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Published in:
Journal of controlled release

Link to article, DOI:
10.1016/j.jconrel.2020.10.024

Publication date:
2021

Document Version
Peer reviewed version

Design of a self-unfolding delivery concept for oral administration of macromolecules

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Keywords: Oral insulin; Delivery devices; Elastomers; Permeation enhancers; Protease inhibitors; Polydimethylsiloxane

Abstract

Delivering macromolecular drugs, e.g. peptides, to the systemic circulation by oral administration is challenging due to their degradation in the gastrointestinal tract and low transmucosal permeation. In this study, the concept of an oral delivery device utilizing an elastomeric material is presented with the potential of increasing the absorption of peptides, e.g. insulin. Absorption enhancement in the intestine is proposed as a result of self-unfolding of a polydimethylsiloxane foil upon release from enteric coated capsules. A pH-sensitive polymer coating prevents capsule disintegration until arrival in the small intestine where complete unfolding of the elastomeric foil ensures close contact with the intestinal mucosa. Foils with close-packed hexagonal compartments for optimal drug loading are produced by casting against a deep-etched silicon master. Complete unfolding of the foil upon capsule disintegration is verified *in vitro* and the insulin release profile of the final delivery device confirms insulin protection at gastric pH. *In vivo* performance is evaluated with the outcome of quantifiable plasma insulin concentrations in all rats receiving duodenal administration of the novel delivery device. By taking advantage of elastomeric material properties for drug delivery, this approach might serve as inspiration

for further development of commercially viable biocompatible devices for oral delivery of macromolecules.

1. Introduction

Oral administration of macromolecules, e.g. peptides and proteins, has been attempted for decades in order to improve patient compliance [1,2]. Previous initiatives have mainly focused on incorporating protease inhibitors, such as soybean trypsin inhibitor (STI), and permeation enhancers (PEs) in order to decrease enzymatic degradation while increasing absorption from the intestine [1,3]. Co-formulating peptides with such active excipients in tablets or capsules has been the strategy in several preclinical and clinical assessments [2]. However, innovative oral delivery devices have, over the last few years, challenged the conventional concepts of oral systemic absorption by proposing the application of gastrointestinal (GI) injections resulting in >10% oral bioavailability relative to subcutaneous (SC) injection [4–7]. Physical perforation of the outer layers of the absorptive barriers has thereby become an interesting alternative to excipient-induced absorption of macromolecules [8]. While both approaches are interesting platforms for peptide delivery, the risks of repeated administrations of PEs and GI-injections are unknown. Nevertheless, the constant regeneration of the epithelial cells along the GI-tract is a recurring argument for the therapeutic relevance of temporary barrier disruption regardless of being induced by PEs or by physical perforation [5,9,10].

The status as food additive, Generally Recognized As Safe (GRAS) or inactive ingredient held by some PEs, e.g. sodium caprate (C_{10}), salcaprozate sodium (SNAC) and sodium dodecyl sulfate (SDS), have rendered them popular choices in industrial formulation strategies [8]. Notably, C_{10} and SNAC have proven beneficial, and have led to the achievement of therapeutic oral bioavailability of insulin and the glucagon-like peptide-1 agonist, semaglutide, respectively. Moreover, the latter formulation has received approval from the U.S. Food & Drug Administration [11,12]. Thereby, PE-based formulations have proven to be commercially viable, yet they still need to compensate with higher peptide doses due to relatively low oral bioavailability compared to the GI-injecting delivery devices [5,7,11,12]. On the other hand, while the GI-injecting devices are innovative from an engineering perspective, their complexity is likely to impede the rate of potential mass production compared to that of conventional tablets and capsules [4,5,7]. A solution to the high doses required in PE-based oral dosage forms has previously been proposed with unidirectional-releasing devices capable of creating local environments of high

concentrations of peptide and excipients along the intestinal absorptive barrier [13–16]. Such confinement would increase the local effect of active excipients, e.g. PEs and protease inhibitors, while creating a steep peptide concentration gradient across the intestinal mucosa. The proximity between the absorptive barrier and such unidirectional-releasing devices has proven of outmost importance *in vitro* with a 50% decrease in insulin absorption for every distance increase of 130 µm from a Caco-2 cell monolayer mimicking the intestinal absorptive barrier [16].

Insulin release in the gastric environment can be prevented by enteric coating, but ensuring optimal unidirectional release in close proximity to the intestinal epithelium has proven challenging to attain *in vivo* [17]. Moreover, it has proven problematic to conduct *in vivo* studies of enteric coated capsules in rats, due to long-term gastric retention of such dosage forms [18]. Previously, this issue has been circumvented by pre-administration of the prokinetic agent, metoclopramide, to promote gastric emptying, or by direct intestinal insertion of the dosage form through an incision in the proximal small intestine [13,14,19]. Thus, such preclinical *in vivo* studies either alter the normal peristalsis by inclusion of a prokinetic agent or might even possess the risk of absorption at the site of intestinal perforation, thereby causing a false positive result.

An alternative approach to preclinical *in vivo* studies of enteric coated capsules in rats was used in the present work, without neither penetrating the GI-tract mucosa nor using prokinetic agents. This *in vivo* approach, which will be discussed in more detail below, contributed to the overall aim of the present study, namely to conceptualize and design an oral device capable of guaranteeing optimal unidirectional drug and excipient release in close proximity to the intestinal mucosa. The design comprises an elastomeric self-unfolding foil with cavities for drug- and excipient loading rolled up in an enteric coated gelatin capsule. The key to successfully achieving unidirectional release in close proximity to the intestinal mucosa thus lies in the elastomeric nature of the material ensuring purely elastic deformation. For the present proof-of-concept study, polydimethylsiloxane (PDMS) was chosen as the foil material due to its elastomeric properties, while the approximately 6 kDa peptide hormone, insulin, was chosen as the model macromolecular drug.

2. Materials and Methods

2.1 Materials

Human recombinant insulin, SDS and dibutyl sebacate were acquired from Sigma-Aldrich (St. Louis, MO, USA). STI was bought from Thermo Fisher Scientific (Waltham, MA, USA) and SYLGARD™ 184 silicone elastomer kit from Dow Chemical Company (Midland, MI, USA). Eudragit® L 100 and L100-55 were both obtained from Evonik (Essen, Germany). Midazolam (5 mg mL^{-1}) was procured from Hameln (Gloucester, UK) whereas Hypnorm (fentanyl, 0.315 mg mL^{-1}; fluanisone 10 mg mL^{-1}) was acquired from Skanderborg Pharmacy (Skanderborg, Denmark), and pentobarbital/Euthanimal (400 mg mL^{-1}) from Alfasan (Woerden, Netherlands). All additional chemicals and solvents were at least of analytical grade and obtained from commercial suppliers. Ultrapure water was used throughout the studies purified by an Ultra Clear UV system (Evoqua Water Technologies, Pittsburgh, PA, USA).

2.2 Fabrication of hexagonal patterned silicon master

For optimal results during the deep anisotropic etch into the silicon (Si) substrate, a SiO_2 hard mask was used. A 1 µm thick wet thermal oxide was grown in a horizontal furnace (Tempress, Vaassen, The Netherlands) and masked using the conventional positive photoresist AZ® 5214 E (MicroChemicals, Ulm, Germany). In order to increase resist adhesion, hexamethyldisilizane was deposited as part of the procedure for spin coating the 1.5 µm thick resist layer. The UV-exposure was conducted using an MLA100 Tabletop Maskless Aligner (Heidelberg Instruments, Heidelberg, Germany) and a dose of 90 mJ cm^{-2} before developing the exposed pattern for 90 s using AZ® 726 MIF (MicroChemicals, Ulm, Germany). Subsequently, the hexagonal pattern was transferred into the oxide layer using an Advanced Oxide Etcher (STS MESC Multiplex ICP, SPTS Technologies, Newport, UK) with C_4F_8 and H_2 as the reactive gasses. The remaining resist mask was stripped using a combination of energetic oxygen plasma in a barrel asher (300 Semi Auto Plasma Processor, PVA TePla, Wettenberg, Germany) and submersion into concentrated H_2SO_4 with $(NH_4)_2S_2O_8$ salt at 80 °C. The honeycomb trenches were then etched into the Si using an inductively coupled plasma deep reactive ion etching tool (STS Pegasus, SPTS Technologies, Newport, UK). The tool utilizes a Bosch-type process for performing deep anisotropic etching of Si by alternating between Si etching using SF_6 and O_2 and sidewall passivation obtained by deposition of C_4F_8. The substrate temperature was kept

at 0 °C throughout the etching process and the substrate was cleaned using oxygen plasma and a mixture of concentrated H_2SO_4 and H_2O_2 (4:1 v/v, commonly referred to as piranha) before stripping the remaining oxide mask in aqueous buffered hydrofluoric acid (12%, v/v) with NH_4F. As the Si master was intended for foil fabrication by means of casting with PDMS, an anti-stick coating was deposited by molecular vapor deposition (MVD 100 Molecular Vapor Deposition System, Applied Microstructures, Orbotech, Yavne, Israel). This effectively created a monolayer of 1H,1H,2H,2H-perflourodecyltrichlorosilane, which decreased the surface energy of the Si master. This in turn promoted demolding of the delicate honeycomb protrusions after the PDMS casting and ensured that elastomer rip-off was prevented, thereby preserving the pristine master for multiple replication cycles. The width and depth of the hexagonal trenches were measured by vertical scanning interferometry using a PLu Neox 3D Optical Profiler (Sensofar Metrology, Terrassa, Spain).

2.3 Fabrication of PDMS foil

The self-unfolding elastomer foils were fabricated by casting with SYLGARD™ 184, which is a two-component product consisting of a PDMS base and a curing agent. The base resin and curing agent were mixed in a 10:1 ratio (w/w) and degassed in a desiccator for 30 min prior to use. The mixture was then poured onto the silicon master and degassed in a desiccator once more in order to remove potential air bubbles, which would otherwise compromise the structure replication fidelity. The uncured PDMS replica was then kept in an oven at 37 °C overnight and the cured elastomer foil was subsequently peeled from the Si master. The topography of the foils was characterized using vertical scanning interferometry on a PLu Neox 3D Optical Profiler (Sensofar Metrology, Terrassa, Spain). *In vitro* assessment of the self-unfolding properties of the foil was assessed by recording the unfolding of a PDMS foil (7×7 mm^2) as a result of capsule disintegration in water at 37 °C using a Dino-Lite Premier AM7013MZT digital microscope (AnMo Electronics Corporation, New Taipei City, Taiwan).

2.4 Preparation of the final oral delivery device

PDMS foils were loaded with a powder mixture of insulin, SDS as PE and STI (5:3:2, w/w/w) by tapping the powder on top of the foil and gently scraping off any excess amount. A solution of Eudragit® L 100 (1%, w/v) and dibutyl sebacate (0.1%, w/v) in isopropanol (IPA) was then spray coated on top of the hexagonal openings to seal the powder inside

thus enabling subsequent handling of the foils. An ExactaCoat Ultrasonic Spray System (Sono-Tek, Milton, NY, USA) was used for this purpose with an infuse rate of 0.05 mL min^{-1}, path speed of 5 mm s^{-1} and shaping air pressure of 0.02 mbar. The generator power was set to 2.2 W and an AccuMist nozzle was applied with a sample-to-nozzle distance of 50 mm. Immediately after spray coating, the foils were gently rolled between the finger tips and inserted into size 9 gelatin capsules (Torpac, Fairfield, NJ, USA). A flat Si-chip was additionally coated to determine the coating thickness of Eudragit® L 100 by scanning electron microscopy using a Hitachi TM3030 Plus tabletop microscope (Hitachi High-Technologies Europe, Krefeld, Germany) with an accelerating voltage of 15 kV. Nine delivery devices were prepared in total out of which three were used for testing for the uniformity of insulin content, three were used for *in vitro* insulin release studies and three prepared for *in vivo* insulin absorption studies. The gelatin capsules for *in vivo* studies were additionally loaded with a cylindrical power magnet with a diameter and height of 2 × 1 mm, respectively (Magnetz og Magnordic, Hvidovre, Denmark). Enteric coating of the gelatin capsules was carried out by two dip coating cycles, first dipping the capsule body and afterwards the cap in Eudragit® L 100-55 (15%, w/v) and dibutyl sebacate (0.75%, w/v) in IPA giving the final delivery device. Images of the delivery device were captured with a Dino-Lite Premier AM7013MZT digital microscope (AnMo Electronics Corporation, New Taipei City, Taiwan).

2.5 In vitro release of insulin

A test for uniformity of insulin content was initially carried out by fully dissolving the content of three delivery devices in 10 mL of 50 mM phosphate buffer at pH 7 followed by reversed phase high-performance liquid chromatography (HPLC) as described below. *In vitro* release studies were carried out on a 400-DS Apparatus 7 (Agilent Technologies, Santa Clara, CA, USA) equipped with 5 mL sample cells and supplied with a 50 mM citrate buffer at pH 4 and a 50 mM phosphate buffer at pH 7. The oral delivery device was placed in 50-mesh basket sample holder and dissolution carried out under sink conditions at 37 °C for 1 hour at pH 4 followed by 5 hours at pH 7 with a dip speed of 15 dips per minute. Automatic sampling of 0.5 mL was timed at 10, 30, 60, 70, 80, 90, 105, 120, 150, 180, 240 and 360 min, each replaced with fresh dissolution medium. After sampling at 60 min, the total volume of citrate buffer in the sample cell was fully replaced with phosphate buffer. Insulin quantification was immediately carried out by HPLC on a Dionex Ultimate 3000 system (Thermo Fisher Scientific, Waltham, MA, USA) equipped with a Kinetex XB-C18 column (100 × 4.6 mm, 5 µm, 100 Å; Phenomenex, Torrance, CA, USA). The following gradient of

mobile phase A: 0.1% (v/v) trifluoroacetic acid (TFA) in water and B: 0.1% (v/v) TFA in acetonitrile was applied with a flow rate of 0.5 mL min^{-1}: 0 – 6.0 min A:B (77:23 to 50:50, v/v), 6.0 – 6.5 min A:B (50:50 to 77:23, v/v) and 6.5 – 8.0 min A:B (77:23, v/v). Insulin was quantified as the area under the curve of the UV-absorbance peak at 276 nm against a standard curve from 10 - 1000 µg mL^{-1} with an injection volume of 20 µL and column temperature of 22 °C.

2.6 In vivo absorption of insulin

The animal experiments were carried out in accordance with the Danish law on animal experiments as approved by the Danish Animal Experiments Inspectorate in concordance with the EU directive 2010/63/EU under license no. 2016-15-0201-00892. In total, 11 male Sprague Dawley rats (Janvier Labs, Le Genest-Saint-Isle, France) weighing 255 – 310 g were divided into three groups and housed with reversed day/night rhythm (12/12 h). The rats were fasted with *ad libitum* access to water for 12 - 14 h before initiating the study. Bolus anesthesia of fentanyl (236 µg kg^{-1}), fluanisone (7.5 mg kg^{-1}) and midazolam (3.75 mg kg^{-1}) was given as SC injections with repeated SC injections every 30 min of 1/3 of the bolus dose together with 0.4 mL saline. The abdominal cavity was opened to expose the gastrointestinal tract prior to dosing of all 11 rats. Two groups, each of three rats, were administered SC injections of insulin (1 IU kg^{-1}) or saline as positive and negative control, respectively. Five rats were administered the novel delivery device directly to the stomach by the use of an oral gavage dosing tube. Gastric emptying was then facilitated by dragging the delivery device into the duodenum about 3 cm from the pylorus with an external magnet (t = 0 min). Blood samples of 200 µL were taken from the tail vein into Microvette® 200 K3E tubes (Sarstedt, Nümbrecht, Germany) at 10, 20, 30, 45, 60, 90, 120 and 180 min followed by isolation of the plasma by centrifugation at 9,300 × g at 4 °C using a Microcentrifuge 5415 R (Eppendorf, Hamburg, Germany). Plasma samples were stored at -20 °C until insulin quantification was carried out by an enzyme-linked immunosorbent assay (ELISA) as described by the manufacturer (Mercodia, Uppsala, Sweden). The rats were euthanized by intracardiac injections of pentobarbital (100 mg kg^{-1}) after the final blood sampling. Additionally, diluted *in vitro* release samples were analyzed by ELISA in order to confirm preservation of the antibody-binding moieties of insulin upon release from the prepared delivery device.

2.7 Data treatment

All data were treated using Microsoft Excel 2010 (Redmond, WA, USA) and GraphPad Prism version 8.3.0 (San Diego, CA, USA) and expressed as mean ± standard deviation (SD) unless stated otherwise.

3. Results and discussion

3.1 Preparation and in vitro assessment of the foil-based delivery device

An overview of the preparation steps of the drug loaded elastomeric foil is shown in Fig. 1A, and the principle of its proposed absorption enhancing mechanism illustrated in Fig. 1B.

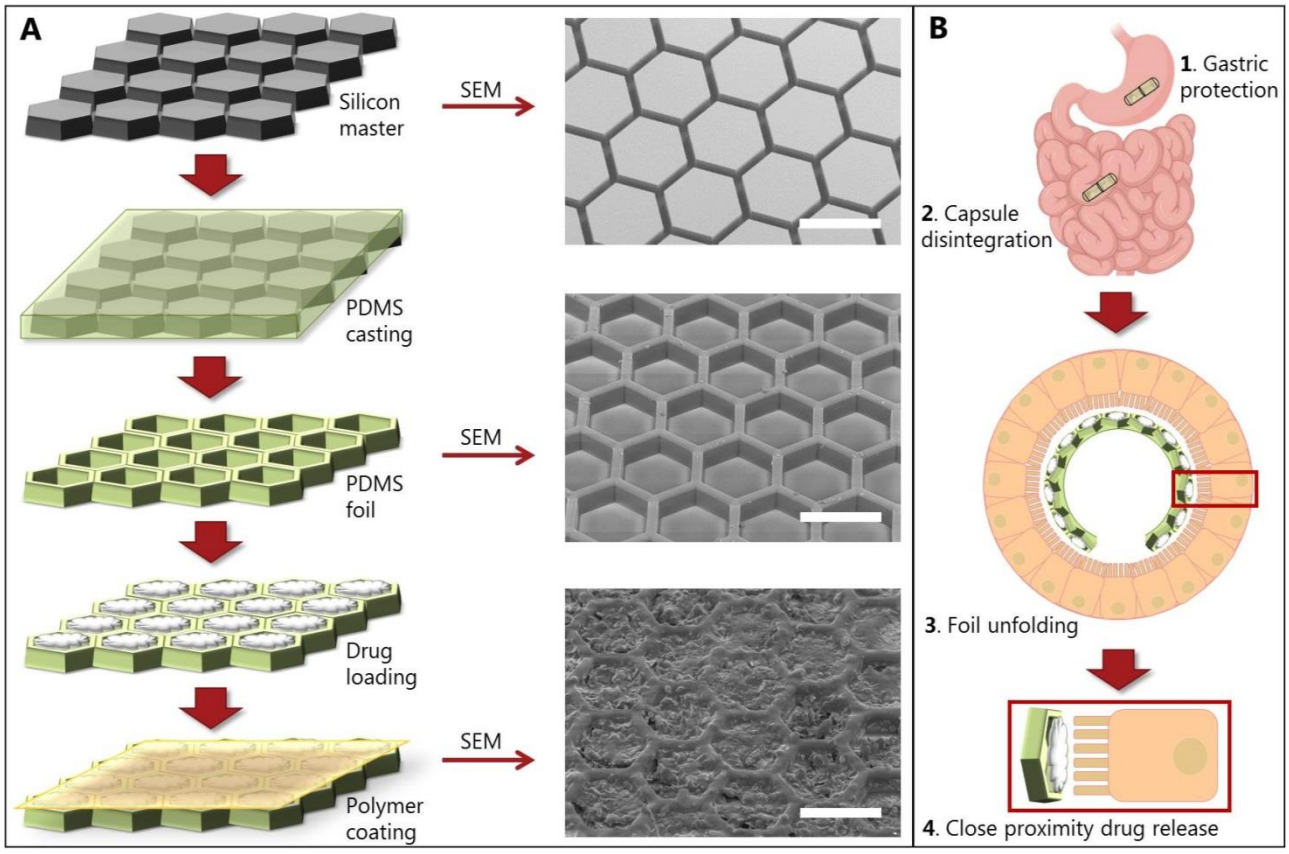

Fig. 1. Illustrations of the preparation steps and the principle of the delivery device (A) Fabrication and preparation steps of drug-loaded polydimethylsiloxane (PDMS) foil with scanning electron microscopy (SEM) images, scale bars: 400 µm (B) Principle of the oral delivery device: Intestinal capsule disintegration is followed by foil unfolding and unidirectional drug release in close proximity to the absorptive barrier (the gastrointestinal tract schematic was created with Biorender.com) - (2-column fitting image).

An early 1st generation design of the cavities for drug- and excipient loading in the PDMS foil was based on previously published cylindrical devices [20,21]. This 1st generation foil

designed with cylindrical cavities was used for initial *in vitro* assessment of the self-unfolding properties of the PDMS foil (Fig. 2, Video S1).

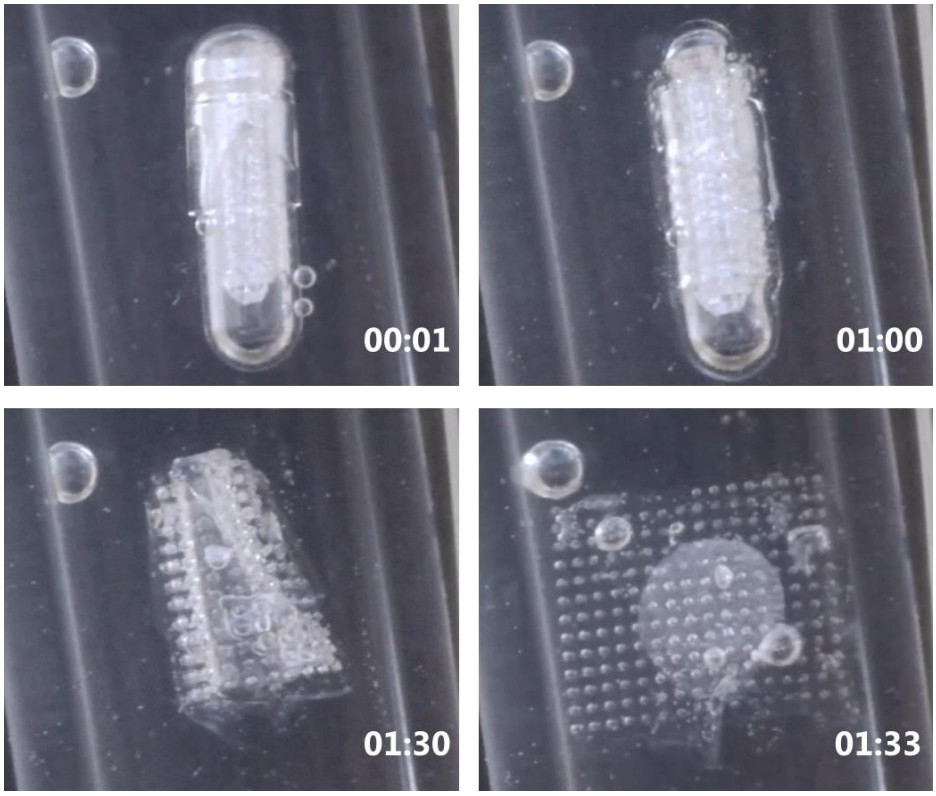

Fig. 2. Real-time disintegration of a size 9 gelatin capsule in water at 37 °C following unfolding of a PDMS foil with cylindrical cavities, timer shown as MM:SS - (1.5-column fitting image).

The confined shape of the foil in the gelatin capsule proved completely reversible with the foil fully restoring its original flat shape upon capsule disintegration. Inside the tubular confinement of the rat duodenum, measuring about 2.5 – 3 mm in diameter, such unfolding would thus result in close proximity between the drug loaded cavities of the foil and the intestinal mucosa [22]. To further enhance the chances of oral insulin absorption, the Si master with a close-packed hexagonal tiling was deep-etched and used for fabrication of the 2nd generation foil (Fig. 1A). The width and depth of the hexagonal trenches of the Si master were 46 ± 2.2 and 127 ± 0.8 µm (mean ± SD), n = 5), respectively (Fig. S1A). Subsequent PDMS casting resulted in thin foils with a well-defined surface topography composed of protrusions arranged in a honeycomb pattern with an average height of 125 ± 0.6 µm (mean ± SD, n = 5), (Fig. S1B). The hexagonal design of the 2nd generation foil resulted in a functional area for drug- and excipient loading of 78% compared to only 21% for the 1st generation foil with cylindrical cavities. The elastomeric PDMS foil with hexagonal cavities was cut into pieces of 7 × 7 mm^2, and loaded with a powder mixture consisting of insulin, SDS and STI. A covering layer of

Eudragit® L 100, soluble in intestinal fluids with pH > 6, was applied by spray coating to seal the powder mixture inside the cavities. The covering layer, measuring approximately 19 µm (Fig. S2), thus ensured that no loss of loaded powder occurred when rolling up and inserting the foil into size 9 gelatin capsules. Finally, dip coating of the gelatin capsules was performed using Eudragit® L 100-55 to allow for rapid capsule disintegration when reaching a pH value above 5.5 in the rat small intestine. The uniformity of insulin content in the delivery devices was quantified as 606 ± 65 µg corresponding to 17.5 ± 1.9 international units (IU), when loading a powder mixture of insulin, SDS and STI (5:3:2 w/w/w). Insulin release from the final delivery device was investigated *in vitro* in media simulating the pH in rat gastric and small intestinal environments to confirm sufficient capsule coating (Fig. 3). The insulin profile confirmed protection even at a relatively high gastric pH of 4, while the exchange of medium to pH 7 initiated the release of insulin, which lasted about 2 – 3 h.

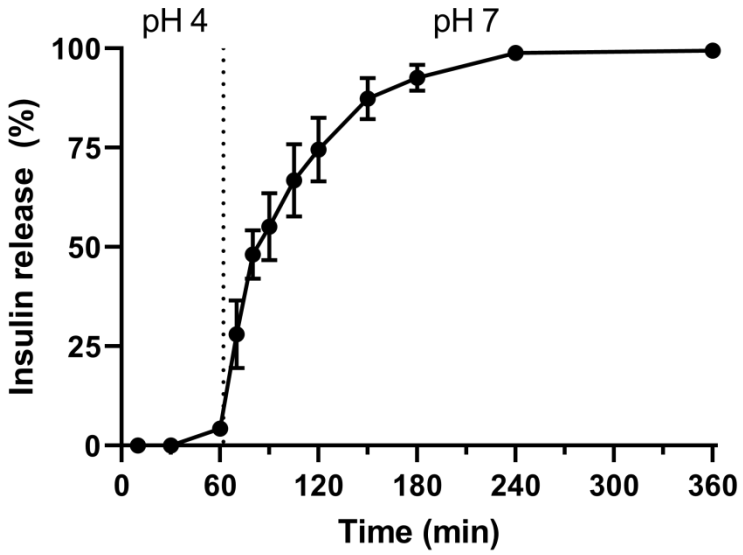

Fig. 3. *In vitro* release of insulin from the final delivery device at pH 4 followed by pH 7 under sink conditions, mean ± standard deviation (*n* = 3) - (1-column fitting image).

3.2 In vivo assessment

None of the preparation steps towards the final oral delivery device included processes that were likely to compromise the physical stability of insulin, e.g. heat, physical stress, solvents. This was supported by ELISA of diluted *in vitro* release samples, which confirmed the preservation of the antibody-binding moieties of insulin upon release from the dosage form. An alternative protocol to standard oral gavage was designed for *in vivo* evaluation of the delivery device, as studies have shown that enteric coated size 9

capsules may not exit the stomach upon oral administration to rats [18]. The procedure was rendered possible by including a cylindrical magnet in the capsule together with the prepared folded foil (Fig. 4A-B).

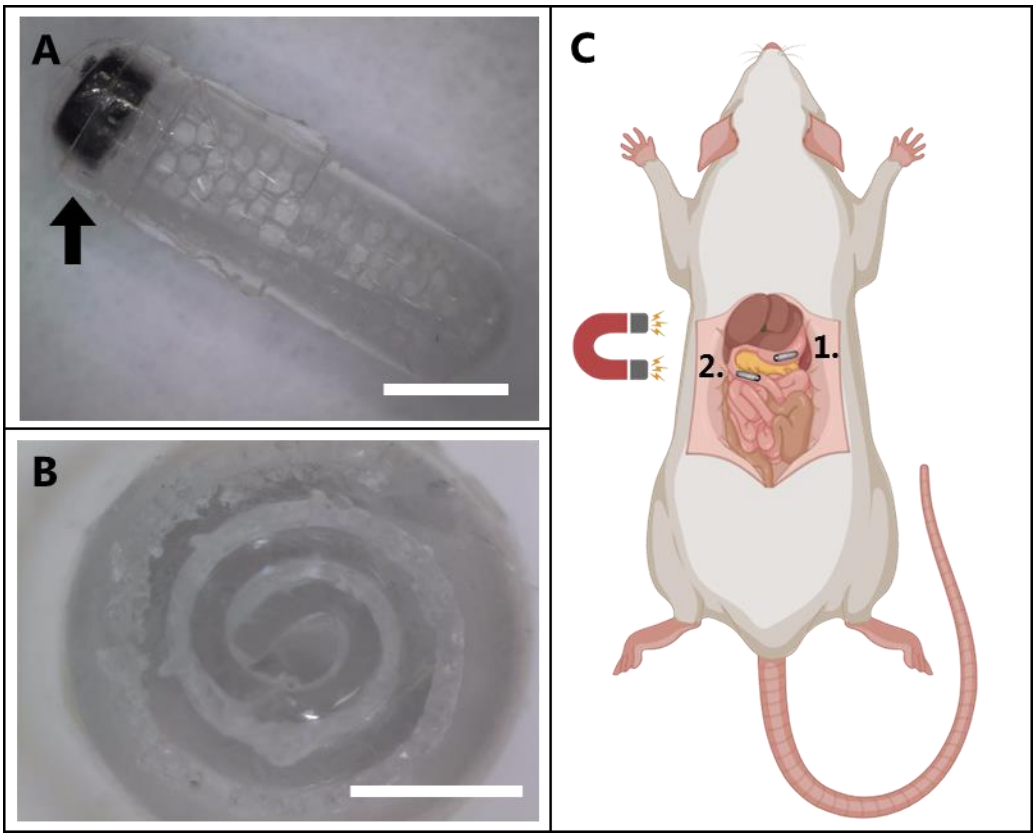

Fig. 4. *In vivo* setup for assessment of the delivery device prototype (A) The delivery device comprised of a Eudragit® L 100-55 coated size 9 gelatin capsule loaded with a magnet (arrow) and a Eudragit® L 100 coated PDMS foil loaded with insulin, sodium dodecyl sulfate and soybean trypsin inhibitor, scale bar: 2 mm (B) Cross-sectional view of the capsule showing the coiled PDMS foil inside the enteric coated size 9 gelatin capsule, scale bar: 1 mm (C) Illustration of the *in vivo* setup in two steps: 1. oral gavage of the delivery device to the stomach, 2. gastric emptying of the delivery device by the use of an external magnet (schematic created with Biorender.com) - (1.5-column fitting image).

The delivery device was administered by oral gavage to the stomach of anaesthetized rats followed by duodenal positioning, approximately 3 cm from the stomach, which was enabled by external magnetic maneuvering of the delivery device through the pylorus (Fig. 4C). Blood samples were taken over 3 h after which fully unfolded empty PDMS foils were retrieved from the small intestines (20 – 30 cm from pylorus) with no residual remains of the gelatin capsules (Fig. 5A). Changes in blood glucose levels were not used for evaluating insulin absorption, as previous data have shown significant blood glucose

lowering effects by anesthesia [23]. Instead, insulin absorption was assessed by plasma human insulin quantification by ELISA, as shown in Fig. 5B.

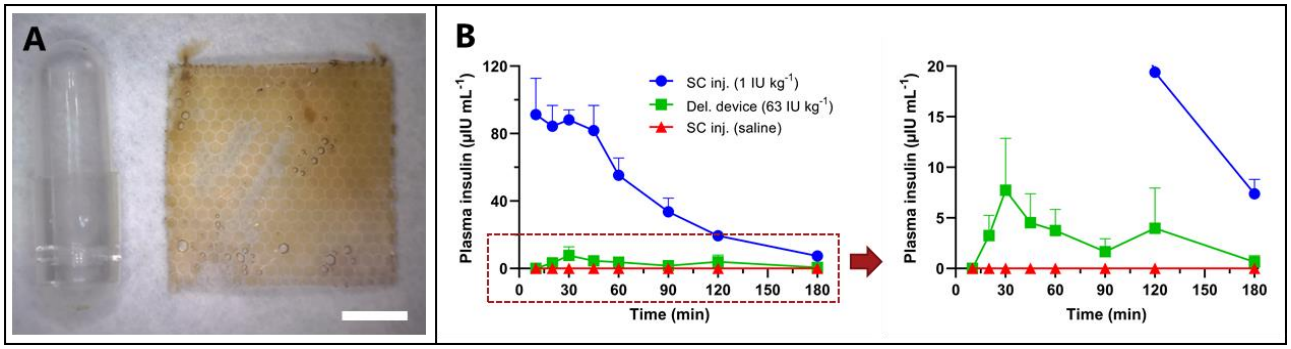

Fig. 5. *In vivo* performance of the delivery device prototype (A) PDMS foil retrieved after the *in vivo* study and placed next to a size 9 gelatin capsule for comparison, scale bar: 2 mm (B) Plasma insulin concentrations in rats as micro international units (IU) per mL after duodenal insertion of the oral delivery (Del.) device compared to subcutaneous injections (SC inj.) of either insulin or saline shown as mean + standard error of the mean (*n* = 3-5) - (2-column fitting image).

Insulin was present in quantifiable concentrations in the plasma of all five rats receiving the foil-based delivery device, although in relatively low concentrations compared to the SC insulin injections. Additionally, no traces of insulin were detected in any of the negative control plasma samples from rats receiving SC saline injections. The relative oral bioavailability (F_{Rel}) of the delivery device compared to the SC insulin injection was found to be 0.12 ± 0.07% (mean ± standard error) based on the respective doses and the area under the curve (AUC) of the plasma insulin profiles, calculated by the following formula.

$$F_{Rel} = 100 \cdot \frac{AUC_{oral\ administration} \cdot 1\ IU\ kg^{-1}}{AUC_{SC\ injection} \cdot 63\ IU\ kg^{-1}}$$

Although the relative bioavailability achieved might appear low, oral formulations of the antidiuretic hormone, desmopressin, have previously shown to be both therapeutically and commercially viable with a mean relative bioavailability of 0.1% compared to SC injection [24]. Moreover, commonly investigated peptides for oral delivery, e.g. desmopressin, octreotide and leuprolide, might comprise a smaller absorption challenge compared to insulin due to its larger size (51 amino acids), two-chain structure and higher susceptibility to proteolysis [1,12,25]. However, whether higher bioavailability of such simpler peptides could be achieved by the delivery device remains uncertain at this stage. Other oral delivery strategies have previously resulted in a markedly higher oral insulin bioavailability of >10%, with the highest numbers being based on physical perforation of the mucosa by

GI-injecting delivery devices [4-7]. Another study based on local release of thiolated polycarbophil as PE together with insulin from mucoadhesive patches has previously shown a relative oral bioavailability of 2.2% [26], suggesting that greater absorption by the present unfolding foil might be achievable by incorporating alternative PEs or by improvement of the design of the device itself. The present oral delivery principle could therefore be of general interest to both material scientists and also researchers in the field of oral delivery of peptides and even some small molecule drugs with low oral bioavailability. Class III drug compounds in the Biopharmaceutics Classification System are defined as having high solubility, but low permeability and could possibly benefit from the delivery principle of the foils by creating a local environment of high drug concentration and thus a steep gradient across the intestinal absorptive barrier [27]. However, since the current results are based on an early prototype of utilizing self-unfolding foils, further in-depth studies are needed to investigate the true potential of the delivery concept. Moreover, while the elastomer, PDMS, proved advantageous for achieving self-unfolding properties of the foil, the material possesses the notable disadvantage of not being biodegradable. While PDMS is already used for medical prosthetics and plastic surgery and generally considered nontoxic [28], its lack of disintegration represents a possible risk of accumulation in the GI-tract upon repeated oral administration. Hence biodegradability would be a considerable advantage for proceeding further from preclinical studies, yet a challenge lies in the creation of a biodegradable elastomeric foil with similar properties. Several approaches towards such materials have previously been investigated for biomedical applications based on alginate, poly(glycerol-sebacate) and even combinations of PDMS and starch [28–31]. For the purpose of oral peptide delivery, it might furthermore be of specific interest to investigate different cavity structures for drug loading and the unfolding forces of different elastomers. The interplay between those aspects might aid perforation through the intestinal mucus thus further decreasing the distance between the point of peptide- and excipient release and the absorptive barrier.

4. Conclusion

A new oral delivery concept comprising an elastomeric PDMS foil in an enteric coated gelatin capsule was designed and tested both *in vitro* and *in* vivo. The *in vitro* studies confirmed protection at gastric pH and fully unfolding properties of the PDMS foil upon capsule disintegration. A new *in vivo* assessment for enteric coated capsules was applied to ensure gastric emptying of the designed delivery device, which showed promising properties for oral delivery of macromolecules as all rats had quantifiable insulin plasma

concentrations despite insulin being one of the more challenging peptides to deliver orally. In general, drug compounds with low oral bioavailability, due to low permeation and/or stability, could benefit from confinement in and subsequent release from the foil [27,32]. Excipient-driven absorption mechanisms of macromolecules might furthermore gain increased efficiency from co-localization, leading to a reduced requirement of drug. Thus, the concept might have the potential to serve as a platform for a range of drug compounds, yet further studies is needed to fully unravel its potential.

Acknowledgements

This work was supported by the Danish National Research Foundation (DNRF122) and Villum Foundation (Grant No. 9301), Center for intelligent drug delivery and sensing using microcontainers and nanomechanics (IDUN) and performed in part at DTU Nanolab, the National Centre for Nano Fabrication and Characterization at the Technical University of Denmark. The graphical abstract was created with Biorender.com.

Declaration of interest

JRJ, LHET, AB, TR and AM have filed a patent application to the European Patent Office on the design of the delivery device.

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