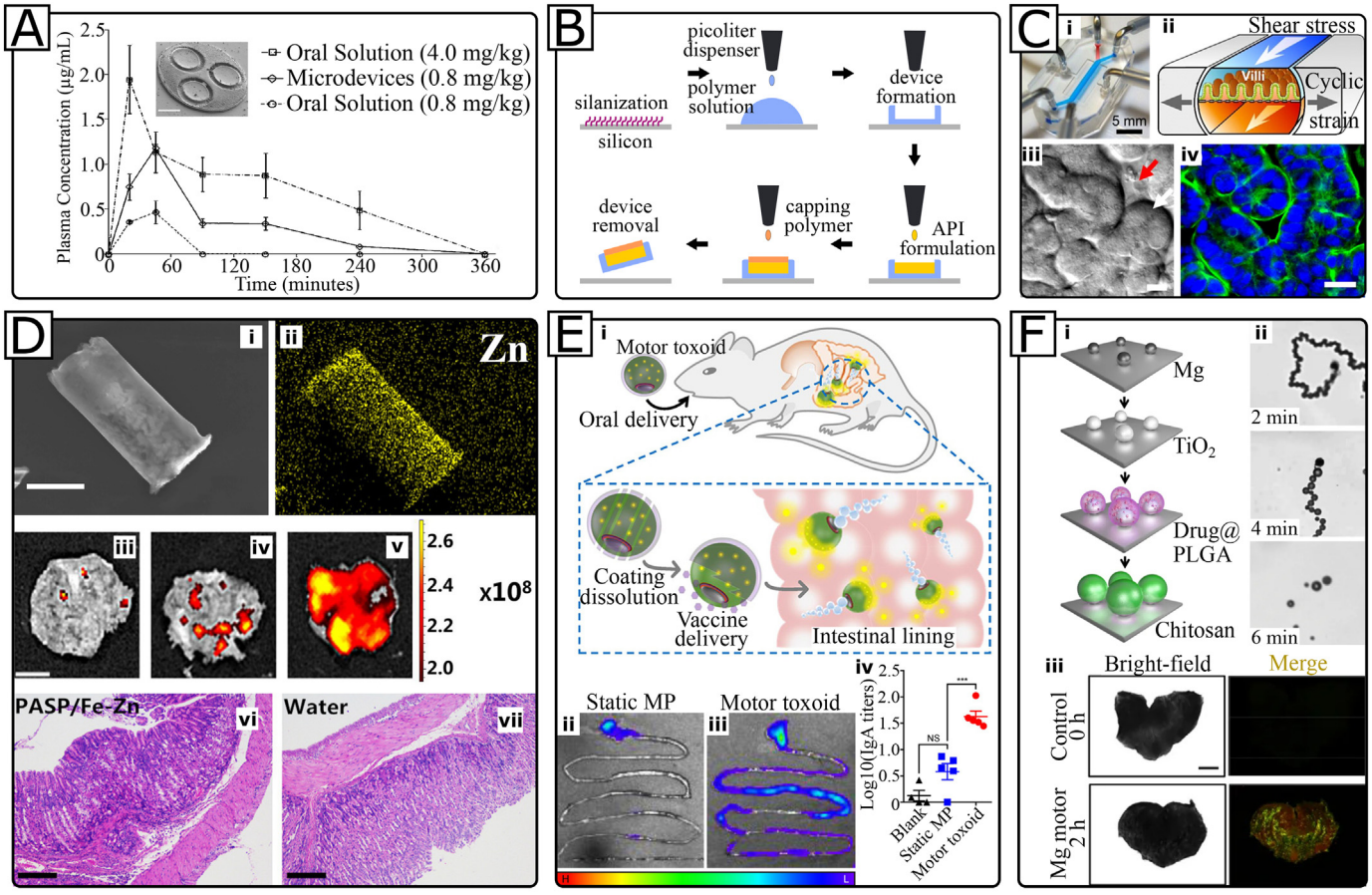

Fig. 3. Examples of passive and active microdevices for oral drug delivery and as advanced *in vitro* cell model. 3A) Pharmacokinetic profile showing the enhanced *in vivo* bioavailability of acyclovir using planar microdevices (inset) compared to an oral solution with the same concentration of acyclovir. Reprinted from [30] with permission. 3B) Schematic of the printing process of bottom-up fabricated enteric devices for oral delivery. The polymer dispersion was ejected onto the silicon wafer by a picoliter dispenser, where after evaporation of the solvent forms the device body. The same dispenser was used to print drug formulation into each device and a second polymer was applied on top to seal the device before removal from the silicon wafer. Adapted from [36] with permission. 3C) Human gut-on-a-chip microdevice. (i) Photograph of the microdevice, where blue and red dyes fill the upper and lower channels, respectively. (ii) Cross-sectional schematic of the device showing how suction to side channels (grey arrows) applies peristalsis-like mechanical constrictions and fluid flow (white arrows) generates shear stress. (iii) Micrograph showing intestinal basal crypt (red arrow) and villi (white arrow) formed by human Caco-2 cells grown for ~100 h in the microdevice. (iv) Confocal immunofluorescence image showing a horizontal cross-section of intestinal villi similar to the ones shown in (iii). Scale bars represent 50 μm unless indicated otherwise on Fig. 3C. Reprinted from [43] with permission. 3D) Self-propelled microrockets for targeted drug delivery in the stomach. (i) SEM image of a full DOX/poly (aspartic acid)/Fe-Zn microrocket and (ii) energydispersive X-ray spectroscopy mappings of Zn inside the microrocket. (iii) Superimposed fluorescent images of the whole stomachs of mice collected 30 min after administration of ultrapure water and (iv) DOX/poly (aspartic acid)/Pt microrockets and (v) DOX/poly (aspartic acid)/Fe-Zn microrockets. (vi) Histological evaluation of gastric tissue 24 h after administration of poly (aspartic acid)/Fe-Zn microrockets and (vii) water. Reprinted with permission from Zhou et al., Self-propelled and targeted drug delivery of poly(aspartic acid)/iron-zinc microrocket in the stomach, ACS Nano, 13. Copyright 2019 American Chemical Society. 3E) Biomimetic micromotors for delivery of antigens for oral vaccination. (i) Schematic of the formulation concept; after oral ingestion of micromotors, the coating is dissolved in the small intestine, which activates the motor to provide enhanced retention and stimulation. (ii) Images of the GI tract of mice 6 h after oral administration of labeled static microparticles or (iii) micromotors. (iv) Data showing a significantly higher level of IgA titers against α-toxin after administration of micromotors compared to static microparticles. Reprinted with permission from Wei et al., Biomimetic micromotor enables active delivery of antigens for oral vaccination, Nano Letters, 19. Copyright 2019 American Chemical Society. 3F) Micromotors for local treatment of stomach infection *in vivo*. (i) Schematic of the preparation of micromotors; a dispersion of Mg microparticles is dispersed on a glass slide followed by TiO_2 atomic layer deposition and coating with drug-loaded PLGA and chitosan. (ii) Time-lapse images of the propulsion of the micromotors after 2, 4 and 6 min in simulated gastric fluid (pH ~1.3). (iii) Retention of the micromotors visualized with bright-field and fluorescence overlay images of freshly removed mouse stomachs 0 h after oral gavage of ultrapure water as control and 2 h after oral gavage of micromotors. Shared under a Creative Commons Attribution 4.0 International License with copyrights reserved with the authors [51].

[31–33]. Recently, microcontainers were developed in poly-ε-caprolactone (PCL) in order to have a biodegradable oral drug delivery device in microscale [34]. In a pharmacokinetic study in rats, the PCL microcontainers revealed trends towards a higher AUC when compared to paracetamol in coated gelatin capsules (60 ± 33 and 39 ± 18 μg min ml^{-1}, respectively).

In another study, Nemeth et al. demonstrated drug loading by inkjet printing inside a planner PMMA reservoir-type microdevices (Fig. 3B) [35]. Silanization of the microdevice was carried out to increase its hydrophobicity, which proved to allow drug loading using droplets of nine times the reservoir volume due to increased droplet confinement. This reduced the number of loading iterations required significantly. The effect of silanization on cell toxicity was further concluded by an MTT assay in a Caco-2 cell model, and confirmed the devices to be 'safe to use'. Later, drug loading and capping process were all conducted in a single platform using a picoliter dispenser by inkjet printing polymer/drug solutions on a silanized silicon substrate (Fig. 3B) [36]. To do so, the authors took advantage of the coffee-ring effect by deposition of water droplets with 5% (*w*/*v*) Eudragit® FS 30D on a hydrophobized substrate. Although Eudragit® polymers are non-biodegradable, they are FDA approved for pH sensitive release of drugs in the GI tract [36]. So far, these devices have not been tested in animals.

While passive microdevices offer extensive flexibility in terms of fabrication, the very idea of a unidirectional release may take a *hit*

when they are inside the GI tract. Tissue wall localization requires constant motility and navigation through the ~9 m GI tract. The challenge is further amplified by periodic smooth muscle contractions from peristalsis, which pushes the luminal content through the upper GI tract, causing turbulent convective flow regimes of up to 4 cm/s [37,38]. To counter this challenge, devices have been designed to penetrate or adhere to the mucus layer, such as by nanostraw patterning, to take advantage of these random flow patterns and stick to the intestinal wall. Once adhered to the GI mucosa, nanopatterned devices create zones of cellular diffusion *via* topography-mediated adhesion together with chemical permeation enhancers, like cell-penetrating peptides, for enhanced drug absorption. However, over 25% of nanostraw devices, on average, attach facing the wrong way (by landing on the wrong side without surface indentation), or never attach at all [25]. Academically, researchers have overcome the situation by applying several, sometimes thousands, of these microdevices [39] – as expected, dose variability is inevitable leading to limited clinical translation potential [40]. Nonetheless, passive microdevices offer fast prototyping in terms of fabrication, which can potentially pave way for delivery of toxic drugs with a narrow therapeutic index.

To make the efforts more relevant, suitable *in vitro* models need to be developed to provide realistic simulation of the GI microenvironment. An example of such *in vitro* model is a human gut-on-a-chip microfluidic device that enables human intestinal epithelial cells (Caco-2) to be cultured in the presence of physiologically relevant luminal flow and peristalsis-like mechanical twists (Fig. 3C i-ii) [41]. These conditions promoted formation of basal crypts and villi (Fig. 3C iii-iv) lined by all four epithelial cell linages of the small intestine (absorptive, goblet, enteroendocrine and Paneth), thereby also promoting secretion of mucus, necessary for realistic models. Furthermore, the intestinal epithelium inside the gut-on-a-chip device has been shown to support the presence of the microbiota that normally colonizes the human small intestine [42]. Such a microfluidic device has potential applications in modeling of human intestinal inflammation *in vitro*. Furthermore, Kim et al. implemented key characteristics of intestinal inflammation diseases, including destruction of intestinal villi and associated compromise of the permeability barrier [43]. These damages are believed to origin from interplays between the intestinal epithelium, gut microbes and immune cells and changes in luminal flow due to altered peristalsis [44,45] The developed *in vitro* human gut-on-a-chip microfluidic device could potentially be further developed to work in a patient specific manner to advance personalized medicine in the future – passive OIMs can play a key-role in developing personalized medicine and can be tested in these gut-on-a-chip systems as well [46,47,48] For instance, Workman et al. demonstrated induced pluripotent stem cells (iPSCs) derived intestinal organoids to express intestine markers (post-14 days differentiation), and their association with IBD was studied upon exposure to the IFN-γ cytokine [49]. A two-channel PDMS mold was created where cell-monolayer was maintained in the top-channel (1000 μm high), followed by a thin porous membrane (7 μm ~ pore size), and growth media being circulated in the bottom-channel (200 μm high). A similar setup can be designed with passive OIMs for high-throughput screening of drugs as well as food allergens – much like a miniaturized version of a 96-well plate. Also, till date, it is not possible to co-culture living epithelial cells (like Caco-2), together with gut microbes using conventional *in vitro* models, or even more sophisticated intestinal organoid cultures [50]. Passive OIMs can bridge this gap by acting as a 'gut-microbe carrier' for greater understanding of intestinal diseases and their pathophysiology. Therefore, it is necessary to develop passive microdevices that can aid our current understanding of host microbiome together with relevant gut *in vitro* models.

2.2. Active microdevices for oral drug delivery: mucopenetration for therapeutic efficacy

Conventionally, all oral drugs must dissolve in the aqueous environment of the GI tract before they can be absorbed [52]. Such a seemingly simple process is a considerable challenge for compounds that are poorly water-soluble, or degradable in the lumen, such as biologics [53] In such a situation, self-propelling or self-actuating microscale devices can play a key role by delivering therapeutics directly across the GI mucosa. Several self-propelling microscale devices (*i.e.* micromotors) have been reported, which utilize a gas-evolution reaction towards self-propulsion, resulting in mucopenetration/mucoadhesion. Such a reaction can be initiated *via* acid hydrolysis of a metal (like Zn) [54] or hydrolysis of metal oxides (like MgO) in the GI environment [55]. In fact, the ability to penetrate mucus without damaging the underlying GI epithelial layer has been a key-driver for micromotor technology in the gut.

Zhou et al. reported cylindrical micromotors with a length of ~5.4 μm and ~ 2.4 μm diameter, designed with multiple concentric layers for oral delivery of chemotherapeutics [56]. The outermost layer is comprised of polyaspartic acid (PAA), which is robust in acidic pH, but dissolves in the neutral pH of the intestine. In neutral solution, PAA has a negative zeta potential (−30.5 mV) by virtue of its carboxyl groups, which facilitates electrostatic binding with the amino groups of doxorubicin (DOX). A thin Fe layer underneath, allowed magnetic control and promoted galvanic corrosion of the Zn particles core (Fig. 3D i, ii). In an acidic environment, these produce hydrogen gas, which propels the DOX incorporated micromotor at an average speeds of 31.8 ± 7.8 μm/s for a time period of 135 ± 37 s. The microrockets with DOX-Fe (loaded with 0.074 mg DOX per mg microrocket) were dosed to mice in water and control groups were dosed with non-propelling microrockets (with DOX-Pt) in water or the same volume of ultrapure water. After 30 min, the mice were euthanized and the gastric tissue was cleansed and evaluated with fluorescence imaging (Fig. 3D iii-v**)**. Owing to the innate fluorescence of DOX and propulsion effects of microrockets with DOX-Fe, these microrockets showed strongest fluorescent signal all over the gastric tissue, whereas only a very small and local signal was detected from the controls (ultrapure water and microrockets with DOX-Pt). This study showed that the propulsion effects were sufficient to impart enhanced penetration of the mucus layer, with no adverse effect to the underlying GI epithelium as confirmed *via* hematoxylin & eosin staining (Fig. 3D vi-vii).

In another study, Wei et al. showed active delivery of antigens for oral vaccination [57]. Mg-microparticles were coated with red blood cell membranes that displayed the Staphylococcal α-toxin, and subsequently with a layer of chitosan to facilitate mucoadhesion (Fig. 3E i). Finally, an enteric layer of Eudragit® L100–55 was provided to protect the drug from the acidic conditions in the stomach. When administered orally to mice, micromotors safely passed through the stomach, after which the enteric coating was dissolved and the motors were activated. Images of intestines from mice dosed with the vaccine showed that the micromotors accumulated in the intestinal wall much better than non-motorized particles (Fig. 3E ii-iii). Furthermore, the micromotors stimulated the production of IgA antibodies against the Staphylococcal α-toxin about ten times more than the static particles (Fig. 3E iv).

Micromotors have also been applied to treat local infections in the stomach. De Ávila et al. demonstrated micromotors loaded with clarithromycin (CLR) for treatment of *H. pylori* infection in a mouse model [51]. The micromotors were fabricated around a 20 μm Mg-core with a thin layer of TiO_2 around it. This was followed by a CLR-loaded PLGA layer and then a thin (~100 nm) layer of chitosan. See fabrication scheme in Fig. 3F **i**. The coating process intentionally left an opening (~2 μm), which serves two purposes: Firstly, it allowed the galvanic corrosion reaction between Mg and gastric acid protons, which increased pH and produced hydrogen gas that propelled the micromotor.

Secondly, it imparted surface asymmetry, which causes uni-directional motion with speed: 120 μm/s for up to 6 min (Fig. 3F ii). Finally, the authors concluded mucopenetrative efficacy based on intense fluorescent signals (*via* incorporation of DiD & FITC dyes), meaning that the micromotors were efficiently distributed and retained throughout the mouse stomach 2 h after oral gavage (Fig. 3F iii). Therapeutic efficacy was further confirmed by quantification of bacterial burden in the stomach.

Clearly, micromotors can also become highly relevant for pH-sensitive drugs where the bioavailability could benefit from delivery in the stomach rather than the small intestine. Such a system could create a suitable physiological micro-environment, *i.e.* near-neutral pH, for drug release in the stomach. However, from a clinical translation perspective, there is an immediate need for long term study to demonstrate its safety, toxicity and foreign body response in the gut. Further, the amount of drug loaded in such microdevices may be of relevance in murine studies. However, in case of larger animals, like porcine models, a significantly larger amount of devices and drug will be required to achieve similar therapeutic efficacy. While price parity is a different discussion all together, active microdevices need to address some of the above challenges before they can emerge as key-challenger for some of the well-established oral drug delivery technologies [58–60].

2.3. Macrodevices for GI manipulation (mm scale): Drug delivery

Key success criteria for OIMs in GI tract include: a) chemical stability in low pH and enzyme-rich environment; b) mechanical properties with a design which is conducive for soft tissue navigation (*i.e.* no sharp edges or exposed metal surface to cause an allergic reaction); and **c**) minimal toxicity or foreign body response. In case of electronic microdevices, radio-frequency (RF) radiated power and electromagnetic compatibility (*i.e.* the device does not affect itself or other devices in its vicinity) are of high importance [61,62] On-board energy storage systems can amount more than 50% of the mass of an OIM, and in a way, govern overall toxicity [63]. This is especially the case with unintended device retention, which is also one of the key-risks identified by the FDA – a *meta*-analysis of wireless endoscopy suggests a pooled retention rate between 1.2 and 2.6% [64]. Since, gastric transit time and risk of retention increases dramatically with the device size, it is vital to utilize flexible, biodegradable materials [65].

Ideally, a device must dissolve completely within 24 h to prevent clinical obstructive symptoms. To this end, FDA has established a list of materials generally regarded as safe (GRAS) [66], which includes gelatin, cellulose, PLA, PVA, various derivatives of PLGA and several other natural polymers and metals like Fe and Zn [67]. Readers interested to know more about biodegradable polymers are suggested to look elsewhere [68,69] FDA regulation allows device size measuring 11 mm × 26 mm (like video capsule endoscope like Pillcam®) [70] as an *infrequently dosed diagnostic device* – though such a size is not very practical for regular oral drug administration [71].

Li et al. presented a 3D printed macrodevice comprised of two concentric compartments [72]. The authors explored fused deposition modeling (FDM) to 3D print a tablet (DuoTablet, 10.5 mm × 3.95 mm) with a controllable drug release profile (Fig. 4A i), achieved through its multilayer design; in this case, layers of polyvinyl alcohol containing glipizide for diabetes treatment. The use of 3D printing allowed for easy manufacturing which could be exploited in the field of personalized medicine with customized release profiles (Fig. 4A ii inset). For compatible drug and filament combinations (*i.e.* no chemical reaction between the drug and filament) DuoTablet's coating could protect the drug from degradation in the low pH environment of the stomach, or act as an initial high release rate followed by a more gradual release rate. Furthermore, flexibility in in the 3D printing process makes it easy to dimensionalize the tablet as per requirement.

Another strategy for controlled drug release *via* an ingestible device includes pH sensitive poly(N-isopropylacrylamide-*co*-methacrylic acid) (PNIPAm-MAA) nanoparticles loaded in polydimethylsiloxane containers (size 10 mm) [74]. Upon pH decrease, these nanoparticles shrink, which opens up channels for drug release as shown in Fig. 4B i-ii. However, subcutaneous implantation of an empty control device triggered an inflammatory reaction, suggesting a need for better material properties. To this end, Liu et al. demonstrated an ingestible hydrogel device that can be ingested as a standard-sized pill, which swells rapidly into a large soft sphere, and maintains robustness under repeated mechanical loads in the stomach for up to one month (as demonstrated by large animal tests) with no signs of toxicity [75].

Macroscale devices routinely incorporate mucoadhesive coatings to aid correct device orientation and increase retention time. Generally, the remainder of the device surface is made of a hydrophobic polymer such as cellulose acetate or polydimethylsiloxan (PDMS) to impart greater protection against acidic/enzymatic degradation. Overall, such a dual-feature design has shown to improve oral bioavailability [76,77], including oral delivery of insulin [78]. As an example, gastric patches comprising a mucoadhesive surface of chitosan, alginates or cellulose derivatives have been loaded with a drug [79]. Miyashita et al. utilized a self-unfolding stomach patch, which expanded five times when deployed in the gut towards patching of stomach wounds [80]. In fact, it will be interesting to document adhesive forces between such polymeric origami structures to attain greater information on possible medical applications.

To this end, Terry et al. investigated adhesive forces of different capsule robot materials (polycarbonate, stainless steel and micro patterned PDMS) against intestinal mucosa [81]. Mucoadhesion was evaluated using both tack and peel adhesion tests *ex vivo*. They found the peel adhesion to porcine mucosa (0.198 ± 0.070 mJ cm^{-2}) to be several orders of magnitude less than that of the commercial adhesive on a polypropylene surface (87 ± 36 mJ cm^{-2}). Further, tack separation required higher force (0.055 ± 0.016 mJ cm^{-2} and 45 ± 2 mJ cm^{-2}) than the peel mode; something that could potentially be utilized in the device design, especially towards delivery of hemostatic agents in the GI tract.

While mucoadhesion will bring the device closer to the GI epithelium, a key-challenge remains in getting the drug across the thick mucus layer and tight junctions. This problem has been addressed by incorporation of microneedles over a mucoadhesive surface, activated by physio-chemical stimuli (*i.e.* unfold, puncture, expand, contract, float *etc.*), towards therapeutic payload delivery across the underlying GI epithelium. Much like a transdermal microneedle technology, microneedle patches can be coated with a pH sensitive layer, which dissolves in the appropriate site of the GI tract to release drug-incorporated microneedles. In fact, Rani Therapeutics has developed several technologies to deliver macromolecules like proteins and antibodies. RaniPill® is an ingestible capsule device containing a) a guide tube for device orientation for tissue penetration; b) delivery actuation mechanism; and c) a biodegradable release element with drug (*i.e.* microneedles) [82].

Abramson et al. also took advantage of the microneedle concept to design a Luminal Unfolding Microneedle Injection (LUMI) device on top of a compressed spring [83]. When the device enters the pH-neutral small intestine, a polymer that was immobilizing the spring gets dissolved, which leads to ejection of the device (Fig. 4C i – ii). Packed inside a polymeric capsule, LUMI comprises of a spring actuated 3- polymeric arm contraption made of polyethylene oxide and Soluplus®, which causes the device to unfold and expand (Fig. 4C iii). At the end of each arm, multiple drug-loaded microneedles are forced into contact with the intestinal tissue. The arm length was designed to be long enough to ensure contact independent of the deployment orientation (Fig. 4C iv). Furthermore, the optimized device caused penetration (force threshold of 5 mN), but not tissue perforation (threshold of >0.2 N). The microneedles can be loaded with 0.3 mg drug/0.5 cm^2, which is sufficient to illicit a clinical response, as demonstrated towards *in situ* delivery of insulin (Fig. 4C v). Finally, upon successful delivery, the arms slowly degrade and the capsule separates into multiple parts to reduce the risk of mechanical obstruction.

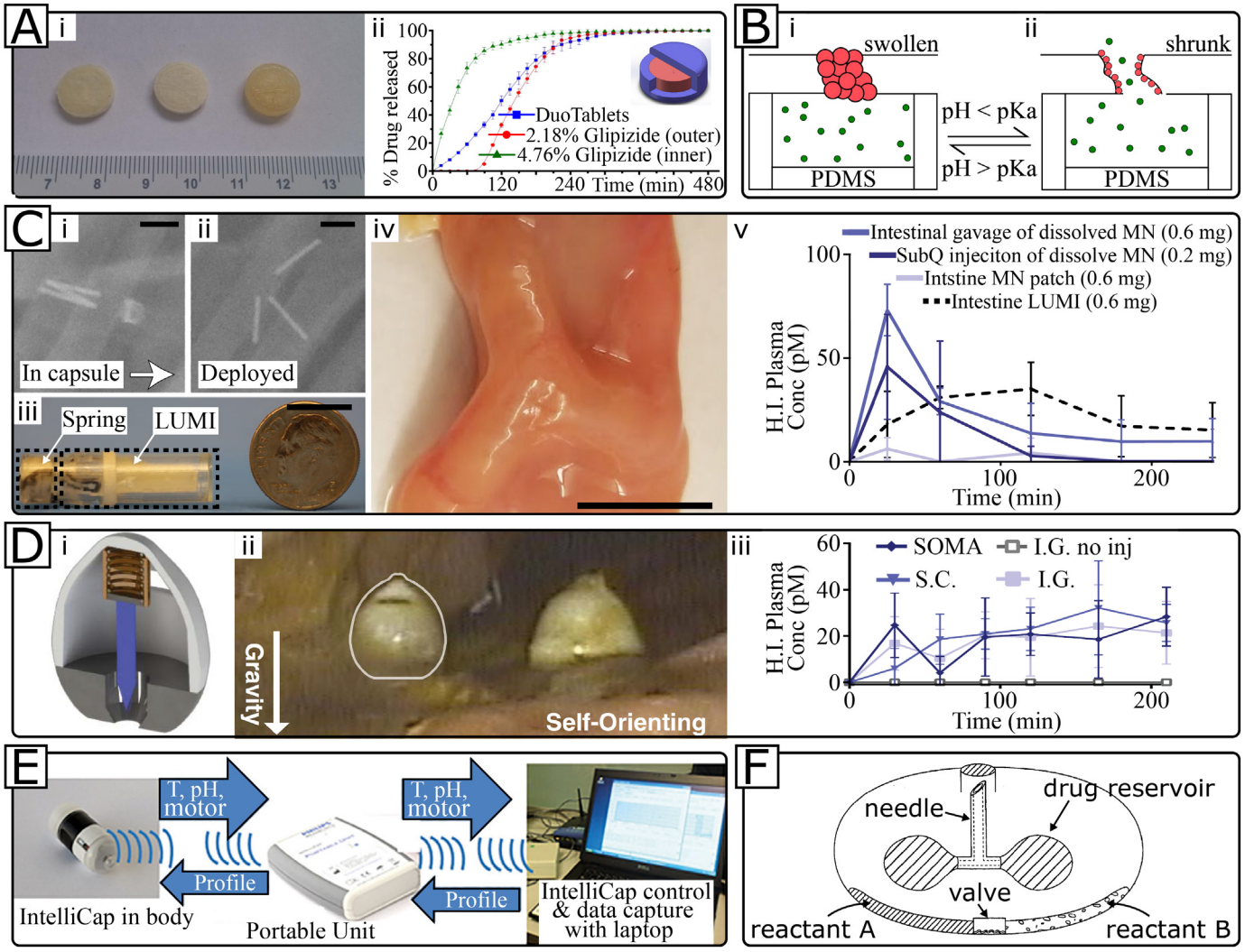

Fig. 4. Examples of orally ingested macrodevices for drug delivery. 4A) 3D-printed DuoTablet with controllable release characteristics. (i) Photograph of three such tablets and (ii) their respective release profiles. Reprinted from International Journal of Pharmaceutics, 525 (1), Li et al., Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing, 5–11, Copyright 2017, with permission from Elsevier. 4B) Polymeric PNIPAm-MAA nanoparticles shrink upon pH decrease, thereby opening a channel for releasing the drug contained. Schematics shown of (i) the high pH swollen/closed state and (ii) the low pH shrunk/open state. 4C) Luminal Unfolding Microneedle Injection (LUMI) device (scale bars: 1 cm). Swine *in vivo* radiographs showing (i) the encapsulated/folded state and (ii) the deployed/unfolded state. (iii) Photograph of the encapsulated LUMI and (iv) deployed inside a small intestine to show needle-to-wall contact regardless of device orientation. (v) *In vivo* human insulin delivery in swine by four different methods. Reprinted by permission from Springer Nature: Nature Medicine, A luminal unfolding microneedle injector for oral delivery of macromolecules, Abramson et al., Copyright 2019. 4D) Self-Orienting Millimeter-scale Applicator (SOMA). (i) A sketch of the device showing the initially compressed spring that will force insertion of the drug-loaded millipost. (ii) The devices have weighted metal bottoms that self-orients in the stomach, which shows here with *in vivo* endoscopy in fasted swine. (iii) Blood plasma levels of human insulin delivered by four different methods to swine *in vivo* model. From [[73]]. Reprinted with permission from AAAS. 4E) IntelliCap® is a device for controlled release drug delivery, which can be pre-programmed, real-time controlled, or triggered at specific temperature/pH changes to deliver with different rates. 4F) Balloon based delivery device. Both the needle injection and liquid drug pumping are actuated by a balloon being inflated upon mixing of reactant A and B.

A different release mechanism was applied in an ingestible self-orienting millimeter-scale applicator (SOMA), where re-coiling action of a stainless steel spring penetrated insulin needles across the gastric epithelium (Fig. 4D i – ii) [73]. Compared to LUMI, SOMA has the advantage that it delivers insulin across the gastric epithelium (Fig. 4D iii), and thus SOMA does not rely on gastric emptying to reach its target. This is an important advantage since gastric emptying typically occurs within 1–4 h, but can vary up to 24 h in diabetic patients [84,85]. Further, oral delivery of LUMI was not possible yet and the results described in the published work relies on device deployment in swine jejunum *in vivo*. Thus, it is still to be shown how LUMI deals with ingestion and gastric emptying rate. Irrespective of their bioavailability, both LUMI and SOMA represent the growing area of self-actuating medical devices for gut engineering. This in itself is an important step, and gives rise to optimism regarding oral delivery of insulin to patients in the near future.

Despite improved bioavailability, these devices do not allow time-controlled or sustained drug release, which can be an important parameter for clinical translation. However, for some applications it is of outmost importance to maintain a plasma concentration above the minimum effective concentration (MEC) of the drug for 12–24 h, which often requires colonic absorption. IntelliCap® offers a new technology to obtain information about the colonic absorption profile of a given drug early in the development process [86]. It is a swallowable device (27 × 11 mm) and can be filled with up to 0.3 mL of liquid formulation and programmed to deliver it over a period of 24 h. IntelliCap® extrudes the drug *via* a piston moved by a spindle connected to a motor. The motor is controlled by an onboard microprocessor, which can be programmed before ingestion or *via* the wireless data exchange unit (Fig. 4E i). It has a built-in pH sensor that enables real-time localization in the gut by monitoring the pH profile, thus allowing for drug release in

a specific region of the GI tract. In a clinical study with healthy volunteers ($n = 14$), an IntelliCap® device with diltiazem HCl was compared to the traditional diltiazem capsule. IntelliCap® reported a faster time (T_{max}) for maximum plasma concentration (C_{max}) and a higher C_{max}. While, overall plasma profiles were found to be similar in many other aspects, IntelliCap® device can be a beneficial tool to assess colonic absorption.

Another interesting technology in terms of self-actuation is a balloon-actuated microneedle device [87]. Fig. 4F shows a schematic representation of this technology where a gas-evolution reaction proceeds when reactant A and reactant B get in contact. The resulting gas expands the polymer balloon, which pushes a needle sitting on top of it. Compressible reservoirs with one or multiple liquid drugs can be connected to the needle, and upon balloon inflation, the drug is squeezed out. Interestingly, upon completion of drug delivery, the balloon continues to expand, which leads to fracturing of the capsule fabricated from separate portions joined by seams. The seams can also be made from biodegradable material, causing them to work also in a spring-actuated version. This fracturing then facilitates safe passage through the GI tract.

2.4. Macrodevices for GI manipulation (mm scale): sensing

Capsule endoscopy obtained clearance by the FDA and CE certification in 2001 paving its way into clinical gastroenterology [88]. Although efforts worth two decades preceded this event, it was in 1997 that Paul Swain swallowed the first wireless capsule endoscope [89] and the rest is history [90]. The initial version of such a wireless endoscope had three major challenges: ever-changing capsule orientation in the wide colon, battery life, and visualization of the mucosa. These challenges were overcome by addition of a second camera monitor (forward and backward), additional battery, and vigorous bowel preparation prior to the ingestion. This resulted in development of a PillCam wireless capsule endoscope to do real-time GI tract monitoring [88]. The second version of PillCam (COLON 2) had two major changes: the angle of view was widened from 154° to 172° and the recorder was updated to take advantage of artificial intelligence (AI) (Fig. 5A i-ii). Further, incorporation of an adjustable frame rate extended the battery life to allow visualization all the way through the GI tract. Lastly, AI detection of the location made it possible to notify the patient regarding possible interventions, such as ingestion of a prokinetic agent or a booster laxative. Clearly, the PillCam technology is a promising tool to diagnose the presence and degree of inflammation in the small and large intestine, but it falls short for early diagnosis before occurrence of any visible symptoms.

In this regard, Mimee and Nadeau reported an early stage detection system in the form of an Ingestible Micro-Bio-Electronic Device (IMBED) [91]. The design of IMBED comprises of a semi-permeable membrane that separates the luminal space from an inner chamber holding genetically modified probiotic *E. coli* Nissle. This bacterial strain generates light upon sensing of certain blood markers, which is detected by photodetectors embedded in the electronics (Fig. 5B i-iv). This was utilized for detection of GI bleeding (induced with indomethacin) in murine fecal sample. Further, a study in pigs demonstrated *in situ* blood detection in the stomach with a sensitivity and specificity of 83% after 60 min increasing to 100% after 120 min (Fig. 5B v). IMBED offers a minimally invasive alternative to diagnose acute bleeding in the upper GI tract, which would otherwise require an endoscopic observation. Also, it supports *in situ* biochemistry studies, which could lead to the discovery of labile biomarkers that would otherwise degrade before excretion in stool. Despite clear advantages, the capsule is still too large for unmonitored ingestion (13 mm in diameter and about 4 cm long) and requires insertion *via* an orogastric tube.

An alternative to IMBED for *in situ* measurements would be sampling of the GI material for post-sampling analysis. To this end, a purely mechanical device (optimally 16 by 8 mm) that samples gastrointestinal material *via* a suction mechanism has been patented by Biome Oxford Limited [92]. One end of the device has sample collection openings, while the other holds a dissolvable filling material (*e.g.* natural polymers like cellulose and starch derivatives) (Fig. 5C). Initially, this material is protected by a pH-sensitive coating, but upon entering the small intestine the coating is dissolved and the material is exposed. This causes the relaxation of a spring, and upon expansion it creates a partial vacuum in the sealed microchamber. The resulting pressure gradient forces the sample collection valves to open and GI fluid rushes into the sample chamber until the pressure difference has dropped below the threshold for valve opening. Similarly, Nejah et al. also developed a suction based sampling device, where a salt-holding chamber made with a semi-permeable membrane forms an osmotic pump, which drives the luminal fluids into the device (Fig. 5D i). Also, the device can be controlled magnetically (Fig. 5D ii) [93]. The authors claimed that such a design promotes continuous sampling throughout the entire intestine as shown in Fig. 5D iii-v (2.5 μL/h for almost 48 h). However, the use of membrane filtering makes it complicated to retrieve absolute information, *e.g.* number of bacteria per volume, and so only allows for proportions between the present species.

Such a suction mechanism was also demonstrated towards intentional sensor retention towards long-term data collection in the GI system. NUtech Ventures has disclosed a patent describing a suction based device to achieve long term data collection by mechanical fastening. The device aims to overcome the challenges of attachment to the GI wall, such as irregularity, slippiness, chemically corrosiveness, and physiological activity from peristalsis [94]. The opportunities to modify the device for sensing or manipulation are manifold. For sensing, trigger mechanisms such as heat, pH, pressure, analytes or flow rate could be implemented. The measurements can be wirelessly transmitted to the outside and/or it can be used to trigger the suction mechanism to induce anchoring in the desired region of the GI tract. Alternatively, the suction can be preprogrammed to activate after a certain time. The sensors and communication system can be powered by a battery or with a power generator driven by peristalsis force. However, intestinal wall proximity prior to suction activation is still a challenge. Since only one attempt at anchoring is possible, this is a critical part of the design. For this reason, two peristaltic pressure sensors are present on the device, which informs about the tissue proximity, and aids the decision about when to actuate.

3. Disruptive innovation in medical devices: understanding the regulatory challenge

One of the major challenges for researchers in medical devices and robotic intervention, both in academia and in industry, is the process of converging a medical device prototype from the lab to the clinic. In order to ensure safety and effectiveness of new medical devices, the prototypes must obtain regulatory approval – something that needs to be conceptualized since the very ideation of the research project. Typically, FDA does not regulate specific materials for an implantable device, but evaluate the device as a whole. To do so, FDA assigns three main regulatory classes: Class I, II and III with increasing level of risk. As an example, wireless endoscopy falls under class II risk profile. The European Commission follows 4 classes (I, IIa, IIb and III). Table 1 provides an overview of the technologies discussed in this review with regard to their material composition, device design and therapeutic outcome. It is evident that the devices discussed in this article rely on complex fabrication procedures – often involving both organic and inorganic materials serving multiple purposes. It can be observed from the detailed descriptions presented in Table 1 that the materials, or more specifically the polymers used in the production of these devices, are often chosen based on the properties needed for the fabrication schemes [95,96]. As depicted in Table 1, several drug delivery technologies are biocompatible but not biodegradable. Likewise, biodegradability will become a challenge if a device is being used for sensing or sampling. The tug-of-war between toxicity and therapeutic efficacy can invariably be won

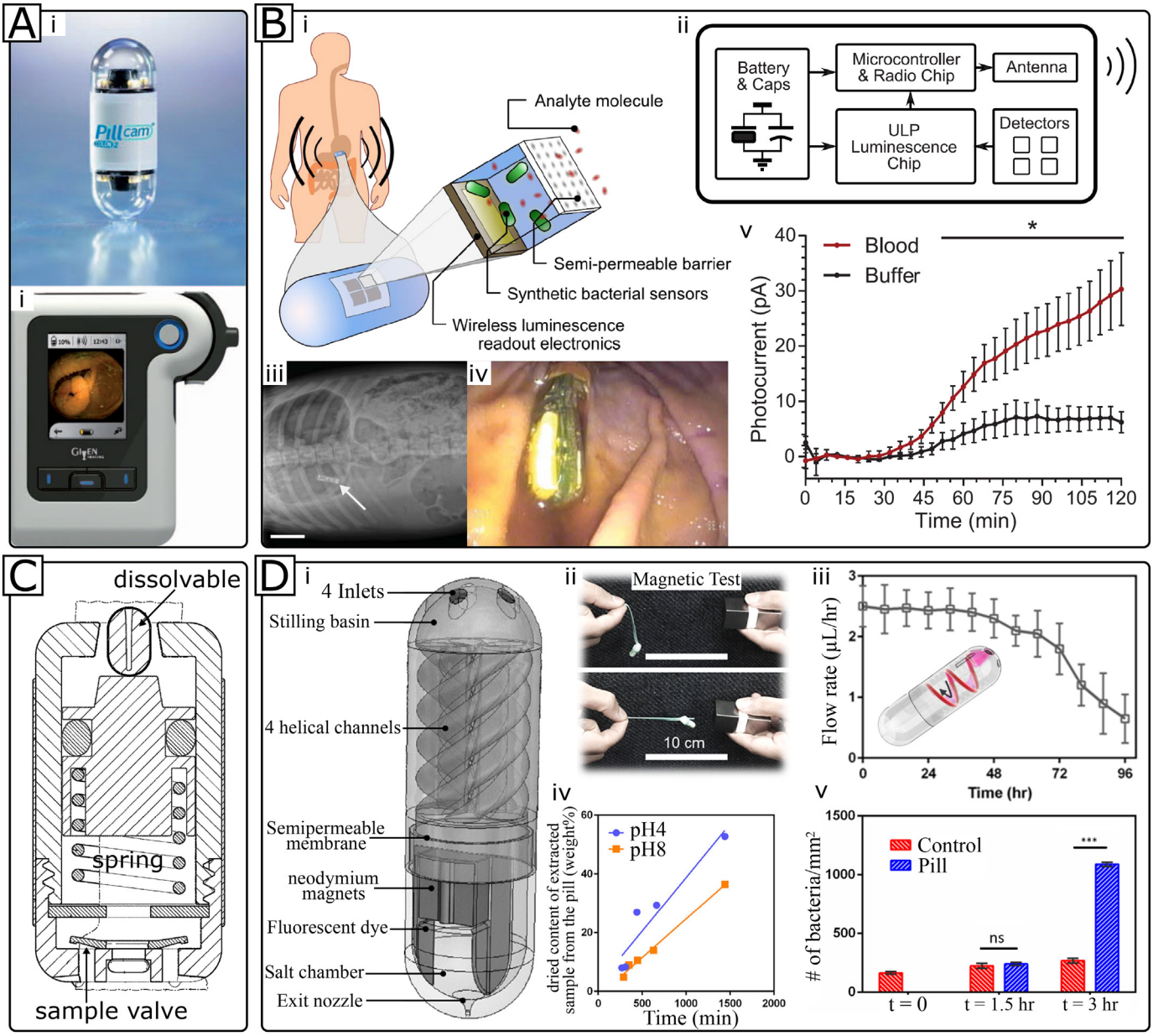

Fig. 5. Examples of orally ingested macrodevices for sensing and sampling. 5A) The first wireless capsule endoscope: PillCam. (i) The endoscope features two wide-angle cameras and a transmitter for real-time monitoring on (ii) Data Recorder 3. 5B) Ingestible Micro-Bio-Electronic Device (IMBED) uses genetically engineered bacteria to detect the presence of biomarkers. (i) Schematic showing the working principle with light generating bacteria and photodectors. (ii) Diagram of the electronic processing: all the way from detecting the light and wirelessly transmitting the information to the operating personnel. (iii) X-ray and (iv) endoscopy images illustrating the location of the device in a swine stomach (scale bar: 5 cm). (v) The generated photocurrent during an intestinal bleeding detection (blood) and a reference (buffer) experiment. From [[91]]. Reprinted with permission from AAAS. 5C) Mechanical suction device for sampling of GI material. A spring is relaxed upon dissolution of a compressing material, thereby creating a partial vacuum that opens the valves and draws in GI fluids. 5D) Osmotic pressure driven suction device for continuous sampling of intestinal material. (i) Overview of the device showing channel system and the osmotic-pressure-creating semipermeable membrane with salt chamber. (ii) The device has an imbedded magnet for optional prolonged retention in locations of extra interest and (iii) can sample continuously for 48 h with near-constant rate. (iv) The device can sample in both pH 4 and 8 environments, but with different rates. (v) The collected bacteria from the microbiome continuous to multiple within the device after their sampling.

by the body, thanks to our immune system, but is it the 'best in class' solution for a particular medical problem? Characteristics such as t_g, tanδ, Young's modulus and solubility in specific solvents lead to the use of specific polymeric materials for very specific fabrication processes. In this manner, engineering polymers with high processability *e.g.* PMMA, PC and PEO or castable elastomers such as PDMS are more compatible with the existing scalable microfabrication techniques [97,98]. On the other hand, production of microdevices by biodegradable and biocompatible polymers, such as polysaccharides (*e.g.* alginates, dextran, chitosan *etc.*), and protein-based polymers such as gelatin can hardly be scalable due to less favorable processability and more importantly, the costs of extraction and purification of such polymer from natural resources. Clearly, device development seems to have been fabrication-driven, which leaves gaping holes in terms of material properties governing *in vivo* safety profile and even clinical studies further down the road.

Future OIMs need to be simple—despite their intrinsic complexity—as well as easy to use, non-toxic, and with superior performance. The common notion of a disruptive innovation, if not being made for a resource-limited setting [99], needs to be checked – a medical devices,

Table 1
Material composition and biocompatibility of micro- and macro-scale ingestible devices for GI manipulation discussed in the present review.

Composition	Physical specifications	Therapeutic outcome	Biocompatibility	Reference
PMMA + PEG-PMMA hydrogel	3 reservoir circular and planar microdevices with 200 μm diameter	Bioavailability of acyclovir loaded devices compared to drug solution was tested in a rat model	Biocompatible Nonbiodegradable	[30]
PCL	Cylindrical microdevices with 300 μm in diameter and 90 μm in height	Trends of higher bioavailability of paracetamol compared to coated gelatin capsules was tested in a rat model	Biocompatible Biodegradable FDA-approved material	[34]
PMMA	circular and planar microdevices with 200 μm diameter 8 μm height	Insulin loaded devices were tested for cytotoxicity *via* MTT assay in a Caco2 cell model	Biocompatible Nonbiodegradable	[35]
Eudragit® FS 30 D + Eudragit® L100/S100	Circular and planar microdevices with 170–250 μm diameter and 13 μm height	Insulin-loaded devices were tested for drug release in simulated intestinal fluid *in vitro*	Biocompatible Nonbiodegradable FDA-approved material	[36]
PMMA + PC + Al_2O_3	Nanostraws attached to a circular planar reservoir with 200 μm in diameter and 17 μm in height	Increased adhesion to a Caco2 cell layer (*in vitro*) and to the intestinal mucus (*ex vivo*) were tested, aimed for better absorption of insulin *in vivo*	Biocompatible Nonbiodegradable	[39]
PAPS + Zn + Fe	Tubular micromotor with 10 μm length 5 μm diameter	Magnetically controlled localization for release of doxorubicin together with toxicity of the devices was tested in an *in vivo* mouse model	Biocompatible Biodegradable	[56]
Mg + TiO_2 + Chitosan + Eudragit® L100–55	Spherical micromotors with 25 μm in diameter	Self-propelled movement and cytotoxicity of the micromotors were tested *in vitro*, after which delivery of vaccines to the stomach and antibody generation were investigated in mice	Biocompatible Nonbiodegradable	[57]
Mg + TiO_2 + PLGA + Chitosan	Spherical micromotors with 20 μm in diameter	Toxicity, retention of micromotors in the stomach and treatment of infection using clarithromycin was tested in mice	Biocompatible Biodegradable	[51]
PVA	Dual compartment tablet with 1 cm diameter	Controlled release of glipizide was tested investigating drug release profiles by chaning the composition of the tablet compartments *in vitro*	Biocompatible Biodegradable FDA-approved material	[72]
PDMS+ ethylcellulose embedded with (PNIPAm-MAA) nanoparticles	Cylindrical microdevicdes with 10 mm diameter 1 mm height	pH –stimulated release of Vitamin B12 loaded devices tested for biocompatibility in an *in vivo* rat model	Nonbiocompatible	[74]
Stainless steel + Soluplus® + polyethylene oxide (PEO)	Luminal Unfolding Microneedle Injection (LUMI) device enveloped in a capsule with 9 mm in diameter and 30 mm in length	Mechanisms of capsule actuation and microneedle unfolding was *tested in vitro* and delivery of human insulin was tested *in vivo* in swine models	Biocompatible Nonbiodegradable	[83]
Stainless steel + PEO + hydroxypropyl methylcellulose	self-orienting millimeter-scale applicator (SOMA) with a 7 mm length	Mechanism of the self-orienting applicator and delivery of insulin to the stomach was tested *in vivo* in a swine model	Biocompatible Nonbiodegradable	[73]
Medication container + pH and temperature sensor in a gelatin capsule	IntelliCap® 27 × 11 mm capsule	Colonic delivery of Diltiazem as a model drug was tested in a clinical study	Not investigated	[86]
Camera + radio transmitter	PillCam COLON 2 endoscopy capsule with 27 mm in length	Wireless real-time monitoring of the gastrointestinal tract; detection of colon polyps was tested in patients	FDA-approved	[88]
PDMS+ PC+ epoxy capsule Parylene C coating ABS cell carrier	Ingestible Micro-Bio-Electronic Device (IMBED), 13 mm in diameter and 4 cm long capsule containing microelectronics, circuit board, cell chambers and a micropore membrane	Detection of gastric bleeding *via* the usage of *E. coli* Nissle which generate light upon contact with blood through a semi-permeable membrane	Nonbiocompatible Nonbiodegradable	[91]
Dissolvable biocompatible material + enteric coating	16 × 8 mm suction-based sampling device	Sampling of gastrointestinal contents for post-sampling analysis	Biocompatible	[93]
3D printed high temperature resin + cellulose acetate	size-0 enteric coated capsule containing helical channels	Sampling of the GI tract contents and microbiome using osmotic pressure was tested *in vitro* and *in vivo* in pigs and primates	Biocompatible	[94]

at the very least, should have a comparable traditional performance and higher ancillary performance to meet regulatory requirements [100].

Another major challenge is the testing of new devices in patients. Absence of such a transparent framework often results in critical setbacks, as was revealed by the *Implant files*, a global investigation into medical devices that were tested inadequately or not at all [101]. The European Union (EU) made an advancement to tackle this issue by revamping its Medical Device Regulation (MDR) policy. Previously in the EU, Class I or low risk devices needed merely a "self-declaration" by the manufacturer. However, *improvised* EU's Medical Device Regulation act, which will apply from May 2020 (postponed until May 2021 due to COVID-19 crisis), puts stringent controls on active medical devices [102]. Invasive control systems, such as active therapeutic devices (with integrated or embedded diagnostic function), which were previously being assigned to Class IIb, will now adhere to the stringent requirements of Class III. The same is applicable for invasive devices (like the ones in GI tract) or devices involving therapeutics delivery (like the insulin pump on skin). Clearly, this will drastically change the medical device development scenario in the EU, as compared to the US, where *510 (k)* filings facilitate regulatory clearance based upon substantial similarity with the previously approved medical devices (*i.e. predicate* device) [103]. Here in the EU, the implications of new MDR policy is yet to be seen, but it is safe to say that more often than before, a clinical trial will be required [104,105]

In the near future, three main focus areas of development will include: i) Safer power sources; ii) non-invasive microsampling

technologies; and iii) imaging modalities *in vivo*. Self-activated microdevices, like micromotors, and stimuli-responsive polymeric origami structures will provide a low-power actuation scheme for specific GI applications. At the same time, controlled motion of a microdevice by wireless power transfer will gain traction [106] – though for GI applications, peristalsis is still a force to reckon with. Biocompatible microfabrication technologies, like 3D printing, and large-scale production *via* additive manufacturing, will dominate microdevice design for exploring new applications in microsampling techniques. Another major focus area will be development of *in vivo* imaging modalities in the gut – both ultrasound and magnetic resonance will have their fair share. In fact, ultrasound may have an additional advantage by providing physical actuation owing to the phenomenon of acoustic cavitation [107,108].

The next generation of such oral microdevices will demonstrate 'intelligence' by implementation of the 'perception–decision–action' loop architecture, which will further blur the lines between medical devices and microrobotics. This is not a distant future – by 2021, the world will have three times as many smart connected devices as people – and more and more medical devices and processes contain integrated sensors [109]. This will give rise to *smarter* OIMs, which will be more patient-specific; thanks to ongoing progress in the AI and huge amount of patient specific data (which these devices will be able to generate/harness). Finally, greater cooperation is needed between researchers and relevant stakeholders *i.e.* pharma companies, clinicians and drug/healthcare regulatory authorities. The evolution from *endoradiosonde* into a 'robotic pill' has already begun and will require us to rethink the 'patient–clinician–technology' relationship in the near future.

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