# Physical methods for enhancing drug absorption from the gastrointestinal tract



**Originally published in:**
Advanced Drug Delivery Reviews 175, https://doi.org/10.1016/j.addr.2021.05.024

**Funding acknowledgement:**
177178 - 3D printing manufacturing of patient-tailored drug releasing stents (SNF)

Advanced Drug Delivery Reviews 175 (2021) 113814

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

# Physical methods for enhancing drug absorption from the gastrointestinal tract

Zhi Luo, Nevena Paunović, Jean-Christophe Leroux *

*Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland*

ARTICLE INFO

*Article history:*
Received 22 March 2021
Revised 17 May 2021
Accepted 20 May 2021
Available online 27 May 2021

*Keywords:*
Oral drug delivery
Bioavailability
Physical methods
Magnetism
Ultrasounds
Biologics
Permeability

ABSTRACT

Overcoming the gastrointestinal (GI) barriers is a formidable challenge in the oral delivery of active macromolecules such as peptide- and protein- based drugs. In the past four decades, a plethora of formulation strategies ranging from permeation enhancers, nanosized carriers, and chemical modifications of the drug's structure has been investigated to increase the oral absorption of these macromolecular compounds. However, only limited successes have been achieved so far, with the bioavailability of marketed oral peptide drugs remaining generally very low. Recently, a few approaches that are based on physical interactions, such as magnetic, acoustic, and mechanical forces, have been explored in order to control and improve the drug permeability across the GI mucosa. Although in the early stages, some of these methods have shown great potential both in terms of improved bioavailability and spatiotemporal delivery of drugs. Here, we offer a concise, yet critical overview of these rather unconventional technologies with a particular focus on their potential and possible challenges for further clinical translation.



**Contents**

1. Introduction . . . 1
2. Physical aspect of the absorption barriers in the GI tract . . . 2
3. Overview of available technologies . . . 3
   3.1. Magnetic retention . . . 3
   3.2. Hydrogel expansion . . . 5
   3.3. Gas empowered system . . . 6
   3.4. Microcontainers . . . 7
   3.5. Microneedles . . . 8
   3.6. Ultrasonication . . . 10
   3.7. Iontophoresis . . . 10
   3.8. Microfabricated smart devices . . . 10
4. General considerations for clinical translation . . . 12
   4.1. Efficacy and robustness . . . 12
   4.2. Production and cost . . . 12
   4.3. Safety and regulatory considerations . . . 12
5. Conclusions and perspectives . . . 12
   Acknowledgements . . . 12
   References . . . 13

* Corresponding author.
*E-mail address:* jleroux@ethz.ch (J.-C. Leroux).

https://doi.org/10.1016/j.addr.2021.05.024
0169-409X/

## 1. Introduction

Oral administration is one of the oldest and most convenient modes of drug delivery, yet still unresolved challenges lead to the continuous development of novel formulation strategies [1]. The innovations have been driven by the specific requirements of different drug compounds to address issues such as stability, solubility, dissolution kinetics, site of delivery and absorption [2–4]. As a result, a variety of formulation technologies (e.g. delayed release coatings, solubilizers, permeation enhancers) have been developed, and are now commonly used in the clinic [1,5–7]. For example, the approval of orally delivered glucagon-like peptide-1 receptor agonist, semaglutide, highlights the recent success in the pursuit of permeation enhancers to promote the absorption of peptides and proteins in the gastrointestinal (GI) tract [8–10].

However, despite these encouraging developments, the oral delivery strategies for macromolecular drugs still lag far behind the rapid advancement of biologics [11,12] and other new pharmacological modalities, such as the proteolysis targeting chimera (PROTAC) [13] and the RNAs therapeutics [14]. The molecular weight and physicochemical nature of these compounds often preclude their efficient permeation through the GI tract [15], which emphasizes the need for other oral drug delivery strategies.

In fact, only few orally formulated peptide drugs for systemic delivery have entered clinical trials over the past 30 years and so far, merely four of them have reached the market, i.e. desmopressin (1069 g/mol) (DDAVP®), cyclosporine A (1203 g/mol) (Sandimmune®/Neoral®), semaglutide (4114 g/mol) (Rybelsus®) and octreotide (1019 g/mol) (Mycappsa®). The first two were commercialized in the 1980's [16,17], while semaglutide and octreotide were both approved only in 2020. Although a variety of excipients (e.g. permeation enhancers, protease inhibitors) and drug delivery technologies (e.g. micro/nanoparticles, hydrogels, bioconjugates) have shown high efficacies in preclinical models [18–21], these formulations rarely proceeded to clinical stages [5,22]. Even with the most common permeation enhancers that have been tested in clinical studies, e.g. salcaprozate sodium (SNAC), sodium caprylate (C8), and sodium caprate (C10), the oral bioavailability achieved for peptides is generally in the order of 1% [8,22,23]. This restricts, at the moment, the application of permeation enhancer-based formulations to drugs with high potency, stability, and a large therapeutic window.

Moving beyond traditional chemical and biological permeation enhancing principles [1,5], a few techniques have exploited the physical forces in order to overcome the GI barriers [24–26]. As illustrated in Fig. 1, instead of depending on the passive or receptor-mediated transport of active pharmaceutical ingredients (APIs), the proposed devices rely on magnetic, mechanical, electrochemical, and acoustic forces to enhance absorption [24,25]. Although still in their infancy, some of these strategies have shown great potential prompting their clinical development. The aim of this review is to offer a focused and critical analysis of this unconventional field, i.e. physical forces assisted drug delivery in the GI tract. A particular attention is paid to the relative efficiency of these formulation approaches in improving the oral bioavailability of poorly permeable drugs as well as the challenges and safety concerns associated with their clinical translatability.

## 2. Physical aspect of the absorption barriers in the GI tract

The numerous biochemical and physical barriers of the alimentary tract afford an efficient protection from infections and certain noxious or immunogenic compounds [27]. However, it also often limits the absorption of orally administered drugs. In the oral cavity and oesophagus, the absorption of most of the drugs is considered negligible due to their short residence time [28]. The first major hurdles impeding the oral delivery of many macromolecular drugs are the denaturation and chemical degradation that can take place in the stomach and the intestine [29]. Typically, the acidic conditions of the stomach (pH 1–2 in fasted state) denature most proteins and initiate their enzymatic degradation. In the small intestine, bile salts can further destabilize biologics in conjunction with their cleavage to oligopeptides and amino acids by various proteases [30]. The remaining components can finally decompose in the colon by bacterial fermentation [31].

In addition to their inactivation by the harsh environment of the GI tract, biologics face physical hurdles that largely prevent them from entering the systemic circulation. The first of those hurdles is the mucus, a thick tenacious hydrogel network that coats the GI tract epithelium. It is formed by the intermolecular crosslinking of the main mucus component, mucins, which are highly glycosylated proteins secreted by goblet cells. The mucus protects the GI mucosa from the enzymatic degradation and microbial invasion. However, concurrently, it also impedes the diffusion of large APIs [32,33]. The mucus mesh pore size (average ca. 200 nm [34,35], with distribution ranging from 60 to 400 nm [36]) represents the threshold for the particle diffusion [37,38]. The diffusion path

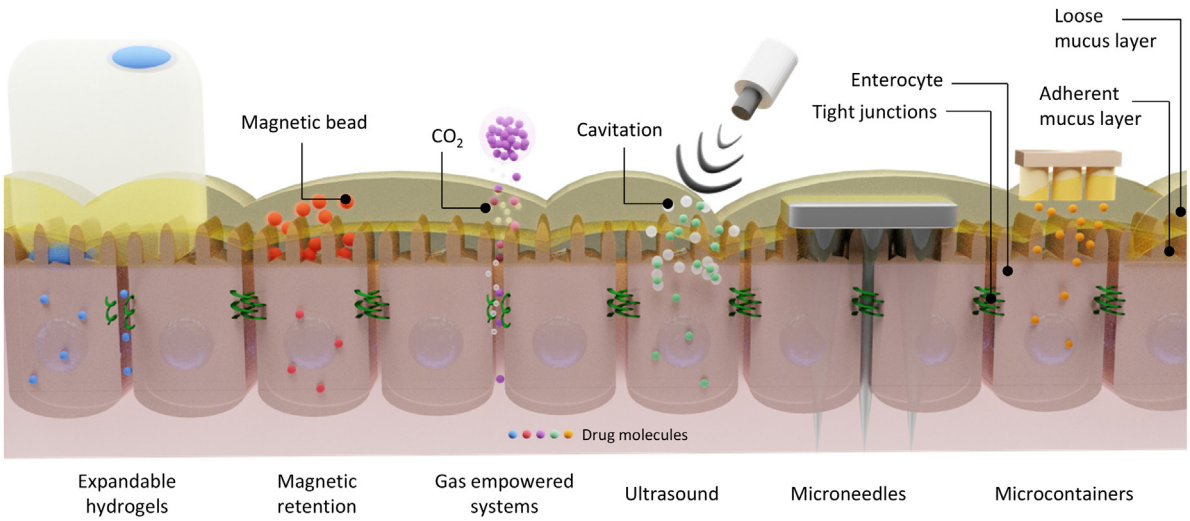


**Fig. 1.** Overview of the physical methods-based technologies for enhancing the GI absorption of therapeutics.

length is further determined by the thickness of the mucus layer, which varies along different regions of the GI tract, e.g. 50–450 μm in stomach [39] and 110–160 μm in colon [40–42]. An additional physical complexity of the mucus barrier comes from the fact that it can be regarded as a two-layer structure. While the inner stratified layer (~50 μm) firmly adheres to the epithelium (glycocalyx), the outer part is loosely attached and creates a slippery surface that is constantly secreted (ca. 10 L per day) [40,41] and renewed (turn over ca. 1 to 4 h) [43]. In addition to these physical barricades, mucus components (mucins, lipids, other proteins, electrolytes, and DNA) can create multiple low-affinity interactions with macromolecules further hampering their diffusion [37]. The negatively charged glycosylated regions of mucins attract positively charged molecules, and reduce their diffusion rates, while negatively charged systems tend to be repelled. As a result, the diffusion and the subsequent absorption of molecules with high molecular weight and charged molecules are highly limited. Notably, Peyer's patches with lymphoid M cells are the least mucus protected part of GI tract (glycocalyx of 20–30 nm) [32,33,44] due to their immunological role, but they account for just 1% of total GI tract surface in humans [45,46].

Drugs that penetrate the mucus layers subsequently face the epithelial lining barrier. In the small intestine, which constitutes the largest absorptive surface of the alimentary tract, the epithelial barrier consists of enterocytes linked together by tight junctions, adherens junctions and desmosomes [47]. Each junction is formed by proteins connected to the cytoskeleton and/or to the neighbouring cell junction proteins. This structural organization of the intestinal mucosa permits the drug to reach the bloodstream (from the gut lumen) through two main pathways – transcellular and paracellular. The transcellular pathway covers the passive diffusion and the facilitated/active transport through the epithelial cells. It is mostly restricted to molecules that comply with Lipinski's rule of five, and substrates that can be taken up by transporters or through transcytosis. Tight junctions effectively seal the intercellular passages, and restrict the paracellular transport of the drugs with molecular weight higher than 1000 g/mol. This protective barrier can, however, be transiently opened by activation of myosin light chain kinase (MLCK), or tyrosine kinases such as JNK2 and c-Src [48]. These kinases cause phosphorylation of light chain myosin II or the main proteins - occludin and zonula occludens (ZO-1) of tight junctions, as well as E—cadherin and β—catenin of adherens junctions. Due to the structural and conformational changes, phosphorylated proteins dissociate from each other and from the cytoskeleton eliciting the junction rearrangement [49]. The junctional disruption allows ions and even macromolecules to reach the systemic circulation.

Mechanical stress, such as stretching or compression, affects both barriers, plasma membrane and junctional complexes, and their associated transport mechanisms [50–52]. The cell membrane reacts to an increased tension upon stretching by decreasing the thickness, unfolding and expanding through insertion of additional phospholipids, which leads to the conformational changes of lipids and transmembrane proteins [50,53,54]. This can cause the disruption of the tight lipid bilayer packing [55], and most often increases the membrane permeability and transcellular transport [50]. Yet, some experiments showed that conformational changes can also increase cell stiffness, and therefore hamper the diffusion through the plasma membrane [50]. On the other hand, short-time cyclic stretch of Caco-2 cells monolayer has been found to increase the paracellular permeability by stress-activated kinases MLCK, JNK2, c-Src, resulting in structural and integrity changes of tight and adherens junctions [51].

Due to the physical nature and mechanical responses of various barriers in the GI tract, it is therefore reasonable to hypothesize that formulations that physically disrupt these barrier functions could facilitate drug absorption. In fact, although permeation enhancers are typically regarded as chemical additives, their working principles are generally based on physical effects, such as disrupting tight junctions, lowering the mucus viscosity and increasing cellular membrane fluidity [1,9]. Despite the successful applications of permeation enhancers in a few commercial formulations, there are still several considerations over their efficacy and safety. First, while the most commonly used permeation enhancers such as SNAC and C10 have proven safe over several clinical trials, these molecules function by perturbing the plasma membrane and the cellular junctions [56]. Thus, the concerns on whether the epithelial damage-repair cycle would impose a long-term risk during chronic administration remain to be addressed [57]. Furthermore, as mentioned above, although permeation enhancers can significantly increase absorption, the bioavailability of orally delivered peptides remains low (<3%) [22], even though relatively high amounts of permeation enhancers were often used, e.g. semaglutide (5 mg)/SNAC (300 mg) [8], desmopressin (0.2 mg)/C10 (330 mg) [58]. Therefore, novel permeation enhancers or other formulation strategies with higher efficiencies are still demanded.

In the last three decades, a variety of physical disruption strategies have been widely explored for transdermal drug delivery [25,59]. Techniques such as microneedles, iontophoresis, ultrasound, and laser or radiofrequency ablations have shown to effectively modulate the barrier functions of the skin [59,60], which is much thicker and less permeable than the GI mucosa. It is, therefore, natural to expect that these methods might also facilitate drug absorption from the GI tract. Furthermore, often the physical delivery modes rely on external stimuli, which can add an extra spatiotemporal control of the drug release and absorption [61]. The following sections provide an overview of the working principles, advantages, as well as potential challenges of various physical methods for the drug delivery in the GI tract.

## 3. Overview of available technologies

### 3.1. Magnetic retention

External magnetic fields are generally regarded as safe under mild exposure [62] (e.g. 0.5 T for static magnetic field), and have been widely exploited in radiology such as magnetic resonance imaging (MRI) [63]. Therefore, the use of magnetic force was among one of the first explored physical methods in oral drug delivery. Nagai and co-workers have reported in 1990 the use of magnetic granules containing bioadhesive polymers (i.e. a mixture of hydroxypropyl cellulose and carboxyvinyl polymer) for drug delivery to the esophageal mucosa [64]. It was found in rabbits that the 2-min application of a magnetic field (0.19 T) was sufficient to fix the magnetic granules at the desired position in the oesophagus for more than 2 h [64]. As this work was only a proof-of-concept study, the drug delivery efficacy and the potential epithelial damage with this system were not examined. The same group later explored magnetic tablets for controlled gastric retention of a model drug acetaminophen [65]. A static magnet field (~0.2 T) was applied to the stomachs of beagle dogs for 8 h, which led to 3 h longer gastric emptying time as well as 2-fold increase in bioavailability of acetaminophen [65]. Similar results were then reported in a series of studies by Gröning *et al.* [66–68], including a small clinical investigation in five healthy male subjects [68]. Using a multilayer tablet containing an internal magnet, the gastric retention times of the dosage forms were significantly prolonged in 4 out of 5 subjects with an average increase from 1.25 to 12 h, although the exact strength of the magnetic field was not reported [68]. Correspondingly, an average mean area under the plasma concentration-time curve (AUC) was 1.8 times higher for the

poorly bioavailable drug acyclovir (225 g/mol) than for oral tablet formulations with a typical bioavailability ranging from 15 to 30% [69]. While in this case the applied magnetic force was not primarily aimed at transiently disrupting the GI barrier function, this study demonstrated the high efficiency of magnetic systems in prolonging the gastric residence time. It also pointed out a few considerations in terms of the robustness of the magnetic retention method [68]. For example, in one of the subjects, the peristaltic wave was so effective that it caused the rapid exit of the dosage form from the stomach [68]. Accordingly, inter-individual variations in the GI motility, as well as the effect of food intake should be taken into consideration for the development of this type of technology.

The magnetic retention was later applied to other formulations such as liposomes, poly(D,L-lactic-*co*-glycolic acid) (PLGA) microparticles and chitosan-alginate core-shell beads [70–75], in order to deliver not only small molecules but also proteins. For example, Cheng and co-workers co-encapsulated micro-magnets (neodymium iron boron, 0.25 T) and $^{125}$I labelled insulin (5808 g/mol) into PLGA microparticles and administered the suspension to fasted mice [74]. The mice were restrained for 90 min after administration with a magnet belt applied near the abdominal area. After 6 h, the recovered radioactivity in the small intestine was 32.5 ± 3.1% and 5.4 ± 4.4% for the groups with and without external magnetic field, respectively. By encapsulating insulin into the formulation, decreased glucose levels were sustained for 36 h, with the corresponding absolute bioavailability being 5.1 ± 1.2% compared to 0.8 ± 0.4% for control group without the magnet [74]. So far, insulin is the only peptide/protein drug that has been tested with this magnetic retention approach. It is unclear whether the reported ~6 fold increase in bioavailability is solely due to prolonged retention or also stemming from higher local concentration. Further research into the absorption enhancement mechanism is required.

The toxicity of the microparticle formulation was then examined on mice (n = 2) after a 24-h treatment. Upon histological evaluation of several organs (small intestine, liver, spleen, and kidneys), no evidence of acute inflammation nor magnetic microparticles were observed. Therefore, compared to nano-sized magnetic particles [70], the microparticle-based formulation led to a better performance as they generated higher forces and were less prone to uptake by the GI mucosa, e.g. absorption via the Peyer's patches [71,74]. However, the long term safety, especially the mucosal damage and its regeneration after application of magnetic forces should be addressed.

To better characterize the magnetic retention, Ménager and co-workers systematically examined the transport kinetics of the magnetic formulation in the rats' GI tracts with MRI and near infrared imaging techniques [72,73]. It was found that magnetic beads were enriched around the location where the magnet was applied, but were not retained at a fixed position due to the gastric emptying (Fig. 2A). Therefore, it was suggested that the forces generated by the magnetic field would need to be at least twice higher than the gastric force in order to achieve the effective retention [72].

While the goal of most magnetic formulations is to prolong GI retention, more advanced instrumentation has also been introduced to quantify and to better control the localization of the magnetic forces *in situ* [61,76]. Mathiowitz and co-workers described an imaging system based on biplanar video fluoroscopy to visualize the real time *in vivo* motion of capsules containing a magnet in rats (Fig. 2B) [61]. By controlling the distance of external magnets, the applied magnetic force could be adjusted at the same time. The system was also tested on human subjects to monitor the gastric forces experienced by the oral capsules and to further evaluate its potential for outpatient settings [61,76]. This type of device could be useful for diagnosing GI tract diseases such as gastric dysmotility disorders while allowing more controllable local delivery of drugs.

Overall, thanks to their safety profile and tuneable nature of the external field, magnetic formulations could be more effective in prolonging the retention time of drugs in the GI tract compared to mucoadhesive materials [73]. However, so far there is still a lack

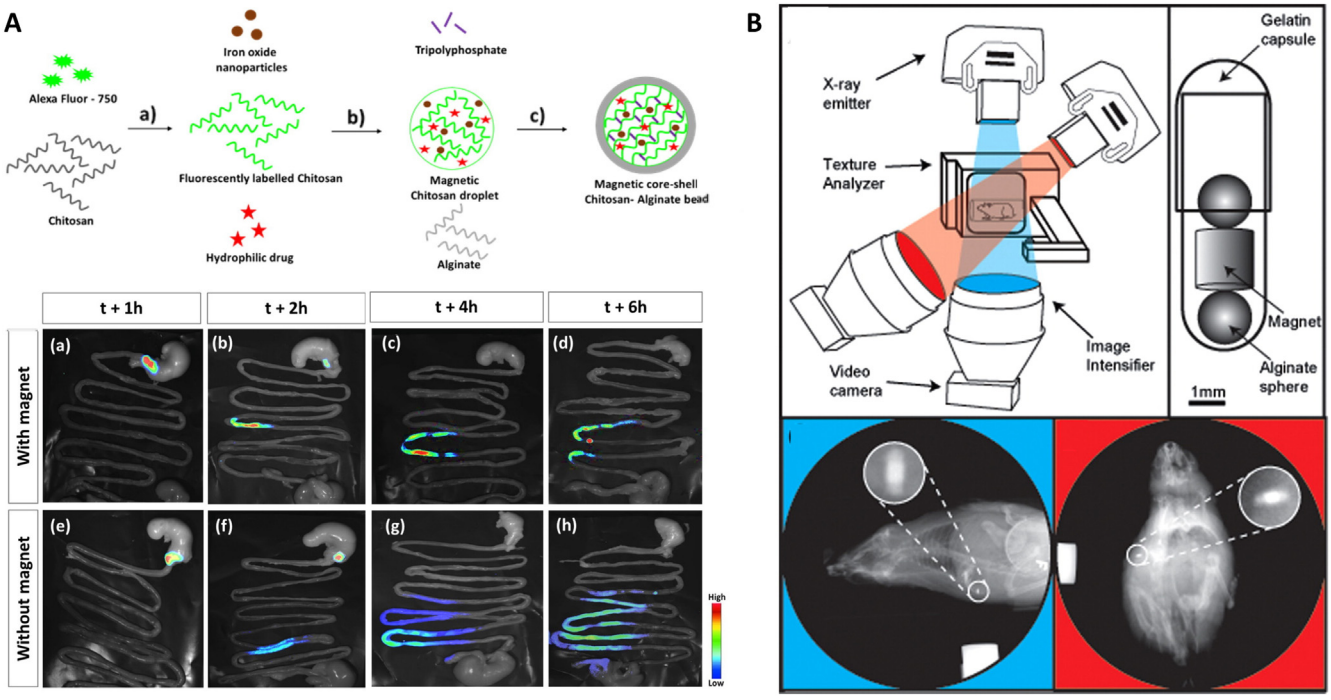


**Fig. 2.** Drug delivery in the GI tract using magnetic formulations. A) Synthesis and GI retention of core-shell magnetic particles containing fluorescently labelled polymers, iron oxide nanoparticles and drugs. Reprinted from [72] Copyright (2016), with permission from Elsevier. B) Biplanar video fluoroscopy system to visualize *in vivo* motion of the magnetic pill. Reprinted from [61] Copyright (2011), with permission from National Academy of Sciences.

of mechanistic understanding in terms of the impact of magnetic forces on drug permeation pathways, such as the disruption of cellular junctions, that are important for the delivery of large APIs. Furthermore, as the magnetic force decays rapidly with increased distance, it is difficult to use stationary external magnets to attract the magnetic carriers 5 cm below the skin [77,78]. It has been reported in drug delivery of anticancer drugs that the external magnets have to be placed as close as possible to the tumour site to ensure the retention [77]. Therefore, it remains to be seen whether portable external magnets could be developed for efficient oral drug delivery in humans. The large inter-individual variations in peristalsis and bowel movements should also be taken into account to establish a robust drug delivery system. The combination with other formulation strategies such as mucoadhesive materials, permeation enhancers, and controlled release dosages could also be used to further improve bioavailability of the drugs.

### 3.2. Hydrogel expansion

One of the advantages of magnetic over mucoadhesive systems is the possibility to control the site of delivery, and to enable higher adhesive strength to the epithelium. Another strategy initially proposed by Juginger and co-workers to achieve site specific and local release relys on the use of superporous hydrogels (SPHs) carrying small drug tablets [79–85]. The hydrogels were synthesized by copolymerizing acrylamide, acrylic acid, and 3-sulfopropyl acrylate monomers in the presence of foaming and stabilizing agents such as sodium bicarbonate, poloxamer 407, and sodium crosscarmellose. The large swelling ratio of these hydrogels enabled the mechanical transient fixation of the expanded formulation onto the intestinal wall [86]. A series of *in vitro* and *ex vivo* experiments were performed to correlate the mechanical pressure generated by the hydrogel to the paracellular permeability of different drugs [80–82]. It was reported that the transepithelial electrical resistance (TEER) of Caco-2 cell monolayers decreased by ~30% after covering the whole apical surface of the confluent cell monolayer with the swelling hydrogel [81]. Furthermore, both F-actin and occludin protein expression patterns were disrupted indicating the opening of tight junctions [80].

*In vivo* experiments were then performed in a porcine model (female pigs of about 35 kg body weight) to evaluate the oral bioavailability of insulin and the peptide drug octreotide [83,84]. As shown in Fig. 3, two types of drug loading methods were explored, i.e. i) embedding the API containing microparticles

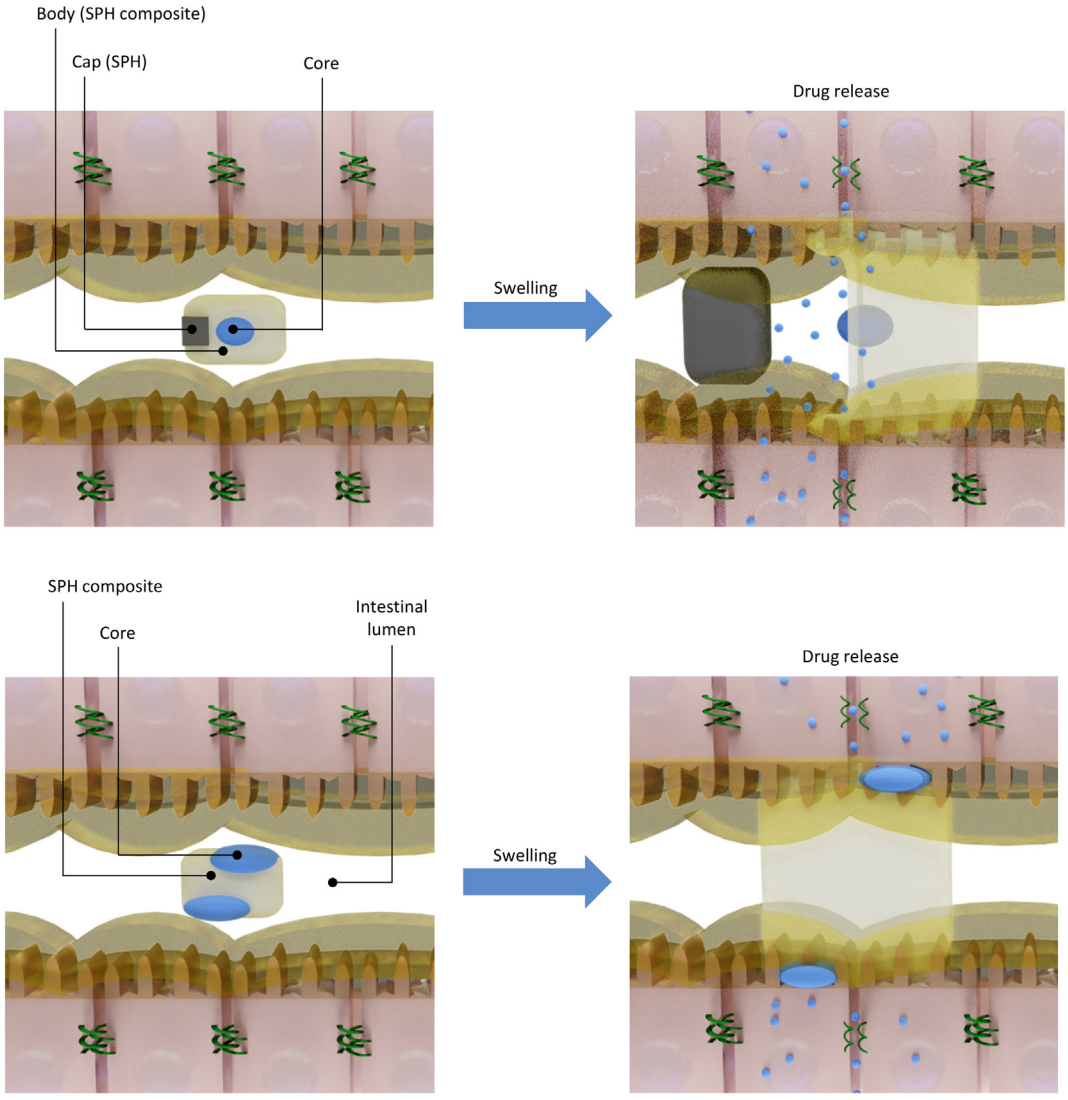


**Fig. 3.** Illustration of the superporous hydrogel (SPH) drug delivery formulation. Up: drug embedded system; drug is being released from the core after swelling of the hydrogel. Bottom: outside attached system; drug is released after the delivery system attaches to intestinal wall. Redrawn from [79] Copyright (2001), with permission from Elsevier.

(<400 μm, synthesized by dispersing the drugs in melted poly (ethylene glycol) (PEG) 6000) inside the swellable matrix (embedded) and ii) gluing two mini-tablets of 4 mm diameter to the surface of the swellable matrix (outside attached). For the delivery of insulin, both formulations were placed in gelatin capsules (size 000) without enteric coating. The capsules were then administered directly to the duodenum of anaesthetized pigs using a custom-made flexible plunger applicator. There was no significant difference in insulin bioavailability reported for these two types of formulations, i.e. both ranged from 1.3% to 1.9% relative to subcutaneous (s.c.) injection. The values were approximately 3-fold higher than the direct intraduodenal administration of the insulin control solution [83]. The authors further examined the delivery of octreotide using the same two formulations [84]. In contrast, the capsules were enteric-coated with Eudragit® S100 and were administered in sedated pigs *via* mouth into the stomach using a plunger applicator. While the bioavailability of the perorally administered octreotide (loaded in enteric-coated gelatin capsules) without the hydrogel system was only around 1.0 ± 0.6%, significantly higher values were achieved with the two hydrogel formulations, i.e. 12.7 ± 3.6% for the embedded and 8.7 ± 2.4% for the outside attached API [84]. Notably, even higher bioavailability (16.1 ± 3.3%) was obtained for the hydrogel system with drug tablet outside attached when co-formulated with an absorption enhancer, i.e. 20 mg of trimethyl chitosan chloride for 7.5 mg of octreotide.

The hydrogel based swelling approach is appealing as it allows a combination of different properties within the same formulation, i.e. local and directional drug release, mechanical fixation, mucoadhesion, and inclusion of permeation enhancers. The main safety concern is whether such formulations would cause obstruction in the GI tract. Therefore, a pilot clinical study was performed in three female and two male healthy volunteers using the embedded hydrogel formulation containing radionuclides (technetium-99 m and indium-111) in the core [85]. The formulation was given orally using the enteric-coated gelatin capsules, and then followed by scintigraphic imaging. The hydrogels transited along the GI tract without significant delays in all five cases. The retention time in the stomach varied from 75 to 150 min, while the transit through the upper small intestine was about 45 to 60 min [85]. Although such results look promising, detailed understanding on the swelling kinetics *in vivo* as well as drug release profiles are still lacking to obtain a complete picture of the behaviour of such hydrogels in the highly dynamic GI environment. Furthermore, so far all animal experiments were conducted in the fasted state, thus it is unclear how the food content would affect the delivery performance of these swellable formulations.

### 3.3. Gas empowered system

Jet injectors, which rely on the application of a high pressure jet to deliver medications across the skin were proposed in the 30′s as an alternative to needle injections [87]. The concept was subsequently exploited in buccal and vaginal drug delivery [88,89], and the RapidMist™ device developed by the Generex Biotechnology Corporation for the administration of insulin, i.e. Oral-lyn™ buccal spray, has reached Phase III clinical trial [90]. This proprietary device is a pressurized metered dose inhaler that can generate aerosol sprays at high velocity (~160 km/h) in the oral cavity [91]. The propelled aerosol particles are claimed to traverse the superficial layers of buccal mucosa and promote insulin absorption. Meanwhile, the formulation is composed of various surface active excipients that can also enhance protein absorption. In this way, the delivered insulin was found to be rapidly absorbed reaching the peak concentration after 44 ± 10 min, which was faster than typical s.c. injections (159.2 ± 68 min) [92,93]. However, the duration of action was also significantly shorter with the Oral-lyn™ spray, i.e. 85.1 ± 25 min compared to 319.2 ± 45 min for s.c. injections [92]. Unfortunately, the outcome from clinical trials did not meet the requirements for market approval in Europe and the USA. The main drawbacks of the technique are the variability and low bioavailability [91]. Often more than 10 sprays are necessary per dose (e.g. 10 U insulin), which is time consuming and not patient friendly [94]. More recently, a similar approach has been investigated for the buccal delivery of vaccines. Liepmann and co-workers developed a 3D printed plastic device named MucoJet that can generate a pressurized liquid jet of vaccine with high velocity [95]. The device is made of two chambers including one 100-μL vaccine reservoir and another propellant reservoir containing citric acid and sodium bicarbonate. Upon application, the water from the outer compartment of the device gets in contact with the chemical propellant and generates $CO_2$ gas reaching ~ 30 kPa in the chamber to eject the vaccine solution. In rabbits, the buccal administration of 100 mg/kg of the model antigen ovalbumin at weeks 0 and 4 induced both systemic and mucosal responses without the use of adjuvants. The histopathological evaluation of the buccal tissue at the site of administration revealed no signs of acute toxicity.

Junginger and co-workers also developed a system based on gas generation to exert mechanical forces in the GI tract [96]. The hypothesis was that the gas pressure would push the drug and excipients towards the intestinal wall, overcoming the low efficiency of passive diffusion. The enhancement of insulin transport was observed *ex vivo* when bubbling rabbit and sheep intestines with $CO_2$. The apparent permeability values of insulin in the absence and presence of $CO_2$ averaged $2.5 \pm 1.2 \times 10^{-7}$ cm/s and $7.5 \pm 1.6 \times 10^{-7}$ cm/s, respectively. The authors further hypothesized that the mechanical forces applied by the gas bubbles increased the paracellular drug transport by transiently opening the tight junctions. To test such formulations *in vivo*, tablets containing granules of citric acid, sodium bicarbonate, human insulin, trimethyl chitosan chloride (TMC, as permeation enhancer and mucoadhesive polymer), PEG, and other inactive excipients were prepared. After optimizing the content of the formulation in terms of $CO_2$ production, disintegration time, and mucoadhesiveness, the tablets were coated with poly(*N*-vinylpyrrolidone) and cellulose acetate phthalate and administered orally by gavage to male rabbits (2–3 kg). The bioavailabilities relative to s.c. injections of insulin were of 0.2 ± 0.1% for the control $CO_2$ generating tablets without permeation enhancer/mucoadhesive, 0.6 ± 0.2% for tablets containing PEG, and 1.1 ± 0.4% for the optimized tablets containing both PEG and TMC [96]. Unfortunately, control formulations without $CO_2$ production were not tested *in vivo* in this study, and thus it is hard to conclude what are the effects of gas generation in the GI tract on drug absorption.

In fact, the permeation enhancement effect of $CO_2$ was described by Eichman and Robinson in 1998 [97]. It was reported that the $CO_2$ bubbling did not induce tissue toxicity when tested *ex vivo* using rabbits' intestines. In contrast, the TEER values fell from the normal range of 75 – 100 Ω $cm^2$ to below 50 Ω $cm^2$ under $CO_2$ bubbling, indicating a change in the epithelial barrier. One plausible explanation is therefore that $CO_2$ gas disrupts the tight junction integrity of the epithelial tissue. This is supported by the observation that the enhancement in permeability decreases with the increase in the molecular weight or the hydrophobicity of the APIs, which indicates that the $CO_2$ influences the paracellular pathway [97]. Furthermore, it should also be mentioned that the effervescent formulations have also been explored for vaginal or rectal drug delivery, although they are mainly used to facilitate the dispersion of the suppositories [98,99] or to stimulate peristalsis and bowel movement [100]. The enhancement of drug permeability through effervescent formulations was also demonstrated

in the buccal and sublingual delivery of several different drugs [101,102]. Clinical results on small APIs, such as fentanyl, have shown an increase in bioavailability with the effervescent buccal formulation, although it is believed that this effect comes from the adjustment of pH by the bicarbonate that led to a higher fraction of the nonionized form of the drug [102].

Compared to other force generating systems, gas empowered formulations may be easier to formulate and adapt to different types of drugs. However, although the release of $CO_2$ in the GI tract is considered as safe with rather weak generated forces, a clear correlation between the force and the degree of barrier disruption has not been established. Typically, only limited amount of gas can be produced due to restricted volume of the formulation, leading to a bioavailability comparable to that of classical permeation enhancers [9]. Mechanistic *in vivo* investigations would be necessary to correlate the *in situ* generated pressure with the permeation enhancing effects as well as potential safety concerns regarding the GI mucosa. Finally, the variability in the gas release kinetics and its impact on drug absorption efficiency in the GI tract should also be assessed.

### 3.4. Microcontainers

Along with prolonged retention and adhesive properties, formulations with unidirectional drug release could promote drug absorption by achieving a high local concentration gradient and better protecting the drug compounds from digestive enzymes. In 2002, Desai and co-workers reported the first microfabrication of a device with multiple reservoirs and bioadhesive properties for oral drug delivery [103]. The versatility of this method to produce formulations with tailored sizes, shapes and surface functionalization as well as *in vitro* cell adhesion was demonstrated. As shown in Fig. 4A, a thin, planar shaped microdevice with a diameter of 200 μm and a thickness of 8 μm was fabricated using photolithographic processing of poly(methyl methacrylate). The drug compound acyclovir was then mixed with PEG dimethacrylate and embedded into the reservoirs on the device surface by photo-polymerization. A large number of microdevices (≈11 000) containing in total 17 μg of acyclovir were administered to mice by gavage (0.8 mg/kg). A significantly higher portion of microdevices was retained in the proximal side of the intestine compared to the control microparticle formulation also made of poly(methyl methacrylate). This is probably due to the fact that a high surface area of the planar microdevice enables higher contact area with the intestine compared to spherical microparticles. Moreover, by coating the device with tomato lectins (*Lycopersicon esculentum*) to increase bioadhesion, another 2-fold higher retention of the device in the mice intestines was observed 2 h after the administration [104,105]. Overall, a 4.5-fold increase in bioavailability of acyclovir in mice was reported with such type of microdevices compared to the oral gavage of the drug solution [105].

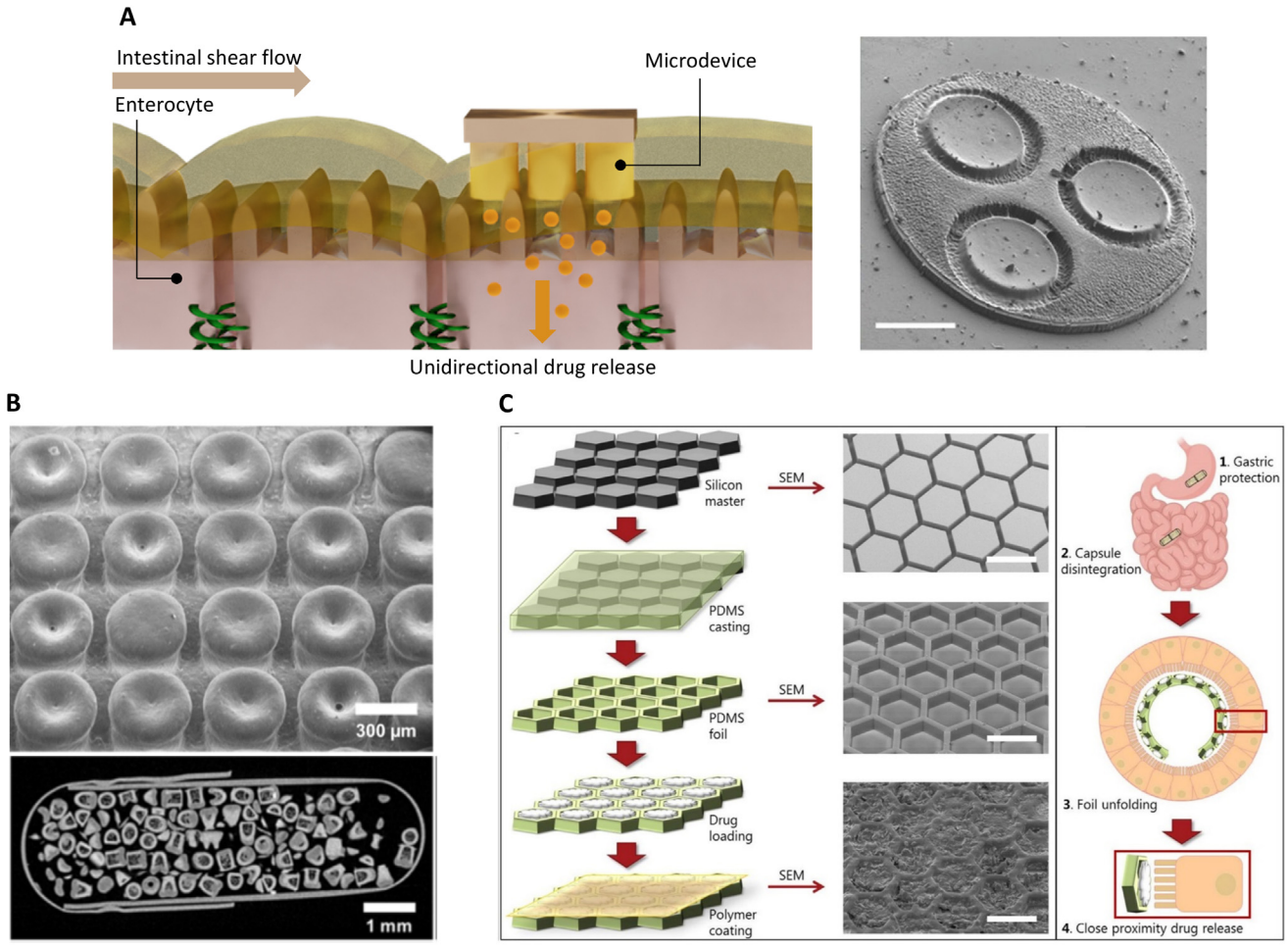


**Fig. 4.** Various types of microcontainer formulations. A) Concept of unidirectional drug release and the scanning electron microscopic (SEM) image of the thin, planar microdevice loaded with acyclovir entrapping hydrogel. The scale bar is 50 μm. Redrawn (A left) and reprinted (A right) from [105] Copyright (2014), with permission from WILEY-VCH Verlag GmbH & Co. B) A SEM characterization of drug loaded microcontainer and the X-ray microtomography image of the microcontainer loaded capsule. Reprinted from [106] Copyright (2017), with permission from Elsevier. C) Illustrations of the preparation of the foil-based microcontainer device, scale bars: 400 μm. Reprinted from [107] Copyright (2020), with permission from Elsevier.

Similarly, Boisen and co-workers have reported the application of microcontainers for the delivery of various drugs, such as furosemide [108], ketoprofen [106], indometacin [109], as well as proteins [110–112]. These microcontainers could be fabricated with biodegradable polymers such as poly(ε-caprolactone), with an opening diameter of a few hundred micrometers (Fig. 4B) [113]. The small devices could then be enteric-coated, combined into arrays or loaded into normal capsules. Besides increasing oral bioavailability, it is interesting to note that the micro-sized confinement played a role in the physical states of the embedded drugs. For example, it was found that microcontainers with a diameter of 174 μm better stabilized the amorphous state of indomethacin, compared to those with a diameter of 223 μm or 73 μm [109]. In addition to the sizes, the drug loading procedure for this type of formulation (e.g. the supercritical $CO_2$ impregnation) and the cooling rate of drug melts, were all found to be critical for their performance [106,114,115]. Furthermore, when ovalbumin was loaded together with glyceryl monooleate by spray drying, the cubic phase of lipids could be maintained in the microcontainer, which is potentially useful for sustained vaccine release [116]. Unfortunately, an enhanced immune response was not observed after oral administration of this formulation to mice [117].

Recently, a growing number of studies on permeation enhancers have pointed out the importance of co-localized and unidirectional release of drug compounds and excipients in high concentrations [8,9]. Microcontainers have the potential to meet such conditions. It was shown in Caco-2 cell monolayers that a nearly exponential increase of insulin transport could be achieved by reducing the distance between the microcontainers and the cells [118]. The localized drug release allows a higher concentration gradient and thus promotes drug diffusion. However, when gastroresistant capsules loaded with microcontainers were administered by gavage to rats, no insulin absorption was observed even when combined with permeation enhancers and enzyme inhibitors [112]. Post-mortem inspection of the GI tract suggested that the failure was due to the lack of retention and proper orientation of the microcontainers in the mucus layer. To address these limitations, Müllertz and co-workers recently developed an elastic foil formulation with close-packed hexagonal containers on top (Fig. 4C) [107]. The foil was then loaded together with a small magnet into an enteric–coated capsule (size 9). As it was reported that large sized capsules may experience difficulty escaping the rat's stomach [119], an external magnet was applied in the duodenum region about 3 cm from the pylorus to facilitate the gastric emptying. Furthermore, permeation enhancers (sodium dodecyl sulphate) and soybean trypsin inhibitor were also included in the formulation. An oral bioavailability of 0.12 ± 0.07% relative to s.c. injections was reported with this foil formulation, in contrast to non-detectable insulin plasma levels in control microcontainer-only formulation. Although the bioavailability may seem low, it should be noted that this is the first example of microcontainer based formulations that shows the potential for local and unidirectional drug release *in vivo*. Without the foil formulation, individual microcontainers may end up randomly oriented and thus lose the advantage to establish steep concentration gradients.

Further studies and additional considerations are required to optimize such a strategy. For example, due to the small overall size, the amount of drugs that can be loaded is limited. Furthermore, similar to magnetic formulations, the impact of inter- and intra-individual differences, such as the GI transit times, intestinal fluid volume and pH, on the performance of the device should be evaluated, especially for drugs having a narrow therapeutic window.

### 3.5. Microneedles

The above-mentioned techniques are non-invasive with working principles that are focused on achieving a close contact with the mucosa or opening the tight junctions to facilitate the drug permeation. However, the efficacy of these approaches is still hampered by the limited passive diffusion of drug compounds through the epithelium. To further enhance the drug permeation, more forceful approaches have recently been investigated. Over the past two decades, microneedles have been extensively explored for the painless transdermal delivery of a wide variety of drugs and vaccines [120]. The minimally invasive nature of microneedles as well as their high permeation enhancement effects have led to several clinical trials in indications ranging from diabetes and pain management to vaccination [121,122]. Microneedles have also been explored for other delivery routes such as ocular, vaginal and oral cavity [121–123]. The application of microneedles in the GI tract has been reported in several patents since 2009 [124]. In a proof-of-concept study [125], G. Traverso *et al.* examined the feasibility of systemic delivery of insulin by submucosal injection in the GI tract using a standard endoscopic needle on intubated pigs. The hypoglycemic onset time was reported to be significantly shorter when insulin was injected in the stomach and duodenum compared to the colon and skin. Furthermore, a cylindrical device carrying multiple 25G needles was fabricated and endoscopically deployed directly on the stomach of three pigs in order to examine the GI transit time as well as the safety profile. After the deployment, radiographs were taken to track the movement of the cylindrical device. Interestingly, the passage time of the device was found to vary greatly, i.e. 7, 19, and 56 days in three different animals. The histology of the GI tract of these animals was further examined and found to be macroscopically normal.

Compared to visible surfaces such as skin, where microneedles can be manually applied, special control or triggers for the injection must be designed to deploy the microneedles in the GI tract. For this purpose, two types of sophisticated devices were recently engineered, i.e. self-orienting millimeter-scale applicator (SOMA) [126] and luminal unfolding microneedle injector (LUMI) [127], for the gastric and intestinal delivery of insulin, respectively. These devices take into account anatomical features in the mechanical designs to achieve reliable needle deployment. As shown in Fig. 5A, the SOMA system was inspired by the leopard tortoise's ability of orientation adjustment in order to position the applicator on the stomach mucosa in the proper direction for the injection step [126]. The LUMI device utilizes three degradable and unfoldable arms to stretch the intestinal tissue and ensures microneedle penetration [127]. However, it should be noted that both devices have only been applied in the GI tract with the help of a gastric endoscope. Their adaptability to a swallowable oral formulation remains to be demonstrated.

Meanwhile, a company, Rani Therapeutics, has also developed a microneedle-equipped device for the delivery of macromolecules in the intestine. The so called "robotic pill" is an enteric-coated capsule loaded with a folded poly(ethylene) balloon, on which a hollow and dissolvable needle (made of PEG) is attached (Fig. 5B) [128]. Sterile solid form peptide drugs could then be packaged inside the needle with a capacity of around 3.5 mg. Once the formulation is released in the intestine, the reaction of citric acid and potassium bicarbonate inside the balloon is triggered resulting in its inflation, and the subsequent needle puncturing into the intestinal wall. Promising preclinical results were reported in the swine model, in which the bioavailability of insulin was reported to be comparable to s.c. injections [129]. A proof-of-concept

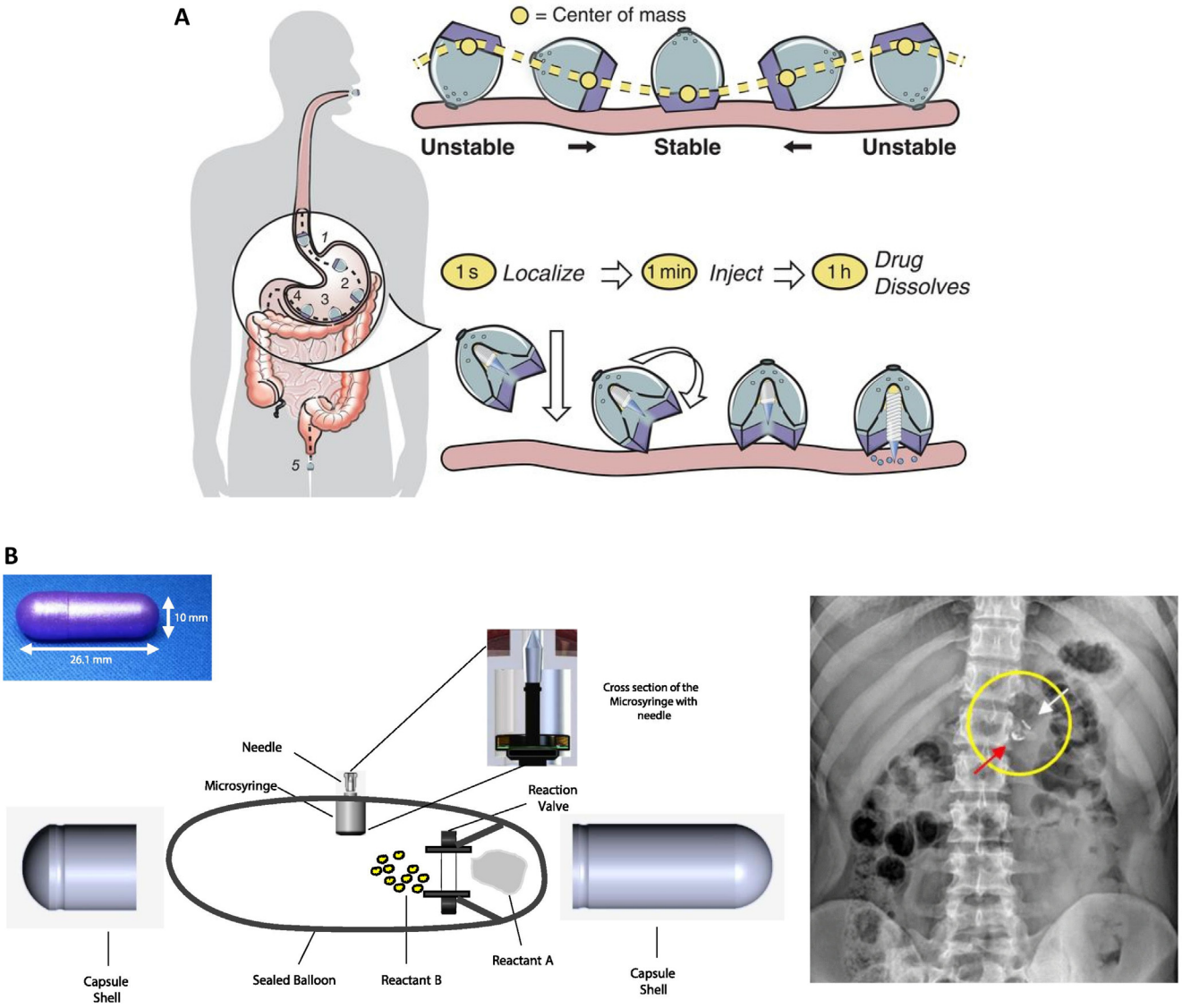


**Fig. 5.** Self-deployable microneedle-based devices for the oral delivery of peptide and protein drugs in the GI tract. A) The SOMA device that is able to localize and orient to the stomach linings before injecting the drug payload through the mucosa. Reprinted from [126] Copyright (2019), with permission from American Association for the Advancement of Science. B) The design of the microneedle-containing pill fabricated by Rani Therapeutics, and a representative X-ray image of the device in the GI tract. Reprinted from [128] under Creative Commons Attribution License 4.0 (CC BY).

clinical study that was carried out on more than 50 healthy subjects was recently published [128]. Three variations of the robotic pills with different balloon sizes (21, 23 and 25 mm) and the same octreotide dose (100 μg) were evaluated. Interestingly, a clear dependence of success rate of the device deployment on the balloon size was reported. While only 3 out of 12 successful deliveries were observed with the 21 mm balloon, higher rates were reported for the 23 mm (10 out of 20) and 25 mm balloon (16 out of 20). For the successfully deployed cases, a mean bioavailability of 65 ± 9% was achieved. Furthermore, through X-ray imaging the averaged gastric emptying times were 114 ± 18 min and 142 ± 16 min for the 21 mm and 23 mm balloon formulations, respectively, while the averaged times for the device deployment in the intestine were 91 ± 6 min and 118 ± 10 min, respectively. It should be noted that no significant effect of food on the device deployment time was observed, although the drug delivery success rates and bioavailability were not evaluated in the fed state.

While promising results have been achieved with these microneedle-based devices, a number of concerns need to be addressed before these technologies reach the market. First, the potential risks associated with frequent puncture of the GI tract by microneedles should be properly assessed. In published studies on SOMA and LUMI, the damage to the GI tissues was found to be minimal. The clinical study by Rani Therapeutics also did not report any pain or issues with tolerability [128,130]. These results are promising and reasonable as the GI tissue can tolerate a certain level of injury as occurring with submucosal injections, gastric tissue biopsies, inflammatory bowel diseases, as well as the accidental passage of sharp items. However, the long-term effects of intraluminal injections in a non-disinfected surface should be further examined, especially for formulations that require multiple injections per day. Issues such as increased exposure to food antigens, digestive fluids and resident pathogens could emerge upon chronic use. While the drug payload in the robotic pills developed by Rani Therapeutics was reported to be sterile, it was not mentioned if the commercial injectable systems would have to be sterilized. Considering the complexity in assembling such devices, sterile manufacturing or terminal sterilization could be challenging.

Secondly, although very high bioavailability could be achieved by both SOMA and the robotic pills from Rani Therapeutics, the total amount of drugs that can be delivered is limited by the size of the device. Thirdly, as mentioned above, the GI tract is a highly dynamic and variable environment, which may affect the dosing of the drug. For example, the devices were tested in the fasted state but the presence of food residues may interfere with the actuation/tissue penetration of the microneedles. Finally, the fabrication of such delicate devices is complex. They are composed of multiple parts such as needle carrying structures, triggering elements and encapsulation materials. Altogether these elements would make these devices more expensive and prone to incidental failure than classical oral formulations.

### 3.6. Ultrasonication

Similar to microneedles, ultrasound has also been extensively explored for transdermal drug delivery [131]. By tuning the intensity and frequency domain, it is possible to control the mechanical vibration energy applied onto the tissue. For example, at low frequencies, void spaces nucleate and form transient cavitation, which disturbs the surrounding fluid and tissue, thus enhancing drug permeation [132]. In 2015, Schoellhammer *et al.* reported the first application of ultrasound for localized drug delivery in the colon [133]. A series of *ex vivo* experiments were first performed to establish the optimal frequencies of the ultrasounds and to explore the mechanism of drug permeation enhancement effects. It was found that 20–kHz ultrasounds effectively induced transient cavitation, and overcame the tissue barriers more effectively than thermal treatment or sonication at 1 MHz. The proof-of-concept was further established in the swine model with mesalamine (153 g/mol) and insulin. Immediately after the instillation of the drug solutions in the rectum, a handheld low-frequency (20-kHz) ultrasound probe was locally applied for 1 min [133]. The short treatment time is in sharp contrast to typical transdermal applications due to the more permeable nature of the colonic mucosa compared to the thick stratum corneum and multi-layered epidermis. For mesalamine, a significant increase (~22 fold) of uptake was detected in the colonic tissue immediately after the treatment. In the case of insulin delivery (10 mL enema containing 100 U total dose of rapid-acting insulin instilled in the colon upon ultrasound application), blood glucose decreased by 83% after the ultrasound treatment. In comparison, for control animals not exposed to ultrasounds, the same drug dose led to almost no change in blood glucose (109 ± 9% of initial levels). Furthermore, a 14-day course of treatment in a rodent colitis model was performed to confirm the efficacy of delivering mesalamine with this approach. In subsequent studies, the application of the ultrasound assisted approach was tested for the administration of RNA [134] and other model compounds [135]. While it seemed that the delivery efficiency and penetration depth were relatively insensitive to the size and surface charge of the payload, the residence and clearance time clearly depended on these parameters [135].

In terms of tolerance [124,133,136], only minor epithelial disruption (~5% area based on image analysis) was reported with the 1-min treatment as revealed from biopsies of the colonic tissue. The repeated daily applications over 14 days also did not lead to any histological damage of the rectal mucosa. Cytokine profiling also revealed minimal proinflammatory response. Such good tolerability might be partly attributed to the short treatment time. These preliminary data are encouraging, but the rectum is a microorganism-rich environment, and is often perceived as an inconvenient administration route, which would make the chronic administration of drugs with an external device less practical and potentially risky. Whether a miniaturized ultrasonication device can be developed for oral delivery or not remains to be explored. There are, however, already attempts to adopt this technology for buccal drug delivery [134].

### 3.7. Iontophoresis

Another example of transdermal delivery technique that has been adapted to the peroral administration of drugs is iontophoresis. The latter is a non-invasive approach that utilizes the electromigration and electroosmosis phenomena to promote drug permeation [137]. A few iontophoretic devices have been approved by the FDA for pharmaceutical and cosmetic applications, although several were later withdrawn from the market due to the safety issues [138]. Most of these commercial products were used to deliver anaesthetic agents and pain management drugs [139]. Recently, iontophoresis was explored for the intestinal administration of insulin [140]. *In vitro* transport experiments were first performed on Caco-2 cell monolayers grown on Transwell® supports with controlled electrical potential and current. A significant decrease in TEER values (~35%) and an increase in the fluorescein labelled insulin transport (~2.6 times higher over 5 h) were observed with iontophoresis setups compared to control cells that were not subjected to electric current. A proof-of-concept *in vivo* study was further conducted in non-diabetic rats using an insulin loaded mucoadhesive patch (50 U/kg) covered with aluminium foil for iontophoresis. After surgically placing the patch onto the small intestine of the rats for 2 h, the blood glucose level dropped by more than 60% compared to patch formulation without the electric current. Histological examination was performed and showed no structural damage of the intestinal tissue. Based on these promising proof-of-concept results, the authors proposed that a swallowable and miniaturized electronic device could eventually be designed to allow the clinical translation of this approach [137].

### 3.8. Microfabricated smart devices

Besides microcontainer and microneedle-based formulations, advanced manufacturing methods, such as microfabrication and 3D printing, have also been explored to conceive sophisticated oral delivery devices. The high-resolution fabrication offered by these processes not only allows the precise control over the fine structures of the devices, but could also lead to the discovery of new mechanisms governing the material-cell interactions. For example, it was demonstrated that the decoration of microbeads with silicon nanowires of large aspect ratios could increase the adhesion towards epithelium cells [141,142]. These types of particles outperformed common mucoadhesive materials leading to a 10-fold increase of residence time in the GI tract compared to non-decorated beads using a beagle dog animal model. While the improved bioadhesion was likely due to a higher binding surface area and multivalent effects [143], it was found that the mechanical interactions could also facilitate the macromolecular transport through the epithelial cell layers [144,145]. As shown in Fig. 6A, the nanowire coated surfaces induced morphological changes in tight junctions as well as cytoskeleton rearrangements [146–148]. Such interactions seem to be rapid, reversible and could even be utilized to enhance the permeation of relatively large proteins such as albumin and antibodies [144,149]. These seminal findings may contribute to a better understanding on how nanostructures and mechanical cues could be utilized for engineering more efficient oral formulations.

Lee and co-workers reported a multilayer hydrogel with different swelling ratios at each layer [151]. Once hydrated, the device curled into a hook-like structure that could grip onto the intestinal mucosa enhancing mucoadhesion. Similarly, Ghosh *et al.* recently reported a shape-changing microdevice that mimics the hookworms in the intestine (Fig. 6B) [150]. The autonomous self-

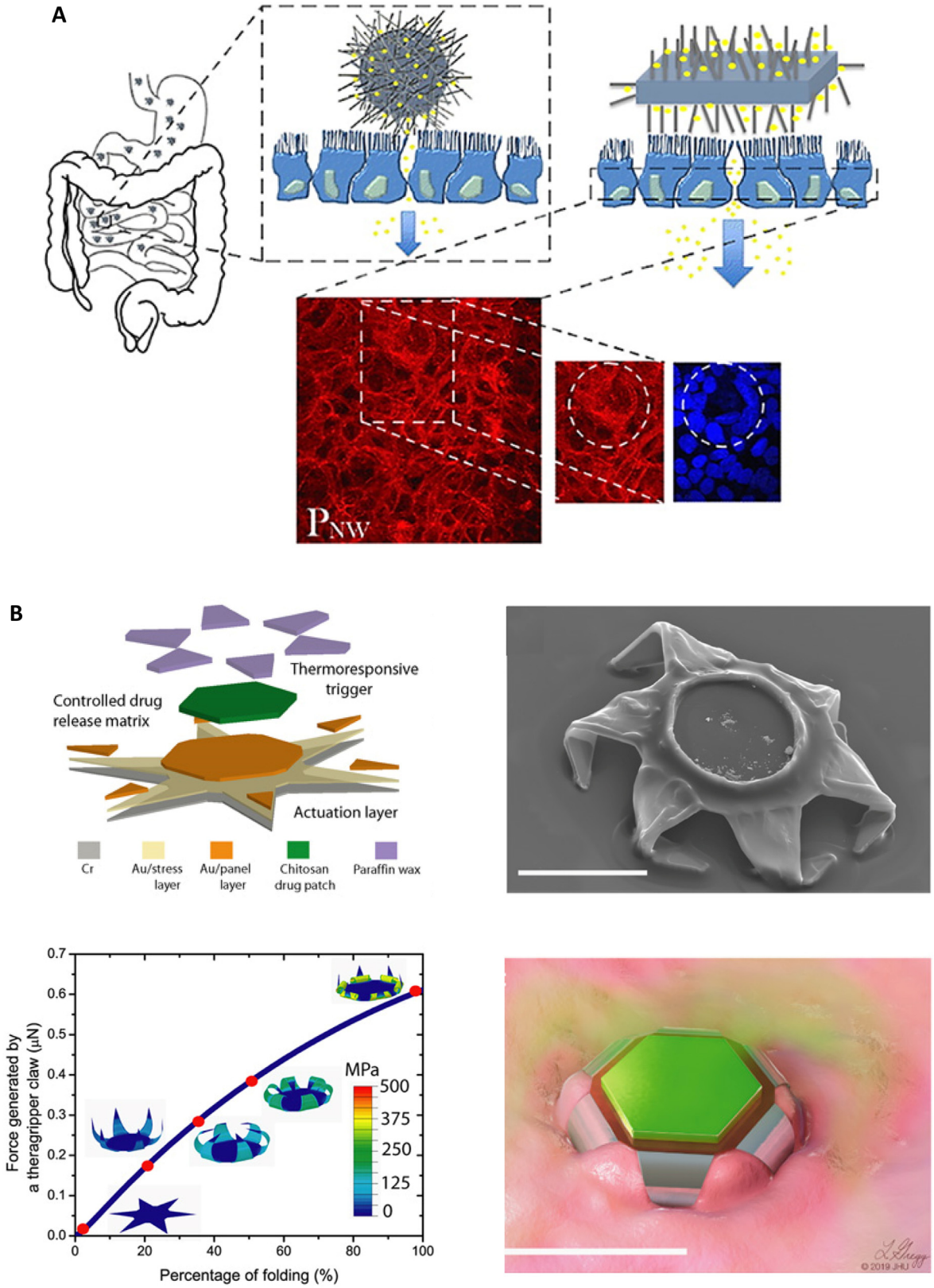


**Fig. 6.** Microfabricated devices to control the interaction with the GI epithelium. A) Nanowire-coated microparticles as transepithelial drug delivery devices, which can improve both the adhesion to epithelium and increase the permeability of drug compounds. Reprinted from [146] Copyright (2012), American Chemical Society. B) The concept and design of self-latching devices to grasp onto colonic mucosa. Reprinted from [150] under Creative Commons Attribution License 4.0 (CC BY).

latching properties of such devices were demonstrated both in the stomach and oesophagus of pigs and in the colon of rats when used to deliver a model analgesic drug, ketorolac (255 g/mol). A retention time in the colon greater than 24 h and a 10-fold higher AUC were achieved with this system after the endoscopy-assisted administration of the liquid containing the gripper devices with a catheter.

Another interesting concept to actively apply forces in the GI tract is the particle system called self-propelled micromotors [152–154]. It utilizes the chemical fuels presented in the GI tract such as the acids and enzymes to generate autonomous motion [155]. The strategy is essentially inspired by the ability of some bacteria to navigate and penetrate the stomach mucosa [156]. Walker *et al.* reported the utilization of urease-functionalized micropropellers to penetrate and manipulate the local structure and rheology of mucin gels similar to the function of *H. pylori* [156]. Wang and coworkers then developed a magnesium loaded mucoadhesive polymer particles that propel and distribute themselves in the acid media and stick to the stomach wall in order to deliver the antibiotic drug, clarithromycin (748 g/mol) [157]. While these proof-of-concept studies are interesting, it remains to be determined how effective these innovative technologies will be in improving the oral bioavailability of peptide- and protein-based drugs.

## 4. General considerations for clinical translation

### *4.1. Efficacy and robustness*

One of the advantages of physical methods is their potential to achieve higher oral bioavailability compared to formulations relying on biological or chemical strategies, which typically lead to only around 1% bioavailability for peptide drugs. Techniques involving microneedles and ultrasounds can produce systemic exposures in the same order of magnitude as parenteral routes. However, with the exception of the capsules developed by Rani Therapeutics, these strategies have generally been evaluated upon the direct deposition of the device onto the GI mucosa through a delivery tube guided by an endoscope. There is currently a lack of evidence that a swallowed formulation would achieve the same level of efficacy in large animal models. The biochemical and physiological variability of the GI tract may represent a major obstacle for reproducibility and robustness of these formulations and devices. Furthermore, most of the preclinical studies were performed in the fasted state, and thus the influence of diet contents has been largely neglected. Specific time points for drug administration may be necessary to avoid the food interference, which might reduce the compliance.

### *4.2. Production and cost*

The commercial manufacturing of a functional and patient-friendly formulation is another challenge associated with this type of devices, since multiple materials and processes are often involved. For example, due to the physiological constraints of the GI tract, large capsules may not be able to easily pass the pylori, adding manufacturing constraints related to the miniaturization of the device. Moreover, due to the inclusion of different functional parts that occupy significant volume in an oral capsule, the drug-loading capacity of these systems is often limited, restricting their suitability to highly potent compounds. Complex manufacturing techniques such as microfabrication and multi-layer coatings are also often used, which may increase the production costs and difficulties in scale-up. Therefore, even if high bioavailability can be achieved, it will have to be determined whether these technologies can become cost-effective compared to other approaches, such as formulations containing permeation enhancers or sustained release parenteral systems.

### *4.3. Safety and regulatory considerations*

So far, several of the permeation enhancers utilized in clinical trials are also used as food additives or have the GRAS status (generally regarded as safe) from FDA, which accelerated their regulatory assessment. For physical force based devices, new safety guidelines would have to be established and their safety profiles would need to be examined carefully before they reach the market. For example, it should be systematically evaluated to what extent the mucosal barrier is breached, and what is the time required for the recovery. The in-depth examination of the toxicity profiles is in general lacking for most of these novel devices, e.g. iontophoresis, gas empowered systems, ultrasounds, etc. Furthermore, compared to transdermal formulations, the disinfection of the application site is almost impossible in the GI tract. Due to the general permeation enhancing effects of these physical methods, risks related to the repeated systemic exposure of pathogens and antigens cannot be excluded. Concerns regarding the repeated application should therefore be addressed in long term studies. This requires, among others, a better understanding of mechanobiology applied to epithelial tissues so that the permeation enhancement effects with these novel strategies can be better characterized. Finally, there is a lack of standardized evaluation criteria for these unconventional formulations, for example, in terms of the device transport in the GI tract, degradation, elimination, and toxicity. Such considerations have to be fully assessed in order to allow the commercial development of these promising technologies.

## 5. Conclusions and perspectives

In summary, leveraging physical methods to improve the oral absorption of poorly-permeable APIs has become an exciting research field with new techniques rapidly emerging. The growing progresses in material science and fabrication methods have allowed formulation scientists to explore novel concepts to overcome physiological barriers with numerous advantages. First of all, some of the mechanical force-based techniques possess great potential in achieving bioavailability comparable to those of parenteral routes. This is especially important for macromolecular drugs such as peptides and proteins, that are poorly absorbed even in the presence of permeation enhancers. Moreover, the analysis of the response of GI tissues to physical stimuli is also of great fundamental interest. A better understanding of the associated mechano-physiology could enable more rational designs of novel devices while minimizing toxicity and related safety concerns. Furthermore, compared to traditional chemical or biological strategies, physical methods allow more precise controls over the release of the drugs, e.g. enhanced retention, localized and spatial/site-specific delivery. Even smarter and more personalized devices could be envisioned in the future with these technologies. However, currently most of these methods are still in the proof-of-concept and pre-clinical stages. There are still numerous challenges that need to be addressed to allow their clinical translation. As discussed in this review, the joint efforts among formulation, material manufacturing, regulatory, and clinical trial design experts are of great importance for the success of this highly interdisciplinary field.

## Acknowledgements

Z.L. is grateful for the financial support from the ETH Zurich Postdoctoral Fellowship program. N.P. acknowledges funding

support by the Swiss National Science Foundation (Sinergia No. 177178). The authors thank Yulia Yuts, Elita Montanari and Michael Burger for proofreading of the manuscript.

## References


[1] E. Moroz, S. Matoori, J.-C. Leroux, Oral delivery of macromolecular drugs: Where we are after almost 100 years of attempts, Adv. Drug Deliv. Rev. 101 (2016) 108–121, https://doi.org/10.1016/j.addr.2016.01.010.

[2] M. Koziolek, M. Grimm, F. Schneider, P. Jedamzik, M. Sager, J.-P. Kühn, W. Siegmund, W. Weitschies, Navigating the human gastrointestinal tract for oral drug delivery: Uncharted waters and new frontiers, Adv. Drug Deliv. Rev. 101 (2016) 75–88, https://doi.org/10.1016/j.addr.2016.03.009.

[3] A. Dahan, A. Beig, D. Lindley, J.M. Miller, The solubility–permeability interplay and oral drug formulation design: Two heads are better than one, Adv. Drug Deliv. Rev. 101 (2016) 99–107, https://doi.org/10.1016/j.addr.2016.04.018.

[4] J.D. Schulz, M. Patt, S. Basler, H. Kries, D. Hilvert, M.A. Gauthier, J.-C. Leroux, Site-specific polymer conjugation stabilizes therapeutic enzymes in the gastrointestinal tract, Adv. Mater. 28 (2016) 1455–1460, https://doi.org/10.1002/adma.201504797.

[5] D.J. Drucker, Advances in oral peptide therapeutics, Nat. Rev. Drug Discov. 19 (2020) 277–289, https://doi.org/10.1038/s41573-019-0053-0.

[6] T.D. Brown, K.A. Whitehead, S. Mitragotri, Materials for oral delivery of proteins and peptides, Nat. Rev. Mater. 5 (2020) 127–148, https://doi.org/10.1038/s41578-019-0156-6.

[7] P. Lundquist, P. Artursson, Oral absorption of peptides and nanoparticles across the human intestine: Opportunities, limitations and studies in human tissues, Adv. Drug Deliv. Rev. 106 (2016) 256–276, https://doi.org/10.1016/j.addr.2016.07.007.

[8] S.T. Buckley, T.A. Bækdal, A. Vegge, S.J. Maarbjerg, C. Pyke, J. Ahnfelt-Rønne, K. G. Madsen, S.G. Schéele, T. Alanentalo, R.K. Kirk, B.L. Pedersen, R.B. Skyggebjerg, A.J. Benie, H.M. Strauss, P.-O. Wahlund, S. Bjerregaard, E. Farkas, C. Fekete, F.L. Søndergaard, J. Borregaard, M.-L. Hartoft-Nielsen, L.B. Knudsen, Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist, Sci. Transl. Med. 10 (2018) eaar7047, https://doi.org/10.1126/scitranslmed.aar7047.

[9] C. Twarog, S. Fattah, J. Heade, S. Maher, E. Fattal, D.J. Brayden, Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10), Pharmaceutics. 11 (2019) 78, https://doi.org/10.3390/pharmaceutics11020078.

[10] J.D. Schulz, M.A. Gauthier, J.-C. Leroux, Improving oral drug bioavailability with polycations?, Eur. J. Pharm. Biopharm. 97 (2015) 427–437, https://doi.org/10.1016/j.ejpb.2015.04.025.

[11] R.F. Beall, T.J. Hwang, A.S. Kesselheim, Pre-market development times for biologic versus small-molecule drugs, Nat. Biotechnol. 37 (2019) 708–711, https://doi.org/10.1038/s41587-019-0175-2.

[12] A. Henninot, J.C. Collins, J.M. Nuss, The Current State of Peptide Drug Discovery: Back to the Future?, J. Med. Chem. 61 (2018) 1382–1414, https://doi.org/10.1021/acs.jmedchem.7b00318.

[13] S.D. Edmondson, B. Yang, C. Fallan, Proteolysis targeting chimeras (PROTACs) in 'beyond rule-of-five' chemical space: Recent progress and future challenges, Bioorg. Med. Chem. Lett. 29 (2019) 1555–1564, https://doi.org/10.1016/j.bmcl.2019.04.030.

[14] D.C. Forbes, N.A. Peppas, Oral delivery of small RNA and DNA, J. Control. Release. 162 (2012) 438–445, https://doi.org/10.1016/j.jconrel.2012.06.037.

[15] B.C. Doak, B. Over, F. Giordanetto, J. Kihlberg, Oral Druggable Space beyond the Rule of 5: Insights from Drugs and Clinical Candidates, Chem. Biol. 21 (2014) 1115–1142, https://doi.org/10.1016/j.chembiol.2014.08.013.

[16] G. KolataOLA, FDA Speeds Approval of Cyclosporin, Science (80-.). 221 (1983) 1273–1273. https://doi.org/10.1126/science.221.4617.1273-a.

[17] D.W. Richardson, A.G. Robinson, Drugs Five Years Later: Desmopressin, Ann. Intern. Med. 103 (1985) 228–239, https://doi.org/10.7326/0003-4819-103-2-228.

[18] S. Sant, S.L. Tao, O.Z. Fisher, Q. Xu, N.A. Peppas, A. Khademhosseini, Microfabrication technologies for oral drug delivery, Adv. Drug Deliv. Rev. 64 (2012) 496–507, https://doi.org/10.1016/j.addr.2011.11.013.

[19] L.A. Sharpe, A.M. Daily, S.D. Horava, N.A. Peppas, Therapeutic applications of hydrogels in oral drug delivery, Expert Opin. Drug Deliv. 11 (2014) 901–915, https://doi.org/10.1517/17425247.2014.902047.

[20] E.M. Pridgen, F. Alexis, O.C. Farokhzad, Polymeric nanoparticle drug delivery technologies for oral delivery applications, Expert Opin. Drug Deliv. 12 (2015) 1459–1473, https://doi.org/10.1517/17425247.2015.1018175.

[21] S. Maher, R.J. Mrsny, D.J. Brayden, Intestinal permeation enhancers for oral peptide delivery, Adv. Drug Deliv. Rev. 106 (2016) 277–319, https://doi.org/10.1016/j.addr.2016.06.005.

[22] D.J. Brayden, T.A. Hill, D.P. Fairlie, S. Maher, R.J. Mrsny, Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches, Adv. Drug Deliv. Rev. 157 (2020) 2–36, https://doi.org/10.1016/j.addr.2020.05.007.

[23] S. Tuvia, J. Atsmon, S.L. Teichman, S. Katz, P. Salama, D. Pelled, I. Landau, I. Karmeli, M. Bidlingmaier, C.J. Strasburger, D.L. Kleinberg, S. Melmed, R. Mamluk, Oral Octreotide Absorption in Human Subjects: Comparable Pharmacokinetics to Parenteral Octreotide and Effective Growth Hormone Suppression, J. Clin. Endocrinol. Metab. 97 (2012) 2362–2369, https://doi.org/10.1210/jc.2012-1179.

[24] G. Traverso, A.R. Kirtane, C.M. Schoellhammer, R. Langer, Convergence for Translation: Drug-Delivery Research in Multidisciplinary Teams, Angew. Chemie Int. Ed. 57 (2018) 4156–4163, https://doi.org/10.1002/anie.201712512.

[25] R. Yang, T. Wei, H. Goldberg, W. Wang, K. Cullion, D.S. Kohane, Getting Drugs Across Biological Barriers, Adv. Mater. 29 (2017) 1606596, https://doi.org/10.1002/adma.201606596.

[26] D. Vllasaliu, M. Thanou, S. Stolnik, R. Fowler, Recent advances in oral delivery of biologics: nanomedicine and physical modes of delivery, Expert Opin. Drug Deliv. 15 (2018) 759–770, https://doi.org/10.1080/17425247.2018.1504017.

[27] M. Vancamelbeke, S. Vermeire, The intestinal barrier: a fundamental role in health and disease, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 821–834, https://doi.org/10.1080/17474124.2017.1343143.

[28] H. Batchelor, Bioadhesive Dosage Forms for Esophageal Drug Delivery, Pharm. Res. 22 (2005) 175–181, https://doi.org/10.1007/s11095-004-1183-5.

[29] M. Goldberg, I. Gomez-Orellana, Challenges for the oral delivery of macromolecules, Nat. Rev. Drug Discov. 2 (2003) 289–295, https://doi.org/10.1038/nrd1067.

[30] S. Khonsary, Guyton and Hall: Textbook of Medical Physiology, Surg. Neurol. Int. 8 (2017) 275, https://doi.org/10.4103/sni.sni_327_17.

[31] K. Windey, V. De Preter, K. Verbeke, Relevance of protein fermentation to gut health, Mol. Nutr. Food Res. 56 (2012) 184–196, https://doi.org/10.1002/mnfr.201100542.

[32] L.M. Ensign, R. Cone, J. Hanes, Oral drug delivery with polymeric nanoparticles: The gastrointestinal mucus barriers, Adv. Drug Deliv. Rev. 64 (2012) 557–570, https://doi.org/10.1016/j.addr.2011.12.009.

[33] R.A. Cone, Barrier properties of mucus, Adv. Drug Deliv. Rev. 61 (2009) 75–85, https://doi.org/10.1016/j.addr.2008.09.008.

[34] B.H. Bajka, N.M. Rigby, K.L. Cross, A. Macierzanka, A.R. Mackie, The influence of small intestinal mucus structure on particle transport ex vivo, Colloids Surfaces B Biointerfaces. 135 (2015) 73–80, https://doi.org/10.1016/j.colsurfb.2015.07.038.

[35] L. Krupa, B. Bajka, R. Staroń, D. Dupont, H. Singh, K. Gutkowski, A. Macierzanka, Comparing the permeability of human and porcine small intestinal mucus for particle transport studies, Sci. Rep. 10 (2020) 20290, https://doi.org/10.1038/s41598-020-77129-4.

[36] M. Abdulkarim, N. Agulló, B. Cattoz, P. Griffiths, A. Bernkop-Schnürch, S.G. Borros, M. Gumbleton, Nanoparticle diffusion within intestinal mucus: Three-dimensional response analysis dissecting the impact of particle surface charge, size and heterogeneity across polyelectrolyte, pegylated and viral particles, Eur. J. Pharm. Biopharm. 97 (2015) 230–238, https://doi.org/10.1016/j.ejpb.2015.01.023.

[37] M. Boegh, H.M. Nielsen, Mucus as a Barrier to Drug Delivery - Understanding and Mimicking the Barrier Properties, Basic Clin. Pharmacol. Toxicol. 116 (2015) 179–186, https://doi.org/10.1111/bcpt.12342.

[38] S.K. Lai, Y.-Y. Wang, J. Hanes, Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues, Adv. Drug Deliv. Rev. 61 (2009) 158–171, https://doi.org/10.1016/j.addr.2008.11.002.

[39] M. Copeman, J. Matuz, A.J. Leonard, J.P. Pearson, P.W. Dettmar, A. Allen, The gastroduodenal mucus barrier and its role in protection against luminal pepsins: The effect of 16,16 dimethyl prostaglandin E 2, carbopol-polyacrylate, sucralfate and bismuth subsalicylate, J. Gastroenterol. Hepatol. 9 (1994) S55–S59, https://doi.org/10.1111/j.1440-1746.1994.tb01303.x.

[40] M.E.V. Johansson, J.M.H. Larsson, G.C. Hansson, The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions, Proc. Natl. Acad. Sci. 108 (2011) 4659–4665, https://doi.org/10.1073/pnas.1006451107.

[41] M.E.V. Johansson, H. Sjövall, G.C. Hansson, The gastrointestinal mucus system in health and disease, Nat. Rev. Gastroenterol. Hepatol. 10 (2013) 352–361, https://doi.org/10.1038/nrgastro.2013.35.

[42] R.D. Pullan, G.A.O. Thomas, M. Rhodes, R.G. Newcombe, G.T. Williams, A. Allen, J. Rhodes, Thickness of adherent mucus gel on colonic mucosa in humans and its relevance to colitis, Gut. 35 (1994) 353–359, https://doi.org/10.1136/gut.35.3.353.

[43] X. Murgia, B. Loretz, O. Hartwig, M. Hittinger, C.-M. Lehr, The role of mucus on drug transport and its potential to affect therapeutic outcomes, Adv. Drug Deliv. Rev. 124 (2018) 82–97, https://doi.org/10.1016/j.addr.2017.10.009.

[44] A. Frey, K.T. Giannasca, R. Weltzin, P.J. Giannasca, H. Reggio, W.I. Lencer, M.R. Neutra, Role of the glycocalyx in regulating access of microparticles to apical plasma membranes of intestinal epithelial cells: implications for microbial attachment and oral vaccine targeting, J. Exp. Med. 184 (1996) 1045–1059, https://doi.org/10.1084/jem.184.3.1045.

[45] M. Shakweh, G. Ponchel, E. Fattal, Particle uptake by Peyer's patches: a pathway for drug and vaccine delivery, Expert Opin. Drug Deliv. 1 (2004) 141–163, https://doi.org/10.1517/17425247.1.1.141.

[46] A. des Rieux, V. Fievez, M. Garinot, Y.J. Schneider, V. Préat, Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach, J. Control. Release. 116 (2006) 1–27, https://doi.org/10.1016/j.jconrel.2006.08.013.

[47] N.N. Salama, N.D. Eddington, A. Fasano, Tight junction modulation and its relationship to drug delivery, Adv. Drug Deliv. Rev. 58 (2006) 15–28, https://doi.org/10.1016/J.ADDR.2006.01.003.

[48] T.Y. Ma, M.A. Boivin, D. Ye, A. Pedram, H.M. Said, Mechanism of TNF-α modulation of Caco-2 intestinal epithelial tight junction barrier: role of

myosin light-chain kinase protein expression, Am. J. Physiol. Liver Physiol. 288 (2005) G422–G430, https://doi.org/10.1152/ajpgi.00412.2004.
[49] L. Shen, C.R. Weber, D.R. Raleigh, D. Yu, J.R. Turner, Tight Junction Pore and Leak Pathways: A Dynamic Duo, Annu. Rev. Physiol. 73 (2011) 283–309, https://doi.org/10.1146/annurev-physiol-012110-142150.
[50] A.-L. Le Roux, X. Quiroga, N. Walani, M. Arroyo, P. Roca-Cusachs, The plasma membrane as a mechanochemical transducer, Philos. Trans. R. Soc. B Biol. Sci. 374 (2019) 20180221, https://doi.org/10.1098/rstb.2018.0221.
[51] G. Samak, R. Gangwar, L.M. Crosby, L.P. Desai, K. Wilhelm, C.M. Waters, R. Rao, Cyclic stretch disrupts apical junctional complexes in Caco-2 cell monolayers by a JNK-2-, c-Src-, and MLCK-dependent mechanism, Am. J. Physiol. Liver Physiol. 306 (2014) G947–G958, https://doi.org/10.1152/ajpgi.00396.2013.
[52] L. Shen, J.R. Turner, Actin Depolymerization Disrupts Tight Junctions via Caveolae-mediated Endocytosis, Mol. Biol. Cell. 16 (2005) 3919–3936, https://doi.org/10.1091/mbc.e04-12-1089.
[53] A. Colom, E. Derivery, S. Soleimanpour, C. Tomba, M.D. Molin, N. Sakai, M. González-Gaitán, S. Matile, A. Roux, A fluorescent membrane tension probe, Nat. Chem. 10 (2018) 1118–1125, https://doi.org/10.1038/s41557-018-0127-3.
[54] J.L. Fisher, I. Levitan, S.S. Margulies, Plasma Membrane Surface Increases with Tonic Stretch of Alveolar Epithelial Cells, Am. J. Respir. Cell Mol. Biol. 31 (2004) 200–208, https://doi.org/10.1165/rcmb.2003-0224OC.
[55] X. Trepat, L. Deng, S.S. An, D. Navajas, D.J. Tschumperlin, W.T. Gerthoffer, J.P. Butler, J.J. Fredberg, Universal physical responses to stretch in the living cell, Nature. 447 (2007) 592–595, https://doi.org/10.1038/nature05824.
[56] C. Twarog, F. McCartney, S.M. Harrison, B. Illel, E. Fattal, D.J. Brayden, Comparison of the effects of the intestinal permeation enhancers, SNAC and sodium caprate (C10): Isolated rat intestinal mucosae and sacs, Eur. J. Pharm. Sci. 158 (2021), https://doi.org/10.1016/j.ejps.2020.105685 105685.
[57] F. McCartney, J.P. Gleeson, D.J. Brayden, Safety concerns over the use of intestinal permeation enhancers: A mini-review, Tissue Barriers. 4 (2016), https://doi.org/10.1080/21688370.2016.1176822 e1176822.
[58] T.W. Leonard, J. Lynch, M.J. McKenna, D.J. Brayden, Promoting absorption of drugs in humans using medium-chain fatty acid-based solid dosage forms: GIPET™, Expert Opin. Drug Deliv. 3 (2006) 685–692, https://doi.org/10.1517/17425247.3.5.685.
[59] H. Lee, C. Song, S. Baik, D. Kim, T. Hyeon, D.-H. Kim, Device-assisted transdermal drug delivery, Adv. Drug Deliv. Rev. 127 (2018) 35–45, https://doi.org/10.1016/j.addr.2017.08.009.
[60] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 26 (2008) 1261–1268, https://doi.org/10.1038/nbt.1504.
[61] B. Laulicht, N.J. Gidmark, A. Tripathi, E. Mathiowitz, Localization of magnetic pills, Proc. Natl. Acad. Sci. 108 (2011) 2252–2257, https://doi.org/10.1073/pnas.1016367108.
[62] J.F. Schenck, Physical interactions of static magnetic fields with living tissues, Prog. Biophys. Mol. Biol. 87 (2005) 185–204, https://doi.org/10.1016/j.pbiomolbio.2004.08.009.
[63] L.H. Reddy, J.L. Arias, J. Nicolas, P. Couvreur, Magnetic Nanoparticles: Design and Characterization, Toxicity and Biocompatibility, Pharmaceutical and Biomedical Applications, Chem. Rev. 112 (2012) 5818–5878, https://doi.org/10.1021/cr300068p.
[64] R. Ito, Y. Machida, T. Sannan, T. Nagai, Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration, Int. J. Pharm. 61 (1990) 109–117, https://doi.org/10.1016/0378-5173(90)90049-A.
[65] J. Fujimori, Y. Machida, S. Tanaka, T. Nagai, Effect of magnetically controlled gastric residence of sustained release tablets on bioavailability of acetaminophen, Int. J. Pharm. 119 (1995) 47–55, https://doi.org/10.1016/0378-5173(94)00368-F.
[66] R. Gröning, M. Berntgen, Estimation of the gastric residence time of magnetic dosage forms using the Heidelberg capsule, Pharmazie. 51 (1996) 328–331.
[67] R. Groning, M. Werner, M. Berntgen, M. Georgarakis, Peroral controlled release dosage forms with internal magnets and extracorporal magnetic guidance investigations into the renal elimination of ribofiavin, Eur. J. Pharm. Biopharm. 42 (1996) 25–28.
[68] R. Gröning, M. Berntgen, M. Georgarakis, Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit, Eur. J. Pharm. Biopharm. 46 (1998) 285–291, https://doi.org/10.1016/S0939-6411(98)00052-6.
[69] O.L. Laskin, Clinical Pharmacokinetics of Acyclovir, Clin. Pharmacokinet. 8 (1983) 187–201, https://doi.org/10.2165/00003088-198308030-00001.
[70] H. Chen, R. Langer, Magnetically-responsive polymerized liposomes as potential oral delivery vehicles, Pharm. Res. 14 (1997) 537–540, https://doi.org/10.1023/A:1012124205524.
[71] J. Cheng, B.A. Teply, S.Y. Jeong, C.H. Yim, D. Ho, I. Sherifi, S. Jon, O.C. Farokhzad, A. Khademhosseini, R.S. Langer, Magnetically Responsive Polymeric Microparticles for Oral Delivery of Protein Drugs, Pharm. Res. 23 (2006) 557–564, https://doi.org/10.1007/s11095-005-9444-5.
[72] A. Seth, D. Lafargue, C. Poirier, T. Badier, N. Delory, A. Laporte, J.-M. Delbos, V. Jeannin, J.-M. Péan, C. Ménager, Optimization of magnetic retention in the gastrointestinal tract: Enhanced bioavailability of poorly permeable drug, Eur. J. Pharm. Sci. 100 (2017) 25–35, https://doi.org/10.1016/j.ejps.2016.12.022.
[73] A. Seth, D. Lafargue, C. Poirier, J.-M. Péan, C. Ménager, Performance of magnetic chitosan–alginate core–shell beads for increasing the bioavailability of a low permeable drug, Eur. J. Pharm. Biopharm. 88 (2014) 374–381, https://doi.org/10.1016/j.ejpb.2014.05.017.
[74] B.A. Teply, R. Tong, S.Y. Jeong, G. Luther, I. Sherifi, C.H. Yim, A. Khademhosseini, O.C. Farokhzad, R.S. Langer, J. Cheng, The use of charge-coupled polymeric microparticles and micromagnets for modulating the bioavailability of orally delivered macromolecules, Biomaterials. 29 (2008) 1216–1223, https://doi.org/10.1016/j.biomaterials.2007.11.018.
[75] P.L. Bardonnet, V. Faivre, W.J. Pugh, J.C. Piffaretti, F. Falson, Gastroretentive dosage forms: Overview and special case of Helicobacter pylori, J. Control. Release. 111 (2006) 1–18, https://doi.org/10.1016/j.jconrel.2005.10.031.
[76] B. Laulicht, A. Tripathi, V. Schlageter, P. Kucera, E. Mathiowitz, Understanding gastric forces calculated from high-resolution pill tracking, Proc. Natl. Acad. Sci. 107 (2010) 8201–8206, https://doi.org/10.1073/pnas.1002292107.
[77] A.S. Lübbe, C. Alexiou, C. Bergemann, Clinical applications of magnetic drug targeting, J. Surg. Res. 95 (2001) 200–206, https://doi.org/10.1006/jsre.2000.6030.
[78] P.M. Price, W.E. Mahmoud, A.A. Al-Ghamdi, L.M. Bronstein, Magnetic Drug Delivery: Where the Field Is Going, Front. Chem. 6 (2018) 619, https://doi.org/10.3389/fchem.2018.00619.
[79] F.A. Dorkoosh, J.C. Verhoef, G. Borchard, M. Rafiee-Tehrani, H.E. Junginger, Development and characterization of a novel peroral peptide drug delivery system, J. Control. Release. 71 (2001) 307–318, https://doi.org/10.1016/S0168-3659(01)00232-2.
[80] F.A. Dorkoosh, C.A.N. Broekhuizen, G. Borchard, M. Rafiee-Tehrani, J.C. Verhoef, H.E. Junginger, Transport of Octreotide and Evaluation of Mechanism of Opening the Paracellular Tight Junctions using Superporous Hydrogel Polymers in Caco-2 Cell Monolayers, J. Pharm. Sci. 93 (2004) 743–752, https://doi.org/10.1002/jps.10570.
[81] F.A. Dorkoosh, D. Setyaningsih, G. Borchard, M. Rafiee-Tehrani, J.C. Verhoef, H. E. Junginger, Effects of superporous hydrogels on paracellular drug permeability and cytotoxicity studies in Caco-2 cell monolayers, Int. J. Pharm. 241 (2002) 35–45, https://doi.org/10.1016/S0378-5173(02)00115-1.
[82] F.A. Dorkoosh, G. Borchard, M. Rafiee-Tehrani, J.C. Verhoef, H.E. Junginger, Evaluation of superporous hydrogel (SPH) and SPH composite in porcine intestine ex-vivo: assessment of drug transport, morphology effect, and mechanical fixation to intestinal wall, Eur. J. Pharm. Biopharm. 53 (2002) 161–166, https://doi.org/10.1016/S0939-6411(01)00222-3.
[83] F. Dorkoosh, J. Verhoef, G. Borchard, M. Rafiee-Tehrani, J.H. Verheijden, H. Junginger, Intestinal absorption of human insulin in pigs using delivery systems based on superporous hydrogel polymers, Int. J. Pharm. 247 (2002) 47–55, https://doi.org/10.1016/S0378-5173(02)00361-7.
[84] F.A. Dorkoosh, J.C. Verhoef, J.H.M. Verheijden, M. Rafiee-Tehrani, G. Borchard, H.E. Junginger, Peroral absorption of octreotide in pigs formulated in delivery systems on the basis of superporous hydrogel polymers, Pharm. Res. 19 (2002) 1532–1536, https://doi.org/10.1023/A:1020416918624.
[85] F.A. Dorkoosh, M.P.M. Stokkel, D. Blok, G. Borchard, M. Rafiee-Tehrani, J.C. Verhoef, H.E. Junginger, Feasibility study on the retention of superporous hydrogel composite polymer in the intestinal tract of man using scintigraphy, J. Control. Release. 99 (2004) 199–206, https://doi.org/10.1016/j.jconrel.2004.06.012.
[86] J. Chen, H. Park, K. Park, Synthesis of superporous hydrogels: Hydrogels with fast swelling and superabsorbent properties, J. Biomed. Mater. Res. 44 (1999) 53–62, https://doi.org/10.1002/(SICI)1097-4636(199901)44:1<53::AID-JBM6>3.0.CO;2-W.
[87] J. Warren, F.A. Ziherl, A.W. Kish, L.A. Ziherl, Large-scale administration of vaccines by means of an automatic jet injection syringe, J. Am. Med. Assoc. 157 (1955) 633–637, https://doi.org/10.1001/jama.1955.02950250007003.
[88] T. Kanazawa, Y. Takashima, T. Tamura, M. Tsuchiya, Y. Shibata, H. Udagawa, H. Okada, Local gene expression and immune responses of vaginal DNA vaccination using a needle-free injector, Int. J. Pharm. 396 (2010) 11–16, https://doi.org/10.1016/j.ijpharm.2010.05.040.
[89] N.N. Dabarakis, V. Alexander, A.T. Tsirlis, N.A. Parissis, M. Nikolaos, Needle-less local anesthesia: Clinical evaluation of the effectiveness of the jet anesthesia Injex in local anesthesia in dentistry, Quintessence Int, (Berl) 38 (2007) 881.
[90] G. Bernstein, Delivery of insulin to the buccal mucosa utilizing the RapidMist™ system, Expert Opin. Drug Deliv. 5 (2008) 1047–1055, https://doi.org/10.1517/17425247.5.9.1047.
[91] M. Bansal, S. Bansal, R. Kumria, The RapidMist™ system for buccal delivery of insulin, in: Mucosal Deliv. Biopharm., Springer US, Boston, MA, 2014, pp. 423–436, https://doi.org/10.1007/978-1-4614-9524-6_19.
[92] S. Cernea, M. Kidron, J. Wohlgelernter, P. Modi, I. Raz, Dose-Response Relationship of Oral Insulin Spray in Healthy Subjects, Diabetes Care. 28 (2005) 1353–1357, https://doi.org/10.2337/diacare.28.6.1353.
[93] S. Cernea, M. Kidron, J. Wohlgelernter, P. Modi, I. Raz, Comparison of pharmacokinetic and pharmacodynamic properties of single-dose oral insulin spray and subcutaneous insulin injection in healthy subjects using the euglycemic clamp technique, Clin. Ther. 26 (2004) 2084–2091, https://doi.org/10.1016/j.clinthera.2004.12.001.
[94] P. Modi, M. Mihic, A. Lewin, The evolving role of oral insulin in the treatment of diabetes using a novel RapidMist™ System, Diabetes. Metab. Res. Rev. 18 (2002) S38–S42, https://doi.org/10.1002/dmrr.208.
[95] K. Aran, M. Chooljian, J. Paredes, M. Rafi, K. Lee, A.Y. Kim, J. An, J.F. Yau, H. Chum, I. Conboy, N. Murthy, D. Liepmann, An oral microjet vaccination system elicits antibody production in rabbits, Sci. Transl. Med. 9 (2017) eaaf6413, https://doi.org/10.1126/scitranslmed.aaf6413.

[96] A.M.M. Sadeghi, M.R. Avadi, S. Ejtemaimehr, S. Abashzadeh, A. Partoazar, F. Dorkoosh, M. Faghihi, M. Rafiee-Tehrani, H.E. Junginger, Development of a Gas Empowered Drug Delivery system for peptide delivery in the small intestine, J. Control. Release. 134 (2009) 11–17, https://doi.org/10.1016/j.jconrel.2008.10.012.
[97] J.D. Eichman, J.R. Robinson, Mechanistic studies on effervescent-induced permeability enhancement, Pharm. Res. 15 (1998) 925–930, https://doi.org/10.1023/A:1011936901638.
[98] L. Wang, X. Tang, A novel ketoconazole bioadhesive effervescent tablet for vaginal delivery: Design, in vitro and 'in vivo' evaluation, Int. J. Pharm. 350 (2008) 181–187, https://doi.org/10.1016/j.ijpharm.2007.08.042.
[99] S. Shambhavi, R. Bagga, P. Bansal, J. Kalra, P. Kumar, A randomised trial to compare 200 mg micronised progesterone effervescent vaginal tablet daily with 250 mg intramuscular 17 alpha hydroxy progesterone caproate weekly for prevention of recurrent preterm birth, J. Obstet. Gynaecol. 38 (2018) 800–806, https://doi.org/10.1080/01443615.2018.1425380.
[100] M. Lazzaroni, V. Casini, G. Bianchi Porro, Role or Carbon Dioxide-Releasing Suppositories in the Treatment of Chronic Functional Constipation, Clin. Drug Investig. 25 (2005) 499–505, https://doi.org/10.2165/00044011-200525080-00002.
[101] G. Di Girolamo, J.A.W. Opezzo, M.I. Lopez, D. Schere, G. Keller, C.D. Gonzalez, J. M. Massa, M.C. de los Santos, Relative bioavailability of new formulation of paracetamol effervescent powder containing sodium bicarbonate versus paracetamol tablets: a comparative pharmacokinetic study in fed subjects, Expert Opin. Pharmacother. 8 (2007) 2449–2457, https://doi.org/10.1517/14656566.8.15.2449.
[102] M. Darwish, E. Hamed, J. Messina, Fentanyl buccal tablet for the treatment of breakthrough pain: pharmacokinetics of buccal mucosa delivery and clinical efficacy, Perspect. Medicin. Chem. 4 (2010) 11–21, https://doi.org/10.4137/pmc.s3928.
[103] A. Ahmed, C. Bonner, T.A. Desai, Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery, J. Control. Release. 81 (2002) 291–306, https://doi.org/10.1016/S0168-3659(02)00074-3.
[104] K.M. Ainslie, R.D. Lowe, T.T. Beaudette, L. Petty, E.M. Bachelder, T.A. Desai, Microfabricated Devices for Enhanced Bioadhesive Drug Delivery: Attachment to and Small-Molecule Release Through a Cell Monolayer Under Flow, Small. 5 (2009) 2857–2863, https://doi.org/10.1002/smll.200901254.
[105] H.D. Chirra, L. Shao, N. Ciaccio, C.B. Fox, J.M. Wade, A. Ma, T.A. Desai, Planar Microdevices for Enhanced In Vivo Retention and Oral Bioavailability of Poorly Permeable Drugs, Adv. Healthc. Mater. 3 (2014) 1648–1654, https://doi.org/10.1002/adhm.201300676.
[106] C. Mazzoni, F. Tentor, S.A. Strindberg, L.H. Nielsen, S.S. Keller, T.S. Alstrøm, C. Gundlach, A. Müllertz, P. Marizza, A. Boisen, From concept to in vivo testing: Microcontainers for oral drug delivery, J. Control. Release. 268 (2017) 343–351, https://doi.org/10.1016/j.jconrel.2017.10.013.
[107] J.R. Jørgensen, L.H.E. Thamdrup, K. Kamguyan, L.H. Nielsen, H.M. Nielsen, A. Boisen, T. Rades, A. Müllertz, Design of a self-unfolding delivery concept for oral administration of macromolecules, J. Control. Release. (2020), https://doi.org/10.1016/j.jconrel.2020.10.024.
[108] L.H. Nielsen, A. Melero, S.S. Keller, J. Jacobsen, T. Garrigues, T. Rades, A. Müllertz, A. Boisen, Polymeric microcontainers improve oral bioavailability of furosemide, Int. J. Pharm. 504 (2016) 98–109, https://doi.org/10.1016/j.ijpharm.2016.03.050.
[109] L.H. Nielsen, S.S. Keller, K.C. Gordon, A. Boisen, T. Rades, A. Müllertz, Spatial confinement can lead to increased stability of amorphous indomethacin, Eur. J. Pharm. Biopharm. 81 (2012) 418–425, https://doi.org/10.1016/j.ejpb.2012.03.017.
[110] L.H. Nielsen, T. Rades, B. Boyd, A. Boisen, Microcontainers as an oral delivery system for spray dried cubosomes containing ovalbumin, Eur. J. Pharm. Biopharm. 118 (2017) 13–20, https://doi.org/10.1016/j.ejpb.2016.12.008.
[111] C. Mazzoni, R.D. Jacobsen, J. Mortensen, J.R. Jørgensen, L. Vaut, J. Jacobsen, C. Gundlach, A. Müllertz, L.H. Nielsen, A. Boisen, Polymeric Lids for Microcontainers for Oral Protein Delivery, Macromol. Biosci. 19 (2019) 1900004, https://doi.org/10.1002/mabi.201900004.
[112] J.R. Jørgensen, F. Yu, R. Venkatasubramanian, L.H. Nielsen, H.M. Nielsen, A. Boisen, T. Rades, A. Müllertz, In Vitro, Ex Vivo and In Vivo Evaluation of Microcontainers for Oral Delivery of Insulin, Pharmaceutics. 12 (2020) 48, https://doi.org/10.3390/pharmaceutics12010048.
[113] J. Nagstrup, S. Keller, K. Almdal, A. Boisen, 3D microstructuring of biodegradable polymers, Microelectron. Eng. 88 (2011) 2342–2344, https://doi.org/10.1016/j.mee.2010.12.014.
[114] L.H. Nielsen, S.S. Keller, A. Boisen, A. Müllertz, T. Rades, A slow cooling rate of indomethacin melt spatially confined in microcontainers increases the physical stability of the amorphous drug without influencing its biorelevant dissolution behaviour, Drug Deliv. Transl. Res. 4 (2014) 268–274, https://doi.org/10.1007/s13346-013-0166-7.
[115] P. Marizza, S.S. Keller, A. Müllertz, A. Boisen, Polymer-filled microcontainers for oral delivery loaded using supercritical impregnation, J. Control. Release. 173 (2014) 1–9, https://doi.org/10.1016/j.jconrel.2013.09.022.
[116] S.B. Rizwan, W.T. McBurney, K. Young, T. Hanley, B.J. Boyd, T. Rades, S. Hook, Cubosomes containing the adjuvants imiquimod and monophosphoryl lipid A stimulate robust cellular and humoral immune responses, J. Control. Release. 165 (2013) 16–21, https://doi.org/10.1016/j.jconrel.2012.10.020.
[117] C. von Halling Laier, B. Gibson, J.A.S. Moreno, T. Rades, S. Hook, L.H. Nielsen, A. Boisen, Microcontainers for protection of oral vaccines, in vitro and in vivo evaluation, J. Control. Release. 294 (2019) 91–101, https://doi.org/10.1016/j.jconrel.2018.11.030.
[118] J.R. Jørgensen, M.L. Jepsen, L.H. Nielsen, M. Dufva, H.M. Nielsen, T. Rades, A. Boisen, A. Müllertz, Microcontainers for oral insulin delivery – In vitro studies of permeation enhancement, Eur. J. Pharm. Biopharm. 143 (2019) 98–105, https://doi.org/10.1016/j.ejpb.2019.08.011.
[119] S. Saphier, A. Rosner, R. Brandeis, Y. Karton, Gastro intestinal tracking and gastric emptying of solid dosage forms in rats using X-ray imagining, Int. J. Pharm. 388 (2010) 190–195, https://doi.org/10.1016/j.ijpharm.2010.01.001.
[120] Y. Ye, J. Yu, D. Wen, A.R. Kahkoska, Z. Gu, Polymeric microneedles for transdermal protein delivery, Adv. Drug Deliv. Rev. 127 (2018) 106–118, https://doi.org/10.1016/j.addr.2018.01.015.
[121] T. Wang, Y. Zhen, X. Ma, B. Wei, S. Li, N. Wang, Mannosylated and lipid A-incorporating cationic liposomes constituting microneedle arrays as an effective oral mucosal HBV vaccine applicable in the controlled temperature chain, Colloids Surfaces B Biointerfaces. 126 (2015) 520–530, https://doi.org/10.1016/j.colsurfb.2015.01.005.
[122] Y. Zhen, N. Wang, Z. Gao, X. Ma, B. Wei, Y. Deng, T. Wang, Multifunctional liposomes constituting microneedles induced robust systemic and mucosal immunoresponses against the loaded antigens via oral mucosal vaccination, Vaccine. 33 (2015) 4330–4340, https://doi.org/10.1016/j.vaccine.2015.03.081.
[123] J.W. Lee, M.R. Prausnitz, Drug delivery using microneedle patches: not just for skin, Expert Opin. Drug Deliv. 15 (2018) 541–543, https://doi.org/10.1080/17425247.2018.1471059.
[124] C.M. Schoellhammer, R. Langer, G. Traverso, Of microneedles and ultrasound: Physical modes of gastrointestinal macromolecule delivery, Tissue Barriers. 4 (2016), https://doi.org/10.1080/21688370.2016.1150235 e1150235.
[125] G. Traverso, C.M. Schoellhammer, A. Schroeder, R. Maa, G.Y. Lauwers, B.E. Polat, D.G. Anderson, D. Blankschtein, R. Langer, Microneedles for drug delivery via the gastrointestinal tract, J. Pharm. Sci. 104 (2015) 362–367, https://doi.org/10.1002/jps.24182.
[126] A. Abramson, E. Caffarel-Salvador, M. Khang, D. Dellal, D. Silverstein, Y. Gao, M.R. Frederiksen, A. Vegge, F. Hubálek, J.J. Water, A. V. Friderichsen, J. Fels, R. K. Kirk, C. Cleveland, J. Collins, S. Tamang, A. Hayward, T. Landh, S.T. Buckley, N. Roxhed, U. Rahbek, R. Langer, G. Traverso, An ingestible self-orienting system for oral delivery of macromolecules, Science (80-.). 363 (2019) 611–615. https://doi.org/10.1126/science.aau2277.
[127] A. Abramson, E. Caffarel-Salvador, V. Soares, D. Minahan, R.Y. Tian, X. Lu, D. Dellal, Y. Gao, S. Kim, J. Wainer, J. Collins, S. Tamang, A. Hayward, T. Yoshitake, H.-C. Lee, J. Fujimoto, J. Fels, M.R. Frederiksen, U. Rahbek, N. Roxhed, R. Langer, G. Traverso, A luminal unfolding microneedle injector for oral delivery of macromolecules, Nat. Med. 25 (2019) 1512–1518, https://doi.org/10.1038/s41591-019-0598-9.
[128] A.K. Dhalla, Z. Al-Shamsie, S. Beraki, A. Dasari, L.C. Fung, L. Fusaro, A. Garapaty, B. Gutierrez, D. Gratta, M. Hashim, K. Horlen, P. Karamchedu, R. Korupolu, E. Liang, C. Ong, Z. Owyang, V. Salgotra, S. Sharma, B. Syed, M. Syed, A.T. Vo, R. Abdul-Wahab, A. Wasi, A. Yamaguchi, S. Yen, M. Imran, A robotic pill for oral delivery of biotherapeutics: safety, tolerability, and performance in healthy subjects, Drug Deliv, Transl. Res. (2021) 1–12, https://doi.org/10.1007/s13346-021-00938-1.
[129] M. Hashim, R. Korupolu, B. Syed, K. Horlen, S. Beraki, P. Karamchedu, A.K. Dhalla, R. Ruffy, M. Imran, Jejunal wall delivery of insulin via an ingestible capsule in anesthetized swine—A pharmacokinetic and pharmacodynamic study, Pharmacol. Res. Perspect. 7 (2019), https://doi.org/10.1002/prp2.522 e00522.
[130] J. Abbasi, Oral Injections Tested in Proof-of-Concept Trial, JAMA. 323 (2020) 916, https://doi.org/10.1001/jama.2020.1740.
[131] S. Mitragotri, D. Blankschtein, R. Langer, Ultrasound-mediated transdermal protein delivery, Science (80-.). 269 (1995) 850–853. https://doi.org/10.1126/science.7638603.
[132] B.E. Polat, D. Hart, R. Langer, D. Blankschtein, Ultrasound-mediated transdermal drug delivery: Mechanisms, scope, and emerging trends, J. Control. Release. 152 (2011) 330–348, https://doi.org/10.1016/j.jconrel.2011.01.006.
[133] C.M. Schoellhammer, A. Schroeder, R. Maa, G.Y. Lauwers, A. Swiston, M. Zervas, R. Barman, A.M. DiCiccio, W.R. Brugge, D.G. Anderson, D. Blankschtein, R. Langer, G. Traverso, Ultrasound-mediated gastrointestinal drug delivery 310ra168-310ra168 Sci. Transl. Med. 7 (2015), https://doi.org/10.1126/scitranslmed.aaa5937.
[134] C.M. Schoellhammer, G.Y. Lauwers, J.A. Goettel, M.A. Oberli, C. Cleveland, J.Y. Park, D. Minahan, Y. Chen, D.G. Anderson, A. Jaklenec, S.B. Snapper, R. Langer, G. Traverso, Ultrasound-Mediated Delivery of RNA to Colonic Mucosa of Live Mice, Gastroenterology. 152 (2017) 1151–1160, https://doi.org/10.1053/j.gastro.2017.01.002.
[135] C.M. Schoellhammer, Y. Chen, C. Cleveland, D. Minahan, T. Bensel, J.Y. Park, S. Saxton, Y.-A.L. Lee, L. Booth, R. Langer, G. Traverso, Defining optimal permeant characteristics for ultrasound-mediated gastrointestinal delivery, J. Control. Release. 268 (2017) 113–119, https://doi.org/10.1016/j.jconrel.2017.10.023.
[136] C.M. Schoellhammer, G. Traverso, Low-frequency ultrasound for drug delivery in the gastrointestinal tract, Expert Opin. Drug Deliv. 13 (2016) 1045–1048, https://doi.org/10.1517/17425247.2016.1171841.
[137] Y.N. Kalia, A. Naik, J. Garrison, R.H. Guy, Iontophoretic drug delivery, Adv. Drug Deliv. Rev. 56 (2004) 619–658, https://doi.org/10.1016/j.addr.2003.10.026.

[138] P. Bakshi, D. Vora, K. Hemmady, A.K. Banga, Iontophoretic skin delivery systems: Success and failures, Int. J. Pharm. 586 (2020), https://doi.org/10.1016/j.ijpharm.2020.119584 119584.
[139] A.C. Watkinson, M.-C. Kearney, H.L. Quinn, A.J. Courtenay, R.F. Donnelly, Future of the transdermal drug delivery market – have we barely touched the surface?, Expert Opin. Drug Deliv. 13 (2016) 523–532, https://doi.org/10.1517/17425247.2016.1130034.
[140] A. Banerjee, R. Chen, S. Arafin, S. Mitragotri, Intestinal iontophoresis from mucoadhesive patches: a strategy for oral delivery, J. Control. Release. 297 (2019) 71–78, https://doi.org/10.1016/j.jconrel.2019.01.037.
[141] K.E. Fischer, G. Nagaraj, R. Hugh Daniels, E. Li, V.E. Cowles, J.L. Miller, M.D. Bunger, T.A. Desai, Hierarchical nanoengineered surfaces for enhanced cytoadhesion and drug delivery, Biomaterials. 32 (2011) 3499–3506, https://doi.org/10.1016/j.biomaterials.2011.01.022.
[142] K.E. Fischer, B.J. Alemán, S.L. Tao, R.H. Daniels, E.M. Li, M.D. Bünger, G. Nagaraj, P. Singh, A. Zettl, T.A. Desai, Biomimetic Nanowire Coatings for Next Generation Adhesive Drug Delivery Systems, Nano Lett. 9 (2009) 716–720, https://doi.org/10.1021/nl803219f.
[143] S.L. Tao, T.A. Desai, Micromachined devices: The impact of controlled geometry from cell-targeting to bioavailability, J. Control. Release. 109 (2005) 127–138, https://doi.org/10.1016/j.jconrel.2005.09.019.
[144] K.R. Kam, L.A. Walsh, S.M. Bock, M. Koval, K.E. Fischer, R.F. Ross, T.A. Desai, Nanostructure-Mediated Transport of Biologics across Epithelial Tissue: Enhancing Permeability via Nanotopography, Nano Lett. 13 (2013) 164–171, https://doi.org/10.1021/nl3037799.
[145] V. Uskoković, P.P. Lee, L.A. Walsh, K.E. Fischer, T.A. Desai, PEGylated silicon nanowire coated silica microparticles for drug delivery across intestinal epithelium, Biomaterials. 33 (2012) 1663–1672, https://doi.org/10.1016/j.biomaterials.2011.11.010.
[146] V. Uskoković, K. Lee, P.P. Lee, K.E. Fischer, T.A. Desai, Shape Effect in the Design of Nanowire-Coated Microparticles as Transepithelial Drug Delivery Devices, ACS Nano. 6 (2012) 7832–7841, https://doi.org/10.1021/nn3019865.
[147] C.B. Fox, Y. Cao, C.L. Nemeth, H.D. Chirra, R.W. Chevalier, A.M. Xu, N.A. Melosh, T.A. Desai, Fabrication of Sealed Nanostraw Microdevices for Oral Drug Delivery, ACS Nano. 10 (2016) 5873–5881, https://doi.org/10.1021/acsnano.6b00809.
[148] X. Huang, X. Shi, M.E. Hansen, I. Setiady, C.L. Nemeth, A. Celli, B. Huang, T. Mauro, M. Koval, T.A. Desai, Nanotopography Enhances Dynamic Remodeling of Tight Junction Proteins through Cytosolic Liquid Complexes, ACS Nano. 14 (2020) 13192–13202, https://doi.org/10.1021/acsnano.0c04866.
[149] L. Walsh, J. Ryu, S. Bock, M. Koval, T. Mauro, R. Ross, T. Desai, Nanotopography Facilitates in Vivo Transdermal Delivery of High Molecular Weight Therapeutics through an Integrin-Dependent Mechanism, Nano Lett. 15 (2015) 2434–2441, https://doi.org/10.1021/nl504829f.
[150] A. Ghosh, L. Li, L. Xu, R.P. Dash, N. Gupta, J. Lam, Q. Jin, V. Akshintala, G. Pahapale, W. Liu, A. Sarkar, R. Rais, D.H. Gracias, F.M. Selaru, Gastrointestinal-resident, shape-changing microdevices extend drug release in vivo, Sci. Adv. 6 (2020) eabb4133, https://doi.org/10.1126/sciadv.abb4133.
[151] H. He, J. Guan, J.L. Lee, An oral delivery device based on self-folding hydrogels, J. Control. Release. 110 (2006) 339–346, https://doi.org/10.1016/j.jconrel.2005.10.017.
[152] J. Li, P. Angsantikul, W. Liu, B. Esteban-Fernández de Ávila, S. Thamphiwatana, M. Xu, E. Sandraz, X. Wang, J. Delezuk, W. Gao, L. Zhang, J. Wang, Micromotors Spontaneously Neutralize Gastric Acid for pH-Responsive Payload Release, Angew. Chemie Int. Ed. 56 (2017) 2156–2161, https://doi.org/10.1002/anie.201611774.
[153] W. Gao, R. Dong, S. Thamphiwatana, J. Li, W. Gao, L. Zhang, J. Wang, Artificial Micromotors in the Mouse's Stomach: A Step toward in Vivo Use of Synthetic Motors, ACS Nano. 9 (2015) 117–123, https://doi.org/10.1021/nn507097k.
[154] M. Medina-Sánchez, H. Xu, O.G. Schmidt, Micro- and nano-motors: the new generation of drug carriers, Ther. Deliv. 9 (2018) 303–316, https://doi.org/10.4155/tde-2017-0113.
[155] S.K. Srivastava, G. Clergeaud, T.L. Andresen, A. Boisen, Micromotors for drug delivery in vivo: The road ahead, Adv. Drug Deliv. Rev. 138 (2019) 41–55, https://doi.org/10.1016/j.addr.2018.09.005.
[156] D. Walker, B.T. Käsdorf, H.-H. Jeong, O. Lieleg, P. Fischer, Enzymatically active biomimetic micropropellers for the penetration of mucin gels, Sci. Adv. 1 (2015), https://doi.org/10.1126/sciadv.1500501 e1500501.
[157] B.E.-F. de Ávila, P. Angsantikul, J. Li, M. Angel Lopez-Ramirez, D.E. Ramírez-Herrera, S. Thamphiwatana, C. Chen, J. Delezuk, R. Samakapiruk, V. Ramez, M. Obonyo, L. Zhang, J. Wang, Micromotor-enabled active drug delivery for in vivo treatment of stomach infection, Nat. Commun. 8 (2017) 272, https://doi.org/10.1038/s41467-017-00309-w.