Journal of Controlled Release 364 (2023) 227–245

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Smart pills and drug delivery devices enabling next generation oral dosage forms

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ARTICLE INFO

Keywords:
Oral drug delivery
Millimeter-sized devices
Personalized therapy
Biologics
Bioavailability
Gastrointestinal tract

ABSTRACT

Oral dosage forms are the preferred solution for systemic treatment and prevention of disease conditions. However, traditional dosage forms face challenges regarding treatment adherence and delivery of biologics. Oral therapies that require frequent administrations face difficulties with patient compliance. In addition, only a few peptide- and protein-based drugs have been commercialized for oral administration so far, presenting a bioavailability that is generally low. Therefore, research and development on novel formulation strategies for oral drug delivery has bloomed massively in the last decade to overcome these challenges. On the one hand, approaches based on lumen-release of drugs such as 3D-printed capsules and prolonged gastric residence dosage forms have been explored to offer personalized medicine to the patient and reduce frequent dosing of small drug compounds that are currently in the market as powdered tablet or capsules. On the other hand, strategies based on mucus interfacing such as gastrointestinal patches, or even epithelium injections have been investigated in order to enhance the permeability of biologic macromolecules, which are mostly commercialized in the form of subcutaneous injections. Despite the fact that these methods are at an early development stage, promising results have been revealed in terms of personalized medicine and improved bioavailability. In this review, we offer a critical overview of novel ingestible millimeter-sized devices and technologies for oral drug delivery that are currently used in the clinic as well as those that could emerge on the market in a not too distant future.

1. Introduction

Providing the right dose at the right place at the right time is the ideal aim for treatment and prevention of disease conditions – and ingestible dosage forms remain the preferred solution for that purpose [1]. However, traditional oral dosage forms face challenges which warrants the continuous development of novel drug delivery technologies [2]. First, commercialized oral drug dosage forms are primarily produced by tableting, and here equipment restrictions limit the fabrication of single unit dosage forms capable of delivering *e.g.* multiple drugs with precise doses and release profiles according to the individual needs of the patient [3,4]. Secondly, there is a lack of patient adherence to therapies that require frequent administrations of one or multiple medicines such as HIV antiretroviral therapies [5]. There are available technologies that aim to overcome this challenge such as Osmotic-controlled Release Oral delivery Systems (OROS), which have been on the market for dozens of years and rely on the principle of osmosis as the driving force for sustained release of pharmacotherapy, reducing the dose frequency to once-daily [6,7]. However, there is still a lack of adherence to daily medications, and therapies that need a weekly or monthly sustained release are limited by the short residence time of traditional dosage forms [8–11]. Finally, there are challenges associated with a low bioavailability of macromolecules such as peptides when using traditional oral dosage forms, due to low mucosal/epithelial permeability and lack of stability in the gastrointestinal (GI) environment [12,13]. The recent commercialization of semaglutide highlights the incorporation of permeation enhancers (PEs) as a way to increase absorption of orally delivered macromolecules [14,15]. However, the oral bioavailability achieved for peptides, even with the PEs that have been commonly tested in clinical studies, is generally low [16,17]. The current state-of-the-art technology for a successful oral peptide delivery provides around 1% bioavailability when delivered as a standard oral tablet utilizing salcaprozate sodium (SNAC) as PE (Rybelsus® oral semaglutide) [14].

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https://doi.org/10.1016/j.jconrel.2023.10.041
Received 9 June 2023; Received in revised form 9 October 2023; Accepted 26 October 2023
Available online 31 October 2023
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These challenges suggest a need to develop novel oral dosage forms that adapt to the specific requirements of the patient and the pharmaceutical industry and to identify methods of improving adherence in the patient populations. Moreover, there is a need to develop oral formulations that protect and enhance the permeability of macromolecules.

The aim of this review is to offer a focused and critical analysis of novel millimeter-scale oral drug delivery technologies for systemic uptake, including smart pills and ingestible engineered devices that are currently used in the clinic or are in preclinical trials, and as well as those that could emerge on the market in a not too distant future. It is considered outside the scope of this review to summarize nano- and micro-particle systems for oral drug delivery. Therefore, readers interested in this topic are suggested to look elsewhere [18–20]. More explicitly, we have focused on engineered formulations for controlled release of pharmaceutics in the lumen such as 3D-printed capsules and prolonged gastric residence devices, which aim to delivery small drug compounds, as well as devices that enhance the bioavailability of biologic macromolecules by mucus embedment/penetration or even epithelium injections using needle-based devices and auto-injectors (Fig. 1).

2. Physiological aspects of the GI tract

The GI tract is characterized by a harsh biochemical environment that ensures the digestion of food and it features several physical barriers that warrants protection against foreign compounds [21]. Therefore, this environment compromises the stability and absorption of certain drugs and limits their bioavailability. Firstly, drug delivery to the buccal cavity and esophagus is challenging due to the short transit time. Subsequently, the volume of the dosage form is limited to enable convenient dosing in the sublingual or buccal pouch [22]. Formulations designed for prolonged residence time in these areas [23–26] are often associated with discomfort and may be undesirable for the patients. Secondly, the low-pH conditions in the stomach (pH 1.7 and pH 5.0 in fasted and fed states, respectively) and the presence of enzymes compromise the stability of a wide range of active pharmaceutical ingredients (APIs) [27,28]. Thirdly, although the small intestine features the largest available absorptive surface area on account of villi, crypts and microvilli structures, unaided absorption of certain drugs is almost impossible due to the presence of digestive enzymes, bile salts, mucosal layer, and intercellular tight junctions [29–32]. Finally, the large intestine presents bacterial enzymes that can degrade the drugs and it is primarily concerned with desiccation of waste with storage in colon and rectum prior to elimination [33].

In particular two important barriers need special attention when it comes to absorption of certain drugs in the GI tract, namely: mucus and tight junctions. Mucus is a lubricating and protective hydrogel network that covers all inner surfaces of the GI tract and it is one of the main blockades that prevents entry of foreign compounds into the systemic circulation. Mucus can be identified as two phase structure: adherent mucus on epithelium and mobile mucus, which is loosely attached and mixes with the intestinal content. It is mainly composed of high molecular weight glycoproteins, called mucin, and 90–98% water. In addition, it contains further compounds such as cholesterol, inorganic salts, and enzymes. Mucus components can interact with certain compounds such as macromolecules and limit their diffusion [34]. Mucins present negatively charged regions that repel compounds that are also negatively charged, whereas positively charged molecules are attracted to the mucus layer, presenting low diffusion rates as well. In addition, the mucus mesh pore size of approximately 200 nm also impedes the diffusion of large particles and insoluble formulations [35].

Compounds that successfully traverse the mucus face the epithelial lining barrier. In the small intestine, the epithelial barrier consists of epithelial cells linked together by tight junctions, adherent junctions, and desmosomes [36]. This structural cellular organization controls what compounds can be transported from the intestinal lumen into the systemic bloodstream *via* paracellular and transcellular pathways. The paracellular pathway is semipermeable and it is mainly size-selective (<600 Da), as determined by the pore size (8–9 Å in diameter) in tight junction [37]. Diffusion of small molecules through these pores is

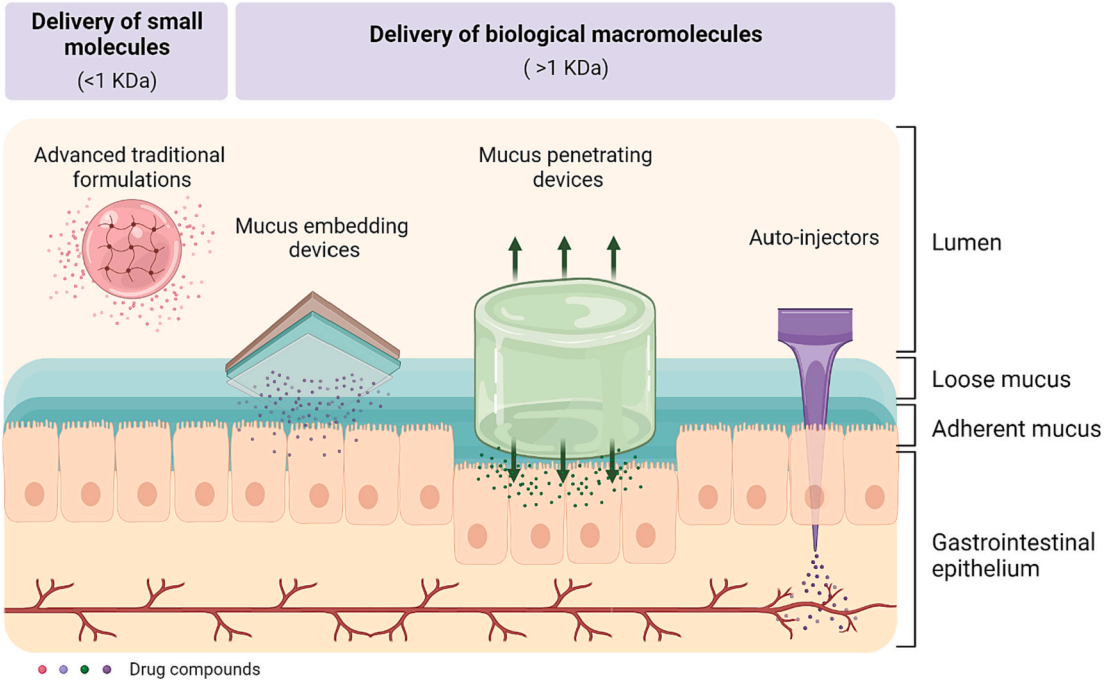

Fig. 1. Overview of the main strategies developed for oral drug delivery when using smart capsules and drug delivery devices. From left to right, the drug is released in closer proximity to the GI epithelium: first, it is released in the lumen, secondly, the device allows mucus interaction/embedment *via* mucoadhesive forces, then mechanical pressures from the device ensure intimate contact with the epithelium and, finally, auto-injectors offer direct drug release across the cell line. *Created with BioRender.com.*

mainly driven by water transport due to electrochemical or trans-epithelial osmotic gradients that induce solvent drag [38]. The trans-cellular pathway is mainly relevant for larger compounds or particles that are typically transported across M cells or by endocytosis in epithelial cells. In the case of antigens, it has been shown that only <0.1% of the luminal protein concentration can be transcytosed intact [38]. Therefore, it is highly relevant to take the aforementioned challenges associated with oral drug delivery into account when developing new delivery systems for: i) site-specific targeting in the GI tract, ii) prolonged residence time (in stomach, intestine or colon) and/or iii) increasing the bioavailability of macromolecules, especially proteins and peptides.

3. Design and delivery strategies of macroscale devices for oral delivery of pharmaceutical compounds

When considering the design of macro-devices for oral drug delivery, swallowability plays an important role [39]. The U.S. Food and Drug Administration (FDA) has provided guidelines for size, shape, and other physical characteristics for generic capsules and tablets that can also be used when designing a macro-device [40]. As a result of this, there are trade-offs between the volume of a device and the maximum drug loading capacity. This is key when considering the suitability of API, with respect to dosage, potency and bioavailability. Therefore, most of the developed macro-devices are inserted in or shaped as capsules or tablets that comply with the guidelines [40]. The design also has a direct influence on the behavior of the device in the different segments of the GI tract, as well as on the mucus adhesion or penetration abilities of the device. Many drug delivery strategies have been developed to address the intrinsic challenges of the oral administration route. Table 1 presents an overview of ingestible novel millimeter-scale devices and smart pills for controlled release and enhanced absorption of pharmaceutics *via* the GI tract to achieve a systemic effect. The table below highlights the variety of techniques employed and the API or model drug selected for dosing. Where appropriate, the absolute or relative bioavailability has been stated. This primarily concerns the delivery of macromolecules, in which bioavailability ascertained from preclinical and clinical studies is often stated relative to a subcutaneous or intravenous injection as a control. Additionally, the development stage is shown to highlight the maturity of the work, signifying if the techniques have advanced toward clinical trials in human, or even to market.

4. Advanced traditional capsules

4.1. 3D-printed engineered tablets and capsules for tailored erosion

For a recent and comprehensive review on utilizing 3D printing for producing oral dosage forms readers are referred to [87]. This particular field has gained a lot of momentum in the last decade: with the expiration of key patents related to stereolithography (SLA), selective laser sintering (SLS) and fused deposition modelling (FDM) [88] and with the continuous evolution of more accessible and user friendly computer-aided design tools, we are currently one step closer to realizing a scenario where *e.g.* oral medication can be tailored to the individual patient and hereafter produced as print-on-demand dosage forms in a suitable point-of-care setting [87,88].

Initially, considering some of the commercial advances in novel methods for producing oral dosage forms, it is clear that one of the main focus areas is scalability when it comes to production volume. To the best of our knowledge, three distinct production methods, bearing resemblance to the aforementioned SLA, SLS and FDM 3D printing techniques, are receiving most attention: i) Binder Jetting or Ink-jet 3D Printing where a binder solution is selectively deposited onto a 2D powder bed in a sequential manner, ii) Melt Extrusion Deposition (MED®) where a powder feedstock consisting of API and excipients is brought into a soft or molten state and then deposited in a layer-by-layer manner according to a predefined design file, and finally iii) advanced screen printing (introduced by Laxxon Medical GmbH as the Screen Printing Innovational Drug (SPID®) technology), where a pharmaceutical paste is applied to a semiflexible meshed screen with prefabricated openings that outline the overall geometry of the produced dosage form. It is somewhat diffuse whether the commercial fabrication methods are true 3D printing methods or merely adaptions of conventional deposition methods, nonetheless most of the commercial players including Aprecia Pharmaceuticals [41], Triastek [42] and Laxxon Medical GmbH [44] are marketing their commercial or pipeline products as 3D printed medications.

Recently, the regulatory framework of the FDA has approved the first and only 3D printed medicine, Spritam® levetiracetam, which is used as an oral prescription adjunctive therapy in the treatment of seizures in adults and children with epilepsy [41]. SPRITAM® utilizes Aprecia's proprietary ZipDose® Technology platform to produce a high-dose drug loaded porous formulation (up to 1000 mg per tablet). The tablets are produced by initial formation of a 2D powder bed consisting of a finely grinded pharmaceutical blend of API and excipients. A binding fluid is then selectively deposited onto the blend to initiate tablet formation. The full process consists of several cycles of powder bed formation and binding fluid deposition in order to build up the final tablet layer by layer. The final formulation rapidly disintegrates with a small amount of liquid (approximately 15 mL), thereby fulfilling a need for patients that struggle to swallow the medication while concurrently eliminating the necessity of having liquid formulation [41]. In addition, Triastek Inc. has received Investigational New Drug approval from the FDA to begin clinical studies of three products, T19, T20 and T21, which have been produced by MED® [42]. As mentioned previously, this technology directly uses a powder feedstock composed of API and excipients, which effectively eliminates the filament production step normally associated with the conventional FDM 3D printing method. Li and co-workers utilized MED® to produce different tablet designs with one or more compartments containing formulations with different drug release profiles to demonstrate the precision and reproducibility of the technology *in vitro* and *in vivo* [43]. Fig. 1A shows two examples of the developed tablet designs with their respective controllable drug release profiles. In their study, they conclude that the tablet designs enabled versatile release characteristics and that the predictability of release behavior of the 3D-printed tablets provides an efficient and reliable tool for pharmaceutical product development [43]. Whereas the production methods chosen by Aprecia Pharmaceuticals and Triastek Inc. bears resemblance to the conventional SLS and FDM 3D printing techniques respectively, Laxxon Medical GmbH has set out to employ an entirely different approach relying on the well-established screen printing process, which is generally believed to originate in China and was used by ancient Greeks and Egyptians for producing *e.g.* works of art [89]. In a recent publication, Schneeberger and co-workers demonstrate key aspects of what is now known as the SPID® technology [45]. Here, a pharmaceutical paste formulated for delayed release and containing the model drug paracetamol is used for making tablets with different shapes and sizes (Fig. 2B). Investigations of size and mass demonstrated high API loading uniformity and physical properties, such as friability, compared favorably to conventionally produced tablets. Drug release studies revealed that the paracetamol release could be tuned by modifying the surface-area-to-volume-ratio [45]. In conclusion, the study shows the potential of producing customized tablets in a one-step screen printing process, and currently Laxxon claims to have a facility capable of producing 1.5 million tablets per day [87].

Besides the commercial activities pertaining to the development of new scalable production methods for producing oral medications, there has also been a massive number of academic publications on dosage forms produced using adaptations of the conventional 3D printing techniques originally conceived in the 1980s (*i.e.* SLA, SLS and FDM). In the following, the main focus will be on few selected applications of FDM for producing tablets for controlled release of drugs [46–49,90] as

Table 1
Studies focused on novel oral delivery devices for systemic drug absorption.

Reference	Drug delivery device	API or model drug	Reported dosage*	BA**	Approximated device dimensions	Equivalent capsule	Development stage
Advanced traditional formulations							
3D-printed engineered tablets and capsules for tailored erosion							
[41]	Powder-binding tablet (Spritam®)	Levetiracetam	1000 mg	-	-	-	Commercialized in the US since 2015
[42,43]	MED® tablet	Metoprolol Levodopa Tofacitinib Topiramate Clonidine	100 mg	-	Disk: Ø 10 mm Oval: 20 × 10 mm	- Size 0	Preclinical and in clinical studies.
[44,45]	Screen-printed tablet	Paracetamol	16 mg 21.4 mg 15.7 mg 13.5 mg 12.7 mg	-	Disk: Ø 7.8 mm Donut: Ø 9.7 mm Cuboid: 9.8 × 4.9 mm Oval: 9.7 × 4.8 mm Grid: 9.8 × 5 mm	- - Size 5 Size 5 Size 5	Preclinical studies: *in vitro*
[46]	FDM tablet	Glipizide	14.5 mg	-	Ø 10.5 mm	-	Preclinical studies: *in vitro*
[47]	FDM tablet	Paracetamol Caffeine	25 mg	-	14.3 × 5.3 mm	Size 4	Preclinical studies: *in vitro*
[48]	FDM tablet	Isoniazid Rifampicin	1.4 mg	-	8 × 2.3 mm	Size 5	Preclinical studies: *in vitro* and *in vivo*
[49]	FDM device with SNEDDS	Saquinavir Halofantrine	-	-	Single-compartment device: 7 × 6.7 mm Dual-compartment device: 10 × 14 mm	- -	Preclinical studies: *in vitro*
Deployable and swelling devices for prolonged gastric residence							
[11]	Swellable formulation	Gabapentin	600 mg	-	-	-	Commercialized in the US since 2011
[9]	Self-unfolding multilayer films (Accordion Pill®)	Carbidopa Levodopa	550 mg	-	-	-	Clinical studies
[50–54]	Self-unfolding star-shaped device (LYNX™)	Risperidone Ivermectin Dolutegravir Rilpivirie Cabotegravir Levonorgestrel Memantine	250 mg	-	Ø 5.4 cm (unfolded state)	Size 00–000 (folded state)	Preclinical and clinical studies
[55]	Hydrogel system	Caffeine	2.5 mg	-	Ø up to 6 cm (swollen state)	Size 000 (shrink state)	Preclinical studies: *in vitro* and *in vivo*
Mucus embedding devices							
Mucoadhesive GI patch systems							
[56]	Two-layered patch	Leuprolide	150 μg	-	Ø 2–3 mm	-	Preclinical studies: *ex vivo*
[57]	Two-layered patch	Salmon calcitonin	0.9 mg	1.5%	Ø 2–5 mm	Size 9	Preclinical studies: *in vitro*, *ex vivo* and *in vivo*
[58]	Three-layered patch	Insulin	2.6 mg	2.2%	Ø 2.5 mm	-	Preclinical studies: *in vitro* and *in vivo*
[59]	Two-layered patch	FITC-Insulin	-	-	Ø 6 mm	-	Preclinical studies: *ex vivo*
[60]	Multi-layered device with self-folding gate	Acid orange 8 Albumin	-	-	Ø 5 mm	-	Preclinical studies: *In vitro*
[61]	Three-layered self-folding patch	Acid orange 8 Albumin	-	-	4 × 4 mm	Size 5	Preclinical studies: *in vitro* and *ex vivo*
[62]	Multi-layered self-unfolding origami	-	-	-	34.3 × 16.7 mm (unfolded state)	Size 000 (folded state)	Preclinical studies: *in vitro* and *ex vivo*
Mucus penetrating devices							
Magnetic systems							
[63]	Two-layered tablet	Acetaminophen	35 mg	-	Ø 6 mm	-	Preclinical studies: *in vitro* and *in vivo*
[64]	Press coated tablet	Acyclovir	200 mg	-	10 × 6.8 mm	-	Preclinical and clinical studies
[65,66]	Beads	DPP-4 inhibitor	4 mg	-	1–2 mm	Size 9	Preclinical studies: *in vitro*, *ex vivo* and *in vivo*
SPED and mucus-clearing devices							
[67,68]	SUF	Insulin	0.6 mg	0.12%	7 × 7 mm (unfolded state)	Size 9 (folded state)	Preclinical studies: *in vitro* and *in vivo*
		Insulin	3.35 mg	1.83%	10 × 15 mm (unfolded state)	Size 4 (folded state)	
		Nisin	37.6 mg	-	50 × 15 mm (unfolded state)	Size 00 (folded state)	
[69–74]	Superporous hydrogel system	BAEE	10 mg	-	Ø 25 mm (swollen state)	Size 000 (dried state)	Preclinical studies: *in vitro*, *ex vivo* and *in vivo*, and clinical imaging studies
		FITC-Dextran	10 mg	-			
		Insulin	24.5 mg	1.9%			
		Octreotide	15 mg	16.1%			
[75]	Mucus-clearing capsule	Insulin	3.5 mg	-	-	Size 000	Preclinical studies: *in vitro*, *ex vivo* and *in vivo*
		Vancomycin	100 mg	-			
Epithelium injectors							
Auto-injectors and needle-based devices							
[76]	LUMI	Insulin	0.3 mg	>10%	Ø 4 cm (unfolded state)	Size 000 (folded state)	Preclinical studies: *in vitro*, *ex vivo* and *in vivo*

(*continued on next page*)

Table 1 (*continued*)

Reference	Drug delivery device	API or model drug	Reported dosage*	BA**	Approximated device dimensions	Equivalent capsule	Development stage
[77,78]	SOMA	Insulin Semaglutide Adalimumab Epinephrine	0.14 mg 4 mg 4 mg 0.24 mg	51% 78% - -	15 × 12 mm	Size 000	Preclinical and clinical studies
[79]	Spring-loaded grabbing applicator (BIONDD™)	Insulin Liraglutide	- -	70% 100%	-	Size 00	Preclinical studies
[80–82]	Self-inflating applicator (RaniPill®)	Human parathyroid hormone analog Insulin Octreotide	- 0.7 mg 3.5 mg	- 100% 65%	21–25 mm (inflated state)	Size 000 (folded state)	Preclinical and clinical studies
[83,84]	Liquid jet injector	Adalimumab Semaglutide	75 mg 1 mg	- 37%	-	-	Preclinical studies
[85]	DOAM	Semaglutide	10 mg	-	Ø 8 mm	Size 00	Preclinical studies: *in vitro, ex vivo* and *in vivo*
[86]	Magneto-responsive microneedle patch	Insulin	1 mg	-	Ø 3 mm	Size 5	Preclinical studies: *in vitro, ex vivo* and *in vivo*

Ø - Diameter, BA – Bioavailability, BAEE – *N*-α-benzoyl-L-arginine ethylester, DPP-4 – Dipeptidyl peptidase-IV, FITC – Fluorescein isothiocyanate, SNEDDS – Self-nanoemulsifying drug delivery system

* Maximum reported dosage in a single or multiple devices (if loaded in the same capsule) of one or the total combination of multiple APIs, if applicable.

** Maximum reported relative or absolute BA of macromolecules compared to subcutaneous or intravenous injection.

well as intragastric floating tablets for sustained release of drugs [91]. Li et al. applied FDM to develop the DuoTablet (10.5 mm diameter), which consists of a double-chamber device in the form of a tablet embedded within a larger tablet (Fig. 2C) [46]. High-dose drug loaded filaments were fabricated by hot-melt extrusion in polyvinyl alcohol (PVA) to realize layers with different contents of glipizine, which is a common prescription drug to treat non-insulin dependent diabetes mellitus. *In vitro* dissolution tests simulating intestinal conditions revealed that the drug incorporated in the internal layer was not released until total drug release and dissolution of the external layer (Fig. 2C). The results fulfilled the clinical motivation behind the designed device and it demonstrates FDM as a promising approach to manufacture versatile and simplified controlled-release drug delivery systems [46].

Whereas the DuoTablet incorporated a single drug, the same strategy has been used to produce engineered macro-devices with controlled release profiles of multiple APIs. Goyanes et al. utilized FDM for producing a similar device called DuoCablet, which was also designed as a two-compartment device comprising a caplet embedded within a larger caplet, and a multilayer engineered tablet (Fig. 2D) [47]. In their work, both macro-devices (14.3 mm × 5.3 mm) contained PVA high-drug loaded filaments (maximum 8–9% loading capacity) of a common commercialized combinational therapy: paracetamol and caffeine. The dissolution tests in biorelevant conditions showed similar release profiles of paracetamol and caffeine from the multilayered tablet whereas experiments on the DuoCablet showed that the release of drug in the internal layer only commenced significantly after complete dissolution of the external layer [47]. Genina et al. applied the same fabrication method to produce a similar dual-compartmental dosage unit (8 mm × 2.3 mm) loaded with multiple drugs and tested *in vitro* and *in vivo* after oral administration to rats (Fig. 2E i-iii) [48]. Rifampicin and isoniazid, which are used for the treatment of tuberculosis, where chosen as combination therapy as there is a need of sequential release in the GI tract due to absorption interactions. As expected, *in vitro* drug release studies in simulated GI conditions revealed sequential release of the drugs (Fig. 2E iv and v). However, it did not result in a substantial retardation of the *in vivo* drug release based on the pharmacokinetic observation [48].

FDM has been used in the production of hydrolysable and biodegradable polymer-based scaffolds. However, it has been avoided to some extent in the printing of pharmaceutics due to the thermolabile nature of most drugs. Techniques to reduce heat exposition and degradation of APIs in FDM such as the utilization of larger nozzle diameters and higher printing speeds have been investigated. However, none of these approaches were successful in preventing drug degradation [92]. Therefore, much effort is being put into development of new polymers that support filament extrusion at lower temperatures thereby minimizing thermal degradation [93,94]. In addition, the development of self-emulsifying systems that can be directly incorporated into the empty cavities of FDM printed devices has also been investigated [49,95]. Markl et al. printed a dual-compartment cylindrical dosage form (10 mm × 14 mm) made of PVA and poly lactic acid (PLA) and loaded it with saquinavir (outer compartment) and halofantrine (inner compartment) self-nanoemulsifying formulations by pipetting [49]. As expected, and in correlation with the previous described studies, *in vitro* dissolution studies revealed that the release of the drug from the inner compartment commenced when roughly 80% of the drug from the outer compartment was already released. In addition, the use of new polymers as well as self-emulsifying drug delivery systems allows for co-administration of lipid-based formulations, which can improve the oral bioavailability of lipophilic drugs [96].

As evidenced by the selected examples presented here, 3D printing or analogously advanced deposition and printing methods are being employed extensively in order to produce new oral dosage forms that can potentially enhance the therapeutic efficacy of orally administered pharmaceutical compounds. The new production methods are aimed at enabling fast prototyping of new drug delivery devices or dosage forms which is especially useful in the early stages of drug development where smaller batches used for pre-clinical or pilot clinical studies are needed in order to evaluate the pharmacokinetic and pharmacodynamic properties of formulations. The new production methods also hold promise in terms of enabling a high degree of personalization when it comes to producing highly tailored and dose adjusted formulations for individual patients. Besides these obvious advantages, 3D printing techniques such as SLA, SLS and FDM also offers entirely new ways of modifying *e.g.* the release profiles *via* the intrinsic porosity and overall geometry of the produced medications. This essentially represents an entirely new trajectory when it comes to the production of oral dosage forms, as the release profile can be modified merely by changing the computer-aided design file as opposed to changing *e.g.* excipients and or coatings used for making traditional tablets and capsules. However, 3D printed of medicines may lead to limitations associated with reaching a satisfactory production volume, keeping the cost of the product sufficiently low, and potential degradation of the pharmaceutical compounds during the production, especially with FDM or MED®, where elevated

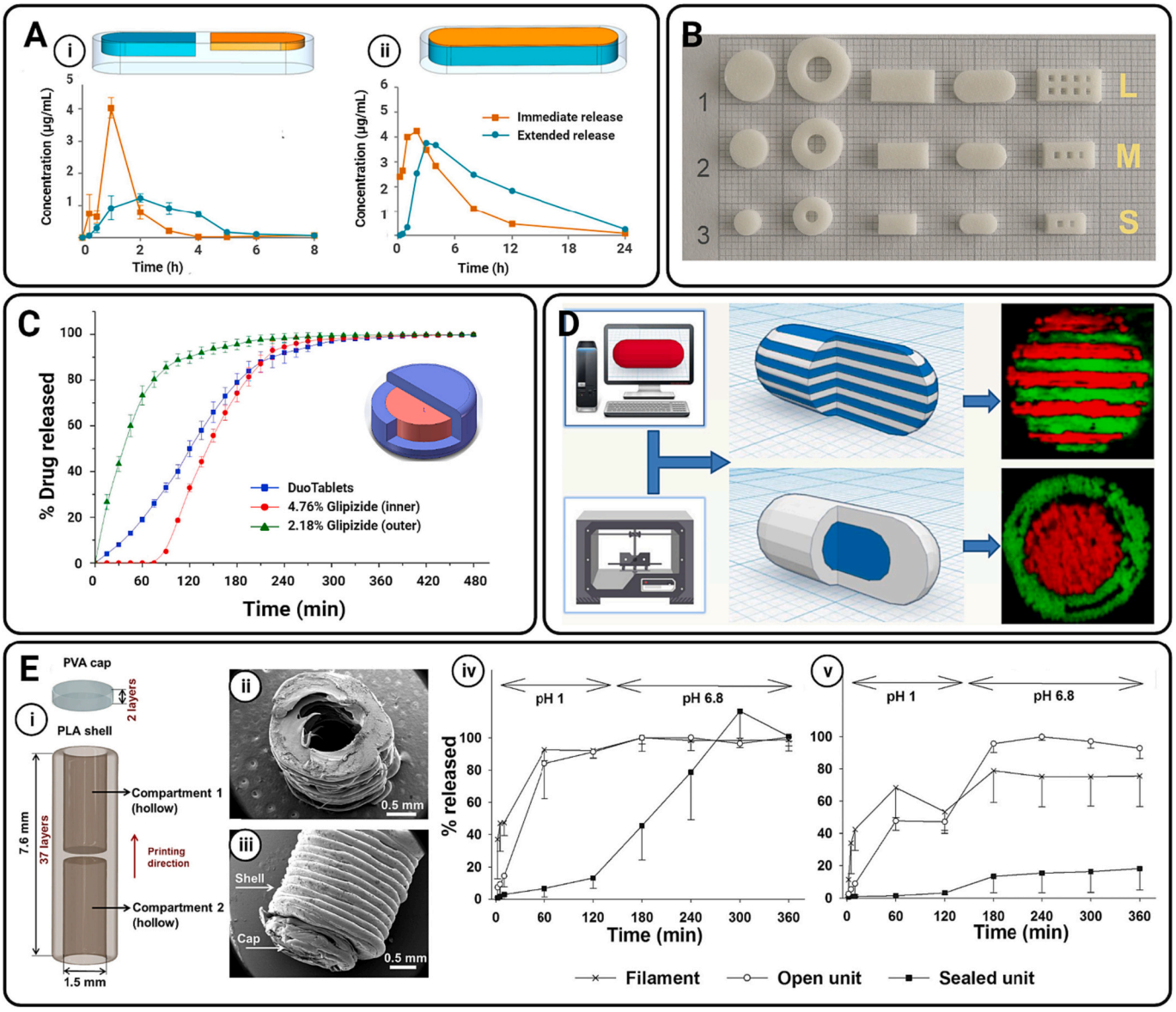

Fig. 2. Examples of 3D-printed tablets and millimeter-sized devices for oral drug delivery. A) MED-printed tablets with controlled release of drugs. (i) Compartment tablet design that combines immediate release and extended release of levodopa from separate compartments and (ii) topiramate from a single compartment and the respective plasma concentrations in beagle dogs after oral administration. Reprinted from [43] Copyright (2021), with permission from Elsevier. **B)** Photograph of multiple-shaped 3D screen-printed tablets on millimeter paper. Reprinted from [45] Copyright (2021), with permission from Elsevier. **C)** FDM-printed DuoTablet and the respective controlled release profile of glipizide *in vitro*. Reprinted from [46] Copyright (2017), with permission from Elsevier. **D)** Scheme of the production and representation of a FDM-printed multilayered tablet (top) and DuoCablet (bottom) with the respective 2-dimensional Raman mapping images of the cross-section (right). Reprinted from [47] Copyright (2015), with permission from ACS. **E)** FDM-printed dual-dosage unit for sequential release of drugs. (i) Schematic of the printed device and (ii) scanning electron micrographs of the empty compartment from top view and (iii) side view. (iv) *In vitro* sequential release of isoniazid and (v) rifampicin from the free filaments and the dual-compartment dosage units with and without sealing. Reprinted from [48] Copyright (2017), with permission from Elsevier.

temperatures are associated. As pointed out in [87], the new production methods will initially inform new regulatory guidelines and both the FDA and European Medicine Agency have established dedicated multi-disciplinary work groups that are suited to tackle all aspects associated with the approval of pharmaceutical products produced using emerging technologies such as 3D printing.

4.2. Deployable/swelling devices for prolonged gastric residence

Smart pills have been designed to achieve oral delivery of long-acting therapies using a standard-sized capsule that expands and retained in the stomach due to steric hindrance of passage through the pylorus. Such devices aim to dramatically reduce the dosing frequency from days to weeks or even months [97]. Depomed Inc. obtained FDA approval for a swelling gastro-retentive formulation of gabapentin for treatment of postherpetic neuralgia, reducing the frequency of administration from three times a day to once-daily [11]. Similarly, Assertio's Acuform® is a technology used in several commercial products and they consist of swelling polymers in a tablet that expands upon hydration to achieve 8–10 h gastric retention [98]. IntecPharma's Accordion Pill™ is currently in clinical trials and it is based on a multilayer film folded into a capsule. Upon capsule dissolution, the film expands to achieve gastric retention of up to 12 h [9].

In addition, Lyndra Therapeutics [50] in collaboration with

Massachusetts Institute of Technology (MIT) and others, applied a similar strategy to deliver a wide range of pharmaceutical compounds that nowadays require multiple dosing such as HIV antiretroviral therapy [51], contraceptives [52] or therapies to prevent malaria [53]. Also, the same collaborators developed a gastric retentive device for prolonged gram-level dosing of tuberculosis treatment. However, this particular device needed to be deployed in the gastric cavity through the nasogastric route [99]. One of the investigated devices consists of an ultra-long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug for days to weeks and potentially longer with no evidence of GI obstruction or mucosal injury (Fig. 3A i-iii) [53]. The device was made of a thermoset elastomer combined with enteric linkers made by Eudragit® L100–55 and Plastoid B that ensure dissolution upon premature passage to the small intestine, thereby providing safe passage through the GI tract. A long-acting formulation was prepared by hot melting the drug ivermectin with excipient polymer for controlled release. Ivermectin is a drug that targets malaria-transmitting mosquitoes, and the formulation was incorporated into the developed star-shaped dosage form. The device demonstrated the delivery of a sustained therapeutic dose of ivermectin for up to 14 days in a swine model [53]. Whereas the previous device delivered a single API, the same research group also developed a similar star-shaped drug delivery system that can achieve week-long systemic levels of several drugs for HIV antiretroviral therapy (Fig. 3B) [51]. The core of the device was made of Elastollan® 1185 or an alternative thermoset elastomer while the arms were made of either PLA or Elastollan® R6000. To enable disassembly, in case of premature passage into the intestine, and following a similar strategy as the previous device, the peripheral arms were connected to the core by a pH sensitive linker. Different drug polymer matrices of dolutegravir, rilpivirine and cabotegravir were synthesized by melt mixing and incorporated into the device. *In vivo* studies in pigs revealed stable systemic levels of the loaded drugs over the course of weeks [51].

Even though previously described devices showed no evidence of GI obstruction or mucosal injury, Liu et al. developed a prolonged gastric-retentive hydrogel that possesses a set of advantages due to hydrogel biocompatibility, high water content and tissue-like softness [55]. The device consist of a PVA hydrogel loaded with superabsorbent particles (sodium polyacrylate homopolymers) that can be ingested as a standard-sized pill. Upon oral administration, the hydrogel swells into a large soft sphere (diameter up to 6 cm), that maintains robustness under repeated mechanical loads in the stomach (Fig. 3C). The device can reside for up to one month with no signs of toxicity and can shrink on demand, to exit the body, in response to a saline solution. *In vitro* data suggested that the hydrogel device could be applied for ultra-long sustained drug delivery. Furthermore, *in vivo* studies of the gastric retention of the hydrogel device in a pig model supported the performance of the device for long-term gastric retention and physiological monitoring [55].

Prolonged gastric residence macro-devices offer the possibility of sustained delivery of multiple therapeutics for weeks and potentially longer in an oral dosage form with no evidence of GI obstruction or mucosal damage. A key aspect of such devices is their ability to deliver the drug consistently, thereby reducing the dosing frequency and minimizing drug plasma concentration peaks compared to daily dosing. The current work suggests that these types of devices may be of benefit for small molecules in BCS class I/II such as Levonorgestrel and

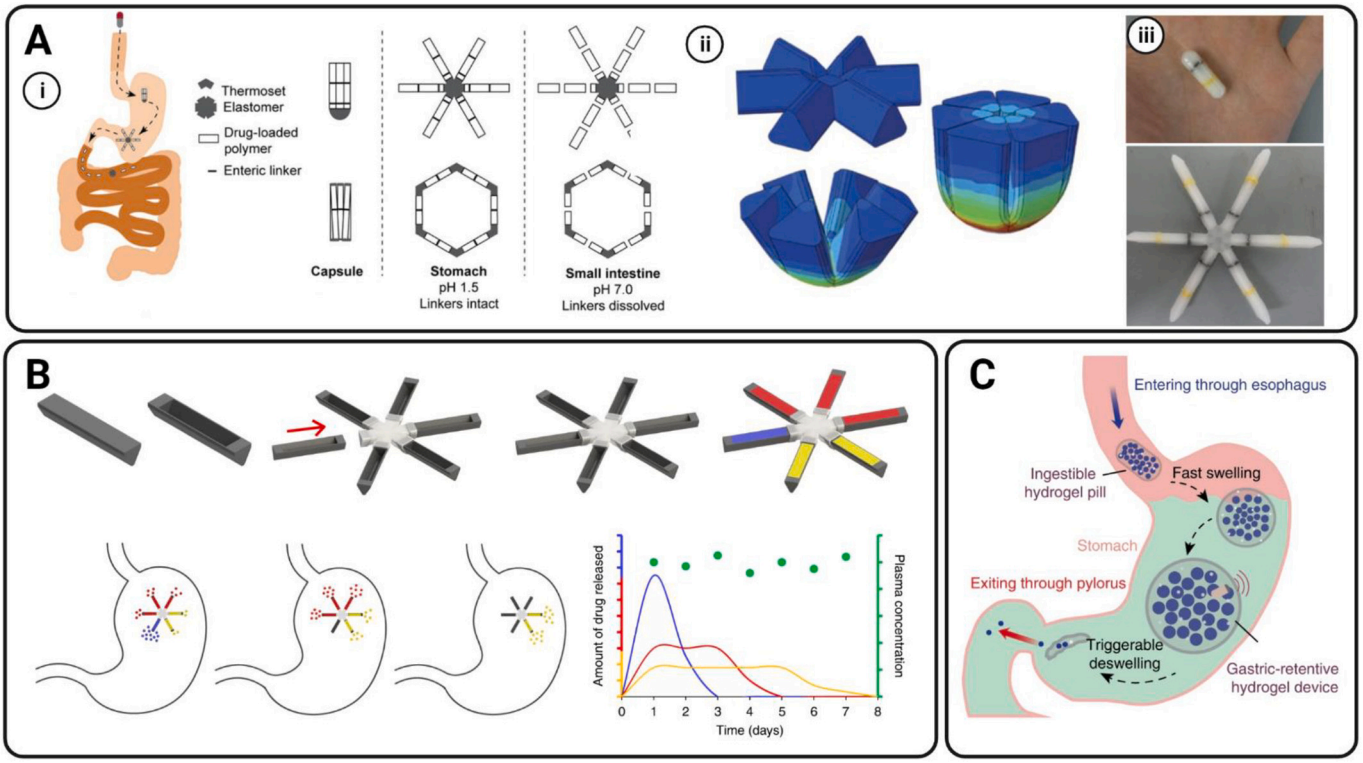

Fig. 3. Examples of prolonged gastric-residence devices for oral drug delivery. **A)** Design of a modular star-shaped device developed to target malaria. (i) Schematic of deployment of gastric residence drug delivery dosage form *via* ingestible capsule and method of dissolution in presence of intestinal pH. Schematic enteric linkers are represented by black lines. (ii) Stress distribution of the flexible element when it is folded into the capsule. (iii) Representative dosage form after assemble and loading into a 00 gelatin capsule. Linkers are yellow and black. Reprinted from [53] Copyright (2016), with permission from AAAS. **B)** Design and concept of a long-acting antiretrovirals. The manufacturing scheme of the dosage form and the expected performance *in vivo* as an ideal system, not experimentally obtained data. Reprinted from [51] Copyright (2018), with permission from Springer Nature. **C)** Concept of a long-term gastric retention hydrogel device. Working principle of the gastric-retentive hydrogel device, which enters through the esophagus into the stomach as an ingestible pill, resided in the stomach in its swollen state for a prolonged period of time, and exits through the pylorus as a shrunken capsule and small particles. Reprinted from [55] Copyright (2019), with permission from Springer Nature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Risperidone. Both compounds could benefit from reducing dose frequency; either for contraceptive care in the case of Levonorgestrel, or for schizoaffective patients in the case of Risperidone. Additionally, there is a collaboration between Gates Foundation and Lyndra Therapeutics to develop a once-monthly oral contraceptive, which aims to address the lack of global family planning options and provide a non-invasive treatment option. This would reduce the necessity for patients to have regular contact with healthcare providers. Similarly, the same collaboration aims to provide expansion of the clinical study pipeline and scale-up manufacturing for a long-acting malaria therapy, which can be distributed around the world. However, the developed devices may face challenges regarding drug degradation and loading capacity, as well as food effect. During manufacturing and oral delivery, drugs can be exposed to elevated temperatures, acidic pH and high humidity, thereby making it challenging to deliver drugs that are unstable under such conditions. Additionally, most the dosage forms do not present a high drug-loading capacity (10–30% by weight of the drug). As a result, only high permeable non-acid labile drugs that have a relatively low daily dose (50 mg or lower) can be effectively administered. Alternately, higher doses in the gram range, can be achieved in the swelling hydrogel-based system, however, the types of API would be severely limited based on solubility/permeability of the drug. Furthermore, most of the devices are tested in fasted conditions, thereby being unknown how the diet would impact on the gastric residence of the dosage form. Due to the long-term residence of the devices in the gastric cavity, this is an inevitable drawback that could lead to variations in the sustained drug delivery.

5. Mucoadhesive GI patch systems

The use of patch systems has been extensively explored for the transdermal delivery of therapeutics such as contraceptives and nicotine [100–102], as well as the delivery of drugs through the oral mucosa [103–105]. Patch systems are usually composed of several layers assisting as drug depots that create steep concentration gradients, which drive the transport of loaded drugs across the skin or mucosa into the bloodstream at a regulated rate. Over the past decades, patches have been applied for the development of oral dosage forms targeting the intestinal mucosa with drugs that possess poor oral bioavailability and accommodate more effective oral drug delivery (Fig. 4A) [106,107]. Such devices offer drug protection, mucoadhesion, unidirectional and controlled release in the desired GI location. In addition, these devices can be loaded with several therapeutic drugs, protease inhibitors and PEs to further improve oral bioavailability. GI patches mostly comprise 2–4 layers of thin and flexible membranes [107]. Two-layered patches include a mucoadhesive drug reservoir and a backing layer. The first layer is commonly made of chitosan and its derivatives, pectin, polyacrylic acids, alginates, PVA and cellulose derivatives. The backing layer is made of water impermeable polymers such as ethyl cellulose and ensures unidirectional release of the API at the mucosal surface. Three-layered patches can also incorporate a pH-sensitive layer and four-layered patches generally have separated mucoadhesive and drug layers [107]. Patches are commonly fabricated using solvent evaporation techniques, in which each layer is produced separately and then bonded; and direct milling, where all compounds are homogeneously

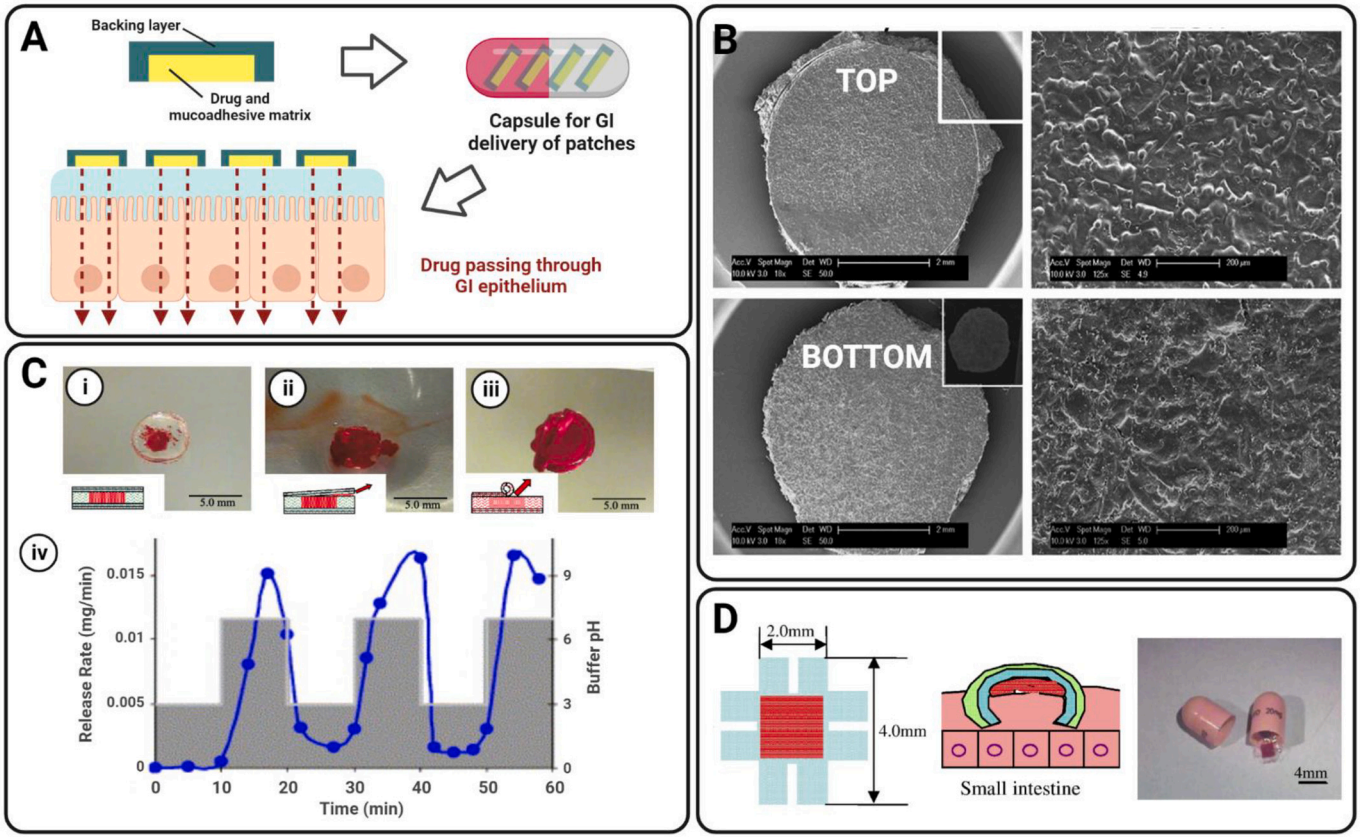

Fig. 4. Examples of mucoadhesive GI patches for oral drug delivery. **A)** Schematic representation of mechanism of adhesion, drug release and absorption across GI epithelium from mucoadhesive devices. Redrawn from [113] Copyright (2016), with permission from Springer Nature. *Created with BioRender.com.* **B)** SEM images of top (mucoadhesive drug loaded layer) and bottom (backing layer) of a GI patch. Reprinted from [57] Copyright (2013), with permission from Elsevier. **C)** Multi-layered device with self-folding hydrogel-based gate for controlled drug release. (i) Dry assembled device and the respective acid orange 8 release at pH 7.3 at (ii) 40 min. and (iii) 80 min. (iv) Graphical representation of the oscillatory acid orange 8 release behavior from the device. Reprinted from [60] Copyright (2004), with permission from Elsevier. **D)** Schematic of the self-folding hydrogel device from top view (left), folding on the small intestine to enhance mucoadhesion after hydrogel curling (middle) and capsule containing devices (right). Reprinted from [61] Copyright (2006), with permission from Elsevier.

mixed and compressed to the desired thickness and then the backing layer is coated [108,109]. Readers interested in knowing more about the formulation methods and materials used to prepare intestinal patches with different structures, as well as the methods used for their characterization are suggested to look in the references [110, 111].

Two-layered [56,57,59,112–116] and three-layered [58,117–121] GI patches with mucoadhesive properties have been extensively described in literature with a special focus on enhancing the oral bioavailability of macromolecules [56–59,112–115,117,118]. One example of two-layered patches was developed by Mitragotri and co-workers for the GI delivery of calcitonin [57], which is a peptide commonly used in the treatment of osteoporosis [122] (Fig. 4B). Despite low plasma concentrations of calcitonin from the patches were obtained compared to subcutaneous injections, a higher relative bioavailability was found compared to intrajejunal injection of the drug solution [57].

To further improve intestinal drug absorption of macromolecules, some patches were also loaded with PEs [58,113–115,117,118,123]. Bernkop-Schnürch and *co*-workers developed an intestinal mucoadhesive patch for oral delivery of insulin containing thiolated polycarbophils [58], which are known to improve mucoadhesion and drug permeation by opening intercellular tight junctions [124]. In their studies, the relative bioavailability of insulin from orally administered patches was 2.2% compared to subcutaneous injections [58]. Another strategy to increase absorption of drug compounds is the incorporation of nano- and micro-structures such as nanoparticles [59,116] and microspheres [121] into millimeter-size patches. Toorisaka et al. developed patches containing surfactant-coated nanoparticles and obtained a higher permeation of insulin than patches containing lyophilized insulin. This permeation enhancement could be attributed to the high affinity of the lipophilic surfactant-coated nanoparticles to the cell membranes [59].

He et al. assembled more complex drug delivery systems that provides a controlled release by using a bi-layered self-folding pH-sensitive hydrogel gate (Fig. 4C) [60]. Two model compounds, acid orange 8 and bovine serum albumin were used in terms of overall device functionality. The drug release from the device was controlled by the pH-dependent swelling properties of the bi-layered gate. At pH 3, no release was observed within 2 h as the gate remained closed and stable due to the similar swelling response of both hydrogel layers (Fig. 4C i). When the pH was increased to 7.3, the increased swelling ratio caused the gate to fold outward, resulting in release of the drug (Fig. 4C ii). After the gate opening (40 min), 90% of the drug was released. Furthermore, when the surrounding media returned to pH 3, the bi-layered gate reverted back to the closed state, resulting in a decreased release rate (Fig. 4C iii). This suggests that pulsatile release can be achieved by altering the pH (Fig. 4C iv) [60]. In a separate study, the same group developed a similar device comprising a mucoadhesive layer made of PVA and Carbopol and a bi-layered hydrogel system that curls and enhances mucoadhesion in the GI tract (Fig. 4D) [61]. Studies in porcine small intestine demonstrated that the device was able to adhere to the mucus and fold whereas *in vitro* drug transport studies across the mucosal epithelium at pH 6.5 showed that the self-folded device improved drug transport as a result of localized high drug concentration [61].

More complex devices such as robotic mucoadhesive patches for local delivery of drugs in the GI tract have also been developed. Whereas in the previously described studies several devices were commonly loaded into a capsule, Miyashita et al. utilized a self-unfolding origami stomach patch for treatment of stomach wounds capable of expanding up to 5 times its initial size [62]. The body of the hybrid device was composed of five biocompatible and biodegradable layers: polyolefin and pig intestinal tissue as structural layers, water soluble drug-loaded layer, heat sensitive layer for self-unfolding actuation and a silicone adhesive layer. *In vitro* studies using artificial stomachs were made to prove the functionality of the device for wound patching and it was shown that the device expanded successfully and sealed an artificial ulcer in approximately five minutes. This demonstration conceptually proved that a biodegradable artificial robot can accomplish medical purposes [62].

GI patches have been developed to improve the bioavailability of biologic macromolecules following oral dosing of capsules. It has been observed that the developed systems can orally deliver peptides such as calcitonin and insulin, presenting a bioavailability of 1.5% and 2.2%, respectively [57,58]. These results suggest that GI patches, which are produced *via* simple fabrication methods that mostly include solvent evaporation and compression, could be a promising platform for the oral delivery of poor permeable drug compounds. Besides the ease to manufacture, considerations regarding the solvents used as well as temperatures applied should be taken into account when including peptides or proteins, as this can lead to degradation or inactivation of the compounds. Despite the stated non-toxicity of the devices and their materials, further safety evaluation, together with stability and mass-production assessment, need to be considered for future clinical applicability. The devices allow localization of the peptide and excipients near the intestinal epithelium *via* mucoadhesion, thereby preventing loss of the drug in the luminal fluids and promoting its absorption by offering increased concentration gradient for its transport. However, the rapid turnover of the epithelial cells in the GI tract suggest that more efforts may be needed to increase the retention time of the developed devices in animal models [125]. It should be acknowledged that the some of the GI patch research discussed was undertaken over 15 years ago. Besides further investigations have been done in the development of buccal patches for the delivery of biologics [24,25], there is limited research in the use of these patches *via* capsule ingestion nowadays. It is possible that limitations in increasing the retention time, successful placement of the patches in the small intestine, or dosage amount may have limited their realization into marketed products. Similarly, more recent trends in oral devices research, as shown in Table 1, show that a higher bioavailability have been achieved in devices that allow more intimate contact with the intestinal epithelium such as self-unfolding systems or even GI injectors.

6. Mucus penetrating devices

6.1. Magnetic systems

The use of magnetic fields has been widely exploited in healthcare to diagnose diseases. An example of one of the methods commonly used is nuclear magnetic resonance. When applied to oral drug delivery, one of the advantages of magnetic devices over *e.g.* traditional pills and mucoadhesive devices is the possibility to deterministically control the site of delivery while simultaneously promoting epithelial proximity. Both things would be beneficial for the oral administration of low permeability drugs, which do not readily cross the biological membranes efficiently and thereby exhibit poor bioavailability [126].

As a proof of concept, Nagai and co-workers reported in 1990 the use of magnetic granules for drug delivery to the esophageal area [127]. A few years later, the same group developed magnetically responsive sustained release tablets (6 mm diameter) for prolonged gastric retention [63]. In their study, the magnetic tablets were developed to study the bioavailability of paracetamol as a model drug by magnetically controlling the gastric emptying time. For that purpose, a magnetic field of 0.2 T approximately was applied in the stomach area of beagle dogs and it was observed that the gastric emptying of the magnetic tablets was postponed by 3 h and the drug bioavailability increased 2-fold compared to administration without magnet application [63]. In a small clinical study performed in healthy subjects, Georgarakis and co-workers obtained similar results when using a multilayered tablet (10 mm × 6.8 mm) containing an internal magnet which enabled extracorporeal magnetic manipulation [64]. A significant increase (average from 1.25 to 12 h) in the gastric retention time was observed in 4 out of 5 subjects. In addition, the bioavailability of a low permeability drug,

acyclovir, increased 1.8 times in the presence of a magnetic field compared to a commercialized formulation [64]. Whereas in these cases the magnetic force was primarily aimed at improving the bioavailability by increasing retention time and not by disrupting the GI barrier such as paracellular tight junctions, promising results have been shown in terms of the use of magnetic devices to prolong the residence time in the GI tract [12].

During the last decade, Ménager and co-workers developed mucoadhesive millimeter sized magnetic chitosan-alginate core-shell beads for increasing the bioavailability of low permeability drugs [65,66]. In their work, the effect of the magnetic retention and the bioavailability of magnetic beads in the GI tract in the presence of an external magnetic field was evaluated. The group observed that 1/3 of the drug was released in direct contact with its absorption site and that the permeation of drug through the intestinal membrane exhibited a threefold increase with the novel delivery system [66]. Furthermore, after the oral administration of a gelatin capsule containing the magnetic beads to rats, a 2.5-fold increase in drug bioavailability was observed compared to a scenario where no external magnetic field was applied and the drug was delivered in an aqueous solution [65]. This suggests that the retention of the magnetic carriers in the presence of an external magnet and their accumulation at a specific localization of the intestine leads to a significant increase in the bioavailability of the drug. However, it was observed that the magnetic field was enhanced locally in vicinity of the external magnet, but the carriers were not retained at a fixed position due to gastric emptying. To achieve effective retention, forces associated with the applied magnetic field should exceed the forces associated with gastric emptying [12,65].

All in all, magnetic formulations for oral drug delivery appear to be safe to use as they are excreted from the body after oral administration and there is no evidence of material accumulation in organs [65]. However, one of the major problems is finding suitable magnetic materials that will be approved for consumption. In addition, inter-individual variations and the GI motility as well as the effects associated with food intake should be taken into consideration for further development of magnetic systems. Furthermore, there is still a lack of mechanistic understanding in terms of evaluating the impact of magnetic forces on drug permeation pathways, such as the disruption of cellular junctions. As the force exerted by a magnet rapidly decreases with the distance, it suggests that the external magnet must be situated in close proximity of the magnetic devices. Additionally the convenience and consistency of applying an external magnetic force at the site of action could limit these delivery concepts to clinical applications. This opens the question to if wearable external magnets could be developed for oral drug delivery in humans. It remains to be seen the first commercialized product combining magnetic devices and a suitable external magnet source. The combination of magnetic fields with other strategies such as PEs, mucoadhesive materials or microneedle patches

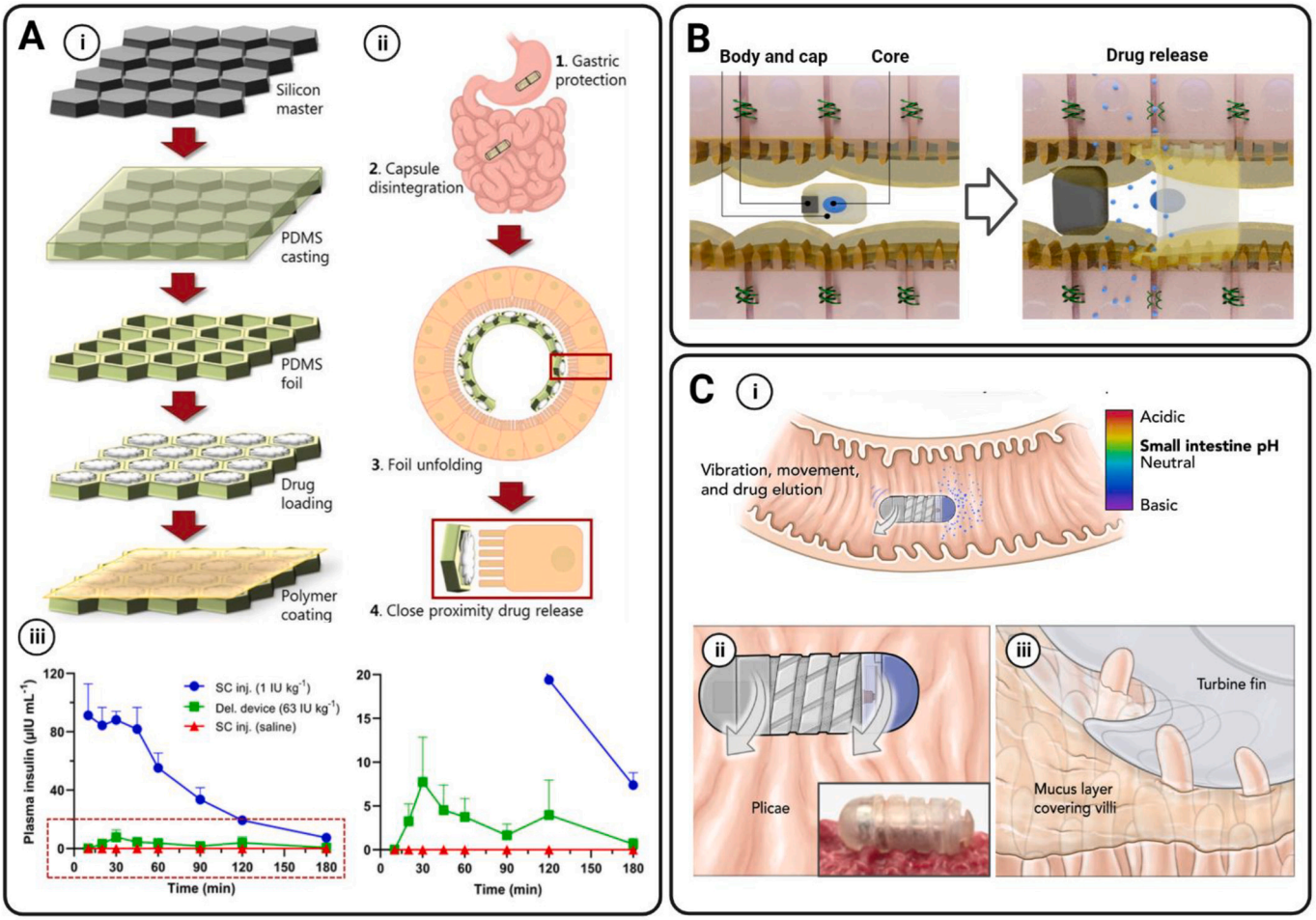

Fig. 5. Examples of ingestible SPED-type and mucus-clearing devices for oral drug delivery. **A)** Self-unfolding foil-based device. (i) Schematic of the preparation steps and (ii) the principle of the delivery concept. (iii) Plasma insulin concentrations after duodenal insertion of the oral delivery device in rats. Reprinted from [67] Copyright (2021), with permission from Elsevier. **B)** Illustrations of super porous hydrogel drug delivery formulations; drug is released after the delivery system attaches to intestinal wall. Reprinted from [12] Copyright (2021) and redrawn from [128] Copyright (2001), with permission from Elsevier. **C)** RoboCap mechanism of action. (i) Activated RoboCap in the small intestine. (ii) Side view of the device where the helical surface grooves enable rotation in the GI tract. (iii) Fin shaped cuts enable the pill to glide and scrape mucus form intestinal villi. Reprinted from [100] Copyright (2022), with permission from AAAS.

could also be developed to further increase the bioavailability of drugs.

6.2. Self-configurable-proximity enabling devices (SPED) and mucus-clearing devices

Another strategy to potentially increase retention time at the target site and achieve site specific release in close proximity of the epithelium is to employ elastic devices with self-unfolding properties [67] or swellable entities that enable an intimate contact to the epithelium *via e.g.* hydrogel expansion [69–74,128].

Jørgensen et al. produced a self-unfolding foil-based (SUF) device with the potential of increasing absorption of peptides subject to oral administration [67]. The device ensures unidirectional release of the drug and close contact with the epithelium as a result of a foil which self-unfolds in the small intestine upon release from an enteric coated capsule (Fig. 5A i-ii). The device was fabricated in a biocompatible elastomeric material, polydimethylsiloxane (PDMS), by casting against a deep-etched silicon master and loaded with a powder mixture of insulin, sodium dodecyl sulfate (SDS) as PE, and a trypsin inhibitor based on preliminary studies in the same group [129]. Then a pH-sensitive polymer was applied to the foil to ensure protection at gastric pH. When performing pharmacokinetic studies in rats, it has been reported that capsules may experience difficulty escaping from the stomach [130,131]. Therefore, SUF was loaded into an enteric-coated gelatin capsule (size 9) together with a magnet to guide gastric emptying by an external magnet. Quantifiable insulin plasma concentrations (bioavailability of approximately 0.12% compared to subcutaneous injections) were reported when using this novel and relatively simple foil-based device (Fig. 5A iii) [67]. Later, Ghavami et al. further explored and enhanced crucial features of the developed foil and obtained a remarkable 15-fold increase insulin bioavailability compared to the initial proof-of-concept study after rectal administration to rats [68]. In their work, it was also demonstrated that SUF can be used for oral delivery of macromolecules in large animals. The absorption of nisin increased four times compared to the control without SUF after surgical placement of the capsule in the small intestine of anesthetized pigs [68]. The results suggest that drug compounds with low oral bioavailability, due to low permeation and/or stability, could benefit from confinement in a in and subsequent release from a foil [67,68].

In a similar manner, Juginger and co-workers developed superporous hydrogels (SPHs) that incorporate drug loaded cores to improve the oral bioavailability of biologics [69–74,128]. The mechanism of this system is based on tailored hydrogel expansion in the small intestine, which applies a mechanical pressure on the epithelium, thereby increasing the paracellular transport of the API and its respective bioavailability (Fig. 5B). In their work, *in vitro* transport studies in Caco-2 monolayers revealed that SPHs were able to increase the transport of octreotide. This was attributed to the ability of these hydrogels to open the tight junctions *via* mechanical pressure, which was confirmed by performing a transepithelial electrical resistance (TEER) test, which showed a 30% decrease in the TEER values compared to the initial values [69]. In a similar study, the accumulative transport of a model drug was also increased by the SPHs compared to the control group and it was found that the transport enhancement was inversely proportional to the molecular weight of the marker compound [70]. The performance of the hydrogel systems was also evaluated *ex vivo* in porcine intestinal epithelium and it was observed that the transport of different model drugs was enhanced 2- to 3 fold when utilizing the developed systems. Additionally, the hydrogel systems were able to attach mechanically to the intestinal wall due to their swelling properties [71]. The group also performed *in vivo* studies in pigs to evaluate the pharmacokinetic properties of insulin [72] and octreotide [73] after administration of the novel delivery system. For that purpose, formulations were developed with a drug loaded core within the hydrogel matrix or attached to its surface. After intra-duodenal administration of the different formulations placed in gelatin capsules (size 000), it was observed that the relative bioavailability of insulin from both formulations was 1–2% compared to the subcutaneous injection [72]. For the *in vivo* evaluation of octreotide, the formulations were loaded into enteric-coated capsules (size 000) and administered perorally to pigs. An impressive octreotide oral bioavailability of 16% and 9–12% compared to intravenous administration was reported when administrating the hydrogels systems with and without trimethylated chitosan (an additional PE), respectively. However, this concept does not appear to have been advanced in the last two decades, maybe illustrating the difficulties in reducing promising technology concepts to highly-loaded oral solid dosage forms that can be synthesized and mass-produced [132].

In correlation with the *ex vivo* studies previously described, it was observed that the developed SPHs were able to induce a mechanical fixation in large animals and increase the retention time of the dosage form at the absorption site [73]. To further study the fixation properties and transit times, the group monitored the location of radiolabeled systems in five healthy volunteers while the subjects were sitting in front of a large field of view gamma camera [74]. After oral administration of the formulation to fasted volunteers, the results showed that the enteric-coated gelatin capsule remained in the stomach for 75–150 min and that the hydrogel systems thereafter were fixated in the upper part of the small intestine for at least 45–60 min [74]. These results suggest that the developed SPHs are promising systems for drug targeting and enhancing the residence time of the drug delivery system in the GI tract.

Another attempt to overcome the mucus barrier and facilitate delivery in close proximity to the epithelium without incorporating PEs was developed by Traverso and co-workers. In their work, they reported the RoboCap, an ingestible robotic capsule that rotates and locally clears the mucus layer, enhances luminal mixing and topically deposits a drug payload in the small intestine to enhance drug absorption of insulin and vancomycin (Fig. 5C i-iii) [75]. The rotating movement was facilitated by an internal motor and the outer surface comprised topographical features that interacted with the small intestinal plicae circulares, villi, and mucus. The drug is loaded in a specific compartment sealed with a pH sensitive polymer to ensure release in the small intestine. Despite the oral bioavailability was not reported, studies in fasted anesthetized pigs revealed an enhancement in absorption, compared to standard oral delivery. After actuation, the sealed capsule containing the key device components such as the motor and its power source (battery) can safely pass through the GI tract [75].

Overall, ingestible devices with self-unfolding/swellable properties or mucus-clearing entities that enable an intimate contact to the epithelium are designed to increase the bioavailability of biologics *via* mechanical interaction and targeted release in close proximity to the epithelium. The obtained bioavailability from the developed systems (2–18% compared to subcutaneous injections) suggest that this could be a promising platform for the delivery of macromolecules without the application of highly invasive methods (*i.e.* tissue perforation). However, when evaluating the clinical translability of these systems, the cost production and the safety considerations need to be contemplated. The product simplicity of the hydrogel and foil systems appear to be compatible with the industrial manufacturing. However, high amounts of peptides are used, which makes challenging to maintain the production at a low-cost level. In addition, the presence of multiple materials and processes involved in the fabrication of the mucus-clearing devices such as the RoboCap appear to be challenging for the commercial manufacturing. When observing the safety considerations, the systems seem to offer intimate contact with the epithelium without generating significant damage to the GI tissue. In the reported studies, no irreversible tissue disruption (*i.e.* opening of the tight junctions) or morphological damage were observed when using such devices in Caco-2 cells and *ex vivo* models [69–71]. In addition, the histology studies performed after actuation of the systems in animal models showed that mucosa, submucosa, muscularis, and serosa layers stayed intact after 4 h of interaction. However, further examination with Coherent anti-Stokes Raman scattering (CARS) revealed slight epithelial disarrangement of

the tissue, which could be attributed to the high local concentration of PEs that are present in the formulation [68]. Despite no discomfort was observed in all five human subjects from the pilot clinical study, there are still concerns regarding if whether such formulations would cause obstruction or if can safely pass through in the GI tract [74]. In addition, the risks associated with repetitive administration of such devices needs to be further investigated. Animal and clinical studies thus far were performed in fasted state, thereby being unknown how the presence of food will affect the bioavailability of the drug. Despite these limitations, the mechanism of such devices appear to be appropriate for enhancing intestinal absorption of peptide and protein drugs, but to the best of our knowledge there are still no commercial products on the market nor in the pipeline.

7. Auto-injectors and needle-based devices

Whereas mucoadhesion and mechanical fixation can bring the device closer to the GI epithelium, a key-challenge remains in getting the drug across the mucus layer and the epithelial lining barrier. This problem has been circumvented by the incorporation of needles or auto-injectors.

Microneedles and auto-injectors have been extensively used for administration of therapeutics through several routes such as subcutaneous or transdermal delivery [133–136]. However, during the past decade this strategy has gained renewed attention for oral delivery of

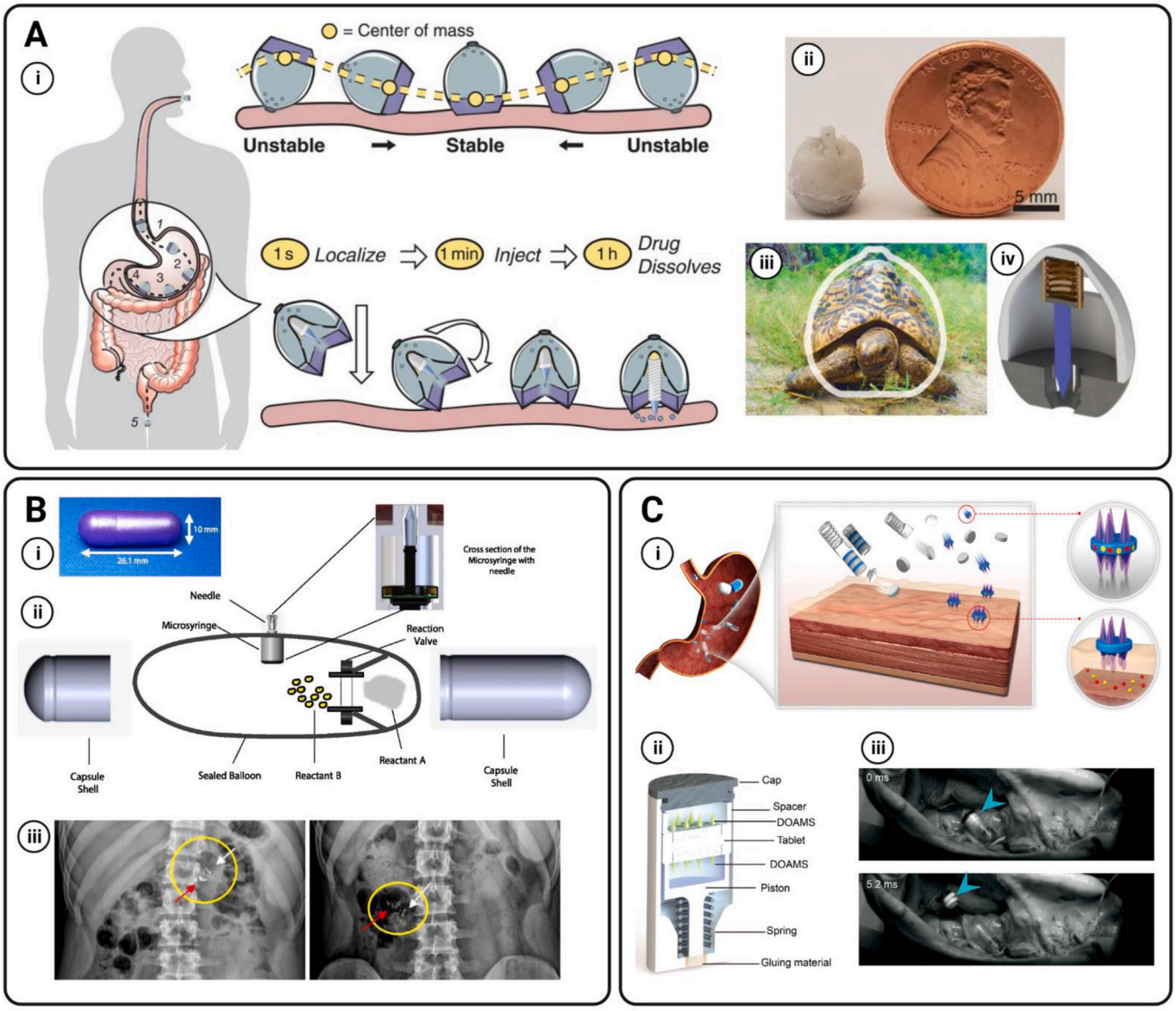

Fig. 6. Examples of microneedle-based devices and auto-injectors for oral drug delivery in the GI tract. **A)** Mechanical API localization and injection for SOMA. (i) The SOMA localizes to the stomach and orients its injection mechanism toward the tissue wall before injecting the drug payload through the mucosa. The drug dissolves and the rest of the device passes out the body. (ii) Image of a fabricated SOMA and (iii) a comparison with the shape of the leopard tortoise. (iv) The SOMA uses a compressed spring to provide a force for drug-loaded millipost insertion. Reprinted from [77] Copyright (2019), with permission from AAAS. **B)** Robotic pill based on self-inflating balloon as drug delivery system. (i) Fully assembled enteric coated robotic pill. (ii) Schematic drawing showing various parts and components of the robotic pill. (iii) Representing X-ray image of an intact (left) and deployed (right) robotic pill residing in the stomach. Reprinted from [82] Copyright (2021), with permission from Springer Nature. **C)** Scheme of DOAMS design and actuation. (i) After ingestion, the device would respond to the stomach low pH and deploy the engineered tablets to the tissue, which securely anchor itself in the mucus by the self-triggered extension. Then, the drug could be gradually released specifically to the tissue surface for a relatively long time. (ii) Design of the device. (iii) Image from a high speed camera before (top) and after actuation (bottom) showing the successful trigger of the device during *ex vivo* tests in swine stomach tissue. Reprinted from [85] Copyright (2022), with permission from AAAS.

biologics such as peptides or proteins.

Traverso and co-workers developed smart capsules designed to systemically delivering formulations of macromolecules with high bioavailability *via* injections in the small intestine [76,137] and stomach [77,78]. One of the designs, termed luminal unfolding microneedle injection (LUMI) device, allows for delivery of drugs by injecting dissolvable microneedles into the intestinal tissue using an elastic device with unfolding arms [76]. Upon exposure to intestinal pH, the polymer that immobilizes the spring dissolves and ejects the LUMI from the capsule. Thereby, polyvinyl chloride (PVP) microneedles (height of 1 mm and a base diameter of 0.4 mm) loaded with insulin and located at the end of each arm are forced into the tissue. Each LUMI held up to 0.3 mg of drug in a total microneedle footprint area of 0.5 cm^2. *In vivo* pharmacokinetic studies in pigs revealed that LUMI provided a systemic uptake >10% compared to a subcutaneous injection. Upon successful delivery, the arms, made of polyethylene and Soluplus®, slowly degraded and the non-degradable elastomeric core made with mediprene passes through the GI tract along with the rest of the capsule, now divided in numerous parts, thereby reducing the risk of mechanical obstruction [76]. In another design, inspired by the leopard tortoise's ability to passively reorient, a different mechanism was applied. Here, an ingestible self-orienting millimeter-scale applicator (SOMA) autonomously positioned itself in the stomach to engage with gastric tissue (Fig. 6A i-iv) [77]. The device then deployed a poly(ethylene) oxide millipost (7 mm length) containing 0.3 mg of insulin through the gastric mucosa. *In vivo* studies in swine demonstrated that SOMA delivers insulin plasma levels comparable to those achieved with subcutaneous millipost administration. Compared to LUMI, when delivering into the stomach tissue rather than the small intestine, the dose delivery time is likely to be more predictable as it does not rely on gastric emptying and its recognized variability [138]. Despite that both LUMI and SOMA represent platforms with the potential to deliver a broad range of biologic drugs, they do have limitations. They have limited dosing amounts (300–700 μg per capsule) and require the presence of GI fluid, filled with degradative enzymes, to interact with the drug formulation for a short period of time before injection. These restrictions prevent the devices from delivering drugs with large dosage requirements, as well as drugs that require fast action. A new version of the SOMA device, that uses a redesigned actuation and delivery system, was developed to address these challenges [78]. The smart capsule can achieve milligram doses of drugs within a liquid formulation ranging from small molecules to monoclonal antibodies with the rapid pharmacokinetics of an injection, reaching an absolute bioavailability of 80% [78].

A similar technology for oral delivery of biologics in the stomach using auto-injectors has been developed by Biograil™, which is a preclinical stage pharmaceutical company [79]. In their conceptual device called BIONDD™, an injection molded pharmaceutical product designed as an oral delivery system that can be loaded in a standard size 00 capsule. Following ingestion, the delivery system is activated in the stomach and releases a spring loaded grabbing mechanism that positions into the stomach wall. The embedded substance is delivered into the tissue and distributed into the blood stream. Then, the spike re-positions in a covered state and the capsule is safely excreted [79].

Another device incorporating for auto-injectors has been developed by Rani Therapeutics. It is based on a self-inflating balloon that exerts mechanical forces to inject a microneedle in the GI tract (Fig. 6B i-iii) [80–82]. As the previously described auto-injectors, this device also aims at delivering biologic drugs that are currently injected subcutaneously. The RaniPill® capsule has been studied with APIs used for the treatment of chronic diseases such as osteoporosis and rheumatoid arthritis. The device is contained in a standard enteric-coated capsule which is swallowed by the patient. Once it reaches the intestine, an outer shell dissolves and a self-inflating balloon is exposed to the intestinal fluids, which allows pre-loaded reactants to mix, thereby creating carbon dioxide. This inflates a balloon and creates the pressure needed to inject a dissolvable drug loaded microneedle into the intestinal wall. Once the needle is delivered, the balloon deflates and is safely excreted [80]. Preclinical studies in anesthetized swine demonstrated that the bioavailability of insulin was comparable to subcutaneous injections after direct placement of the auto-injector device in an isolated loop of the jejunal area [81]. Furthermore, clinical studies have been performed in healthy subjects [82]. These studies demonstrated that the device presented higher rates of delivery of octreotide when the diameter of the balloon was higher: 25%, 50% and 80% success rate for the groups with balloon diameters of 21 mm, 23 mm and 25 mm, respectively. The average bioavailability was found to be 65 ± 9% based on the successful deliveries in the groups where complete pharmacokinetic curves could be obtained [82]. These studies were performed in a fasted stage, thereby not considering the food effect. A separate clinical study revealed that the deployment is not affected by food, however actual drug delivery could not be determined [82].

Another interesting technology that also aims to substitute subcutaneous injections is needle-free liquid jet injections. This platform has been extensively used for transdermal delivery of macromolecules such as insulin and vaccines; and employs a high-speed jet to puncture the tissue and deliver drugs without using a needle [139]. Biora Therapeutics™ took advantage of this concept and developed ingestible smart capsules designed for systemic drug delivery through the GI tract [83]. The developed technology has the potential to increase systemic uptake and bioavailability of a broad range of large molecules including monoclonal antibodies, peptides and nucleic acids. Once swallowed, the capsule with a loading capacity of 400 μL of liquid formulation, transits through the digestive system and triggers in the small intestine, where liquid jets deliver drug directly into the intestinal mucosa. Preclinical studies in swine, where the capsule was placed by intraduodenal endoscopy, revealed an oral bioavailability of 55% of a variant of adalimumab, which is a monoclonal antibody for the treatment of several chronic inflammatory diseases [84].

Whereas the previously described auto-injectors only use physical modes of drug delivery, Chen et al. developed a smart capsule to deliver peptides in the stomach by combining physical (microneedle) and nonphysical (enhancer) modes of drug delivery [85]. The design is inspired by a thorny-headed intestinal worm and consists of a dynamic omnidirectional adhesive microneedle system (DOAM) capable of prolonged gastric mucosa fixation (Fig. 6C i-iii). The smart capsule ejects in the stomach the microneedle-containing tablets loaded with semaglutide (10 mg) and SNAC as PE, which is a formulation commercialized by Novo Nordisk as Rybelsus® as previously mentioned [14]. In this way, the microneedles ensure that DOAM can anchor itself in the gastric mucus and the loaded compounds could be gradually released to the tissue for a relatively long time. *In vivo* studies in swine revealed that DOAM tablets were resistant to physical displacement in the gastric cavity and an enhanced drug absorption compared to needle-free cellulose tablets. However, no comparison was made between DOAM with and without SNAC, thereby being unknown the effect of the PE in the developed device [85].

It is noteworthy to highlight that this strategy is slightly different from other PE-free needle-based devices that also target the gastric tissue to systemically deliver biologics such as SOMA [77,78]. Whereas the millipost included in SOMA is made of poly(ethylene) oxide (PEO 200 k), DOAM needles present a soft outer layer made of Carbopol® and a rigid inner core made of polycaprolactone (PCL). In addition, due to the different heights of the needles, being 1.3 mm and 7 mm for DOAM and SOMA, respectively, differences can be observed when evaluating the stomach tissue after device actuation. Channels with a length of <1 mm were observed in the tissue after DOAM actuation, whereas for SOMA the length was >5 mm [77,85]. This suggest that DOAM present a less invasive physical actuation mechanism to the GI tissue compared to other PE-free devices that target the stomach for systemic uptake of biologics, which could be a possible explanation about the need of incorporating a non-physical mode of delivery such as SNAC in the dosage form.

Similarly, microneedles have been used for insulin delivery by utilizing external magnetic fields [86,140]. Zhang et al. developed a microneedle patch containing neodymium (NdFeB) particles to create a device which can be actuated and manipulated by an external magnet [86]. In their study, gelatin methacryloyl (GelMA) microneedles containing insulin were casted and attached to a magnetic substrate *via* dissolvable connectors. After administration, and benefiting from their polarized magnetic substrate, the tips of the microneedles can orient to the wall of the small intestine, insert into the tissue and deliver the API. After the connectors with the rest of the patch degrade, the tips can be left inside the tissue for continuous active release, whereas the magnetic substrate can be excreted safely. Promising results in anesthetized pigs revealed uptake of insulin after direct deployment of the microneedle patches loaded with 28 U of insulin. In addition, blood glucose levels returned to normal values following application of the loaded devices within 2 h after dosing [86].

Overall, promising results have been achieved by using microneedles and auto-injecting devices for oral delivery of biologics. However, there are some concerns that still need to be addressed. Firstly, despite oral dosage studies were performed in awake large animals such as pigs to track the devices such as the new SOMA as it passed through the GI tract [78], most of the pharmacokinetic studies were performed in anesthetized animals, where the peristaltic movement can be affected [141,142]. In addition, pharmacokinetic studies were performed in fasted state and the devices were deployed directly in the desired location, stomach or small intestine, thereby not considering the food effect and the deployment after ingestion of the device [76–78,81,84,86]. For SOMA, animals with food and liquid in their stomach showed no drug uptake, thereby revealing that SOMA functions *in vivo* when tests are conducted in fasted state [77]. Similarly, clinical studies in healthy subjects showed high bioavailability after oral administration of the Ranipill®, however, the subjects needed to be in fasted state as no drug uptake was observed in the fed state [82]. Secondly, despite that endoscopies showed no signs of damage or abnormalities from GI injections after a week of dosing [77] and clinical studies did not report any pain or issues with tolerability [82], further research will be required to determine chronic effects caused by daily GI injections, foreign body response, and local therapeutic agent exposure. Thirdly, most of the devices incorporate materials such as steel springs or elastomeric materials that are not FDA approved. The acceptance by regulatory authorities and long-term environmental considerations may require a push to develop devices for oral drug delivery within new materials that can perform these functions while minimizing deleterious environmental impacts. Finally, the fabrication and manufacturing of the developed smart capsules is complex as they comprise several parts. The complexity in assembling such devices could be challenging for industrial mass production, which may be translated to high-price products. Irrespective to these limitations, the obtained results suggest that ingestible GI auto-injectors and microneedle-based devices is a growing research area that could supplement or replace, at times, painful subcutaneous injections [1].

8. Discussion and perspectives

New oral drug delivery technologies have shown promising results when it comes to the manufacturing and usage of personalized medicine as well as improving the bioavailability of biologics that are currently administered *via* injections. The development of 3D printing techniques enables production of multiple dosage types including oral dosage forms with versatile and personalized designs and release of multiple APIs tailored to the patient [42,47,48]. The methods used to fabricate these device concepts must be evaluated to ensure they offer appropriate production speeds and robustness. Traditional rotary tablet presses can achieve >1 million tablets per hour by direct compression of tablet blends [143]. In comparison, optimized 3D printing techniques such as MED could achieve approximately 30,000 tablets per day, when utilizing modules such as continuous feeding and mixing [43]. The robustness of 3D printing has been investigated and demonstrated to be capable of producing tablets that satisfy current European pharmacopoeia. Further developments may be required to ensure properties unique to 3D printed tablet forms, such as the strength of printed tablet layers, are appropriately measured to ensure safe products are released to market and patients [144]. Additionally, one of the aspects of 3D printing/personalized medicine is the decentralization of manufacture. This would open up additional considerations into the validation and approval of products given a greater variety of process variables. This may be achieved by submission of a design space, in which the attributes of the products such as release profile and dosage can cover a given range, with the capability to manufacture anywhere within this space in the clinical setting [145]. Finally, it is essential to consider that the novelty of these devices requires engagement with regulatory authorities as they move further from traditional dosage forms. This has been granted for 3D printed dosage forms with Spritam® (Aprecia Pharmaceuticals), which gained FDA approval in 2015.

Whereas 3D printed tablets and capsules aim to enable personalized medicine to the patient, investigations in materials and designs have demonstrated capabilities within gastro-retentive devices that aim to reduce the frequent dosing. Through application of swelling or elastomeric materials, these devices have been successfully dosed and resident for up to one month by physically preventing the device exiting the pylorus. The indications of drugs suitable for devices include therapies that require frequent dosing such as Alzheimer's or HIV medication. High loading is achievable (up to 30 wt%), such that a constant release of a drug over time can be achieved. Similarly in both 3D printed and gastroretentive devices, there is still a requirement to ensure the compatibility and stability between the materials and selected APIs. This may limit the potential applications for said devices when selecting APIs with poor stability in gastric media or poor solubility/permeability in the GI tract. Overall, it is observed that approaches based on lumen-release of drugs such as 3D-printed capsules and prolonged gastric residence dosage forms have been explored to offer personalized medicine to the patient and reduce frequent dosing of small molecules.

The variety and intensity of the research within substituting injections for oral medicine also demonstrates a continued interest in achieving the "holy grail" of improved oral bioavailability of poorly permeable APIs such as peptides. Subcutaneous injections are always the common administration route through which we compare the efficacy of these new concepts. However, there have been a number of oral dosage forms which have reached the market, although it should be noted that the bioavailability achieved by these is still relatively low, ~1% [16]. These marketed products achieve this by formulating the API with PEs such as SNAC and sodium caprate. This offers the possibility of dosing APIs previously formulated as an injectable, to be dosed orally. However there is a possibility that oral dosage forms that only rely on PEs may hit a bioavailability "ceiling" as to what can be achieved purely with a monolithic tablet or capsule.

Similarly, another factor that assists in improving the possibility of dosing peptides orally is the improvements in the molecular engineering of the peptide molecules. Through peptide engineering more stable and longer circulating peptides can be created [16]. In turn the frequency of dosing could be reduced such that an oral device may only require weekly or monthly dosing. Traditionally, small molecule drugs were always considered cheaper to produce compared to biologics, as they could be synthesized *via* traditional chemical synthesis. Improvements in recombinant production of peptides, such as within bacteria or yeasts, has pushed the cost down to comparable levels with chemical synthesis [146]. This enables the business case as the lowered API cost supplements the relative increase in the cost of other components in the dosage system, whether that is PE or materials within more elaborate device concepts. However, the poor permeability of proteins and peptides still remains challenging to ensure a satisfactory bioavailability. Therefore, oral capsules containing devices that allow proximity or even penetrate

the GI epithelium have been developed to address this challenge.

When categorizing the drug delivery systems according to the proximity of the drug release to the epithelium, a trend is observed with this proximity and the resulting enhancement in the oral bioavailability of macromolecules (Table 1). However, this also comes with an increase in the complexity and invasiveness of the drug delivery system, which is a drawback for future commercialization of the technology. Therefore, for complex oral devices which differ greatly from tablet-like dosage forms, the manufacturing techniques used are essential to ensure the final device is repeatability made, as well as feasible for larger scale production. In design concepts with multiple components, it is likely that high volume techniques such as injection molding could be utilized. Consideration must be taken into the assembly of these multi-component devices, as they sit on the boundary of a drug product and medical device. The realization of these devices may require consideration as to the level of sterility the production of the device must adhere to when needed. Additionally, as the functionality of the materials used to create the device becomes a key factor in the success of the API delivery, thus becoming equivalent to a critical process parameter or critical quality attribute. Like in traditional pharmaceutical production techniques such as spray drying or roller compaction, the characteristics of these functional materials would require careful control and monitoring to ensure their consistency and performance. In the case for a novel polymer based system, these critical parameters could consist of molecular weight, polydispersity, young's modulus and swelling properties. The validation of the materials quality and performance becomes more stringent when we consider the interfacing of multiple materials and components in these novel device concepts.

Furthermore, the materials used to fabricate new conceptual devices often fall outside the generally recognized as safe (GRAS) category, as the functionality of the devices falls beyond the boundaries of traditional techniques such as tableting. Thus, selection of suitable and safe materials, both in relation to the API release, function within the GI tract, as well as the excretion and elimination into the environment, becomes a very important part of devising new oral delivery devices which are both effective and reduce potential environmental damage. The material consideration is especially pertinent for device concepts such as magnetic systems, elastomer concepts or auto-injectors such as SOMA that utilize non-degradable materials.

With the movement from monolithic tablets to more complex engineered oral delivery devices, the degree to which the product directly interacts within the GI tract has increased. In recent iterations this has begun to manifest in direct physical interaction with GI tissue, either through directly penetrating solids/liquids through the GI epithelium, or anchoring mechanisms to promote retention and proximity. These are relatively novel techniques for bypassing the barrier function of the GI tissue, however they present a potential new safety concern. The GI tract is in general a robust and dynamic area, however there still remains the possibility for injury *via* perforation, tearing or irritation. These concerns will hopefully be addressed as device concepts such as SOMA and Ranipill®, undergo clinical investigation. These studies should seek to ensure that the impact on the GI tissue is minimal, such that future devices may be able to be applied in chronic diseases with frequent dosing. Similarly, we should be cautious in evaluating the success of these oral devices and their claims of bioavailability comparable to subcutaneous injections. Although often acknowledged within the literature, studies often demonstrate non-responders during clinical trials. This is highly important to evaluate to ensure that the devices offer a robust and reliable dosing, to ensure they are can meet the regulatory requirements. Additionally, there needs to be sufficient data to ensure doctors and patients are willing to use a product which has a far different mode of action than previously seen.

There are various factors which will affect the potential success and applications of this new era of oral delivery. The business case needs to be decided as to whether the gains made in improving the oral bioavailability of compounds outweighs the cost and complexity of manufacturing these products. This may in turn dictate the types of API and the indications which may be suitable for treatment with these more complex, and likely more expensive products. This may firstly limit the types of diseases which will be sought to be treated to those with the feasibility to provide a high "return on investment". Furthermore, the higher product cost may suggest this area will be applied to less frequent dosing regimens, either through deliver of long half-life or potent API with infrequent dosing requirements such as antibodies. Similarly, the type of healthcare system could also impact the utilization of these devices. If one considers the U.S. healthcare system, there is a complex interplay between manufacturers, brokers, and healthcare providers. Subsequently the reimbursement for these devices may be more complex as they would have to "compete" against pre-existing treatment options.

In conclusion, the field of oral devices has garnered much attention and research in the past few years, with research seen in both industry and academia. As these devices begin to enter the clinic, their studies shall be closely monitored for their successes and failures, to direct further research into enabling delivery of macromolecules. Additionally, as non-traditional dosage formats become more commonplace, the regulatory authorities will ensure innovation is permitted without sacrificing safety.

CRediT authorship contribution statement

Carmen Milián-Guimerá: Writing – original draft, Visualization, Validation, Project administration, Investigation, Conceptualization. **Reece McCabe:** Writing – original draft, Validation. **Lasse Højlund Eklund Thamdrup:** Writing – review & editing, Validation, Supervision, Conceptualization. **Mahdi Ghavami:** Writing – review & editing, Validation, Supervision, Conceptualization. **Anja Boisen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgements

This work was supported by the Novo Nordisk Foundation (NNF16OC0022166), the European Research Council (Grant No. 101054945), the Danish National Research Foundation (DNRF122) and Villum Foundation (Grant No. 9301); Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN). All figures were combined in BioRender.com.

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