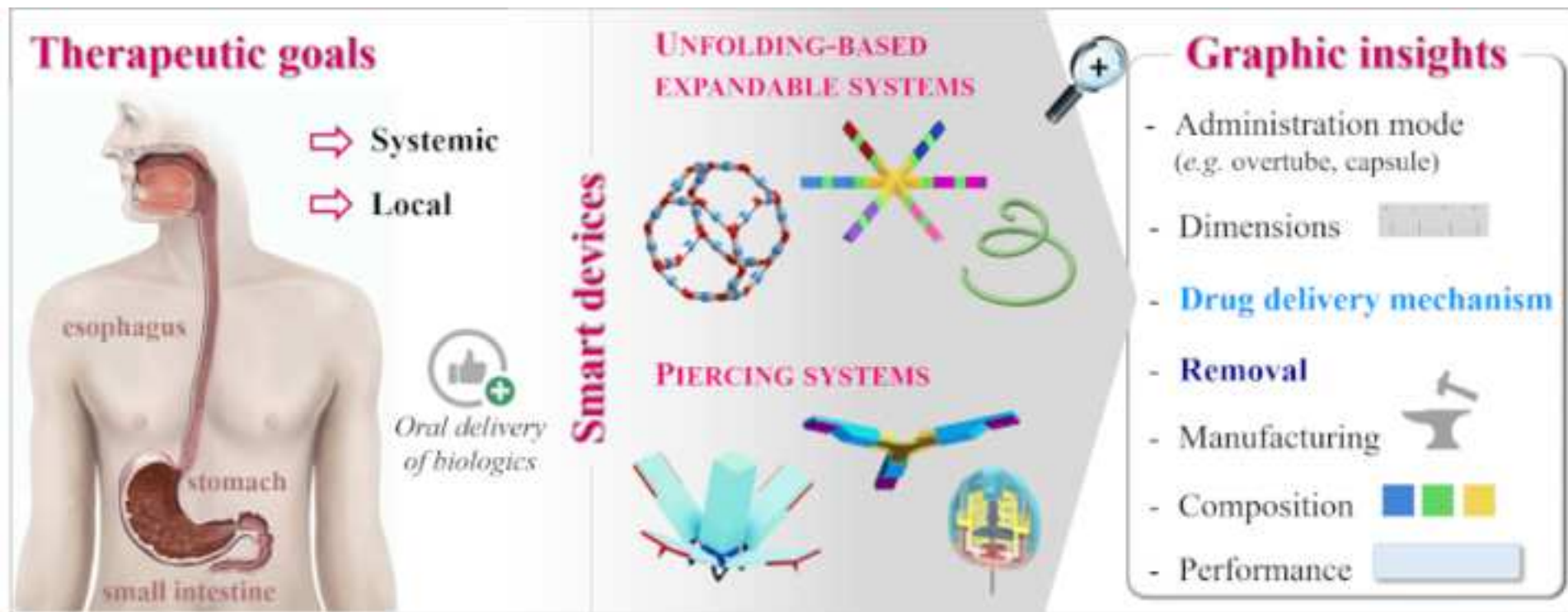


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Administration strategies and smart devices for drug release in specific sites of the upper GI tract --Manuscript Draft--

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Administration strategies and smart devices for drug release in specific sites of the upper GI tract

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Abstract

Targeting the release of drugs in specific sites of the upper GI tract upon oral intake has been traditionally pursued using gastroretentive (GR) systems. They were mainly proposed to meet local therapy goals, to improve the bioavailability of specific drugs or to enhance patient compliance, especially in chronic illnesses of great social/economic impact and involving polytherapies (*e.g.* Parkinson's and Alzheimer's disease, tuberculosis, malaria, HIV, HCV). Low-density, high-density, magnetic, adhesive and expandable GR devices were proposed, the latter being further classified in systems relying on swelling or unfolding mechanisms. More recently, the interest towards oral administration of biologics has prompted the development of novel drug delivery systems (DDSs) able to target the upper GI tract *via* sophisticated approaches. By combining GR strategies and transdermal delivery approaches, devices provided with needles operating injection in the mucosa of the esophagus, stomach or small intestine were designed. Besides comprehensive literature analysis, DDSs identified as smart devices in view of their high degree of complexity, in terms of design, working mechanism, materials employed and manufacturing steps, were discussed making use of graphic tools.

1. Introduction

The administration of drugs in the upper gastrointestinal (GI) tract *via* the oral route may fulfill a range of therapeutic needs, related to both local therapy and systemic absorption [1-9]. This might also concern the delivery of proteins, biologics and other macromolecules, also including nucleic acids, for which finding a route of administration alternative to the parenteral ones, potentially characterized by higher patient compliance and reduced overall costs, would be strategic [10-16]. In addition, retention and absorption in the upper GI tract should be sought for active ingredients that are unstable in the presence of small intestine enzymes or could damage colonic bacteria [17,18].

Although the mouth is widely recognized as the first hollow organ of the GI tract, it is not generally lumped with the subsequent ones, not only for its peculiar physiological characteristics but also for administration as well as compliance issues involved [19,20]. Indeed, it is easily accessible, which would be especially advantageous for self-administration of drug delivery systems (DDSs) and devices that can even be held in place with limited discomfort from the patient perspective. For all these reasons, mouth administration has currently gained its own specificity, leading to formulation of systems devised for being used inside this organ and to dedicated release strategies (*e.g.* fast-dissolving, fast-disintegrating, sustained-release, and mucoadhesive films as well as oral patches) [21-27].

Because the transit of dosage forms in the digestive system is primarily defined by its characteristic peristaltic movements, the goal of targeting the delivery of drugs in the upper GI tract may require special approaches, especially if prolonged release is sought. This objective has traditionally been pursued making use of gastroretentive (GR) systems [18,28-30]. These are conceived to remain in the stomach for a prolonged period of time while releasing, in a controlled manner, the active ingredient conveyed. In this respect, they should be able to withstand the peristaltic contractions and the peculiar characteristics of the surrounding environment, such as the physiological pH, without in principle *i*) obstructing the normal flow of the gastric content through the pylorus, *ii*) altering the typical gastric motility nor *iii*) damaging the gastric mucosa with ulceration or injury. More recently, the so-called

piercing DDSs (*i.e.* systems able to inject the conveyed drug formulation in the submucosal tissue) started to appear in the scientific literature as a new strategy for releasing biomacromolecules in the mucosa of specific sites of the upper GI tract, from the esophagus to the small intestine [31].

Aside from the release target, another aspect that all these DDSs have in common, regardless of the operating mechanisms, is the fact they are expected to be easily removed or eliminated from the GI tract once exhausted, not being harmful for the organs they would pass through.

2. Goals of targeting drug release in the upper GI tract

Besides the treatment of inflammatory diseases and ulcerations of the mucosa, the main objective traditionally targeted with local administration of drugs in the upper GI tract has been represented by the eradication of *Helicobacter pylori* [32-34]. This goal may also be pursued in the treatment of gastroduodenal and peptic ulcers, gastritis and gastric cancer caused or worsened by the presence of infections connected to this pathogen. However, the systemic pharmacological approach to *Helicobacter pylori*'s eradication and associated illnesses is largely affected by failure in achieving effective concentrations of the desired drugs at the target site. At the same time, patient compliance plays a pivotal role, due to poor adherence to the commonly prescribed therapeutic regimens, which generally encompasses repeated and frequent administrations of one or more drugs at quite high dosages (*e.g.* proton pump inhibitor or ranitidine bismuth citrate combined with at least two antibiotics) [35-37]. Focusing on the systemic target pursued with release in specific sites of the upper GI tract, the bioavailability of weakly acidic drugs, which are poorly soluble in basic environment, and of active ingredients having an absorption window in the small intestine, may be largely improved if they are available for preferential absorption before passing the pylorus [38-40].

Regardless of specific objectives, DDSs able to ensure effective concentrations of drugs at the target site for longer periods would overall improve their current administration mode, being particularly suitable for active ingredients with a short half-life. Indeed, if the release could be prolonged over several days, even over one week, following a single oral administration, the current therapeutic

options could be revolutionized, being especially advantageous for patients in poly-therapies. By way of example, levodopa, which still represents one of the most effective drugs in the treatment of Parkinson, is characterized by a narrow absorption window [41-43]. Moreover, when taken with a decarboxylase inhibitor (*i.e.* carbidopa), it also shows a short half-life of approximately 1.5 h. The latter is able to inhibit the conversion of levodopa to dopamine at the peripheral level, thus reducing side effects and increasing the amount of drug that can cross the blood-brain barrier. Another example of a therapy entailing daily intake of multiple drugs at high quantities, for which a single administration would not be enough, is tuberculosis [44-46]. The need for taking, at specific time intervals through the day, different antibiotics (reaching doses up to 100 g during the intensive phase of treatment, for an individual of 60 kg) not only represents one of the main causes of treatment failure, due to reduced adherence, but also contributes to the onset of antibiotic resistant bacteria. To counteract this situation, in 1994 the World Health Organization approved the so-called DOTS (Directly Observed Treatment) strategy [47-49]. This entails the oral administration of fixed-dose combination products, to be repeated every day or three times per week, in a designated clinic and with the presence of specialized personnel. Although some studies have shown the effectiveness of this approach based on patient control in obtaining the desired results, it is also associated with considerable expenses and resources, that are not always available, especially in developing countries [46,50]. In this respect, the introduction of innovative DDSs needing a lower administration frequency would be of great advantage, by simplifying the therapeutic regimen [51,52]. However, they should provide a suitable balance in terms of ease as well as safety of administration and possibility of loading significant quantities of active ingredients.

The availability of delivery platforms like those above described may entail further advantages, particularly in the case of pathologies currently identified as hard-to-treat [50,53,54]. By way of example, eradication of malaria in tropical and subtropical areas, prophylaxis and management of human immunodeficiency virus (HIV) syndrome, and treatment of hepatitis C virus (HCV) infections are among the illnesses that would benefit the most. Indeed, DDSs providing ultralong release pattern,

eventually being retained *in situ* and avoiding physiological elimination with the feces, would allow to overcome the logistical challenges entailed by repeated dosing, especially in the case of drugs with a short half-life. Such difficulties could even worsen in areas characterized by poor resources, where sterility requirements and procedural complications may prevent the effective use of injectable formulations and implants. A major critical aspect in ensuring the effectiveness of HIV or HCV treatment is again represented by the behavior of patients [55-58]. Although the availability of new antiretroviral drugs has definitely improved the prophylaxis and management of HIV, the therapy efficacy is largely compromised by poor compliance (*i.e.* average long-term adherence rate about 70%). Indeed, making the subjects take consistently the combination of prescribed medicines on a daily basis still represents a hard-to reach target. Analogously, even if a novel direct-acting antiviral therapy has been developed for patients suffering from HCV, less than half of infected people are actually treated due to factors like cost, limited access to medical care and inconsistent follow-up. This is unfortunately related to the fact that many subjects suffering from this illness, which is one of the main causes of chronic liver disease worldwide, are homeless with comorbid psychiatric conditions. In these cases, the availability of DDSs ensuring an ultra-long release, for example being administered weekly, could represent a promising strategy for improving the therapy success.

Release of appropriate daily amounts of drugs in the upper GI tract after properly spaced administration intervals have also been considered an interesting approach for improving women's compliance to hormones-based contraception and in the treatment of Alzheimer's dementia [59,60]. Although the chances of unwanted pregnancy associated with lack in hormone-therapy adherence is about 9% per year, women still prefer oral administration to implants, inserts and patches. This choice could be explained by the ease of use, the possibility of self-administration and the rapid recovery of fertility after discontinuation. On the other side, reducing the number of administrations of different medicines thorough the day would be of utmost importance in the case of patients affected by dementia, as their symptoms are known to interfere with the ability to effectively remember and manage the therapeutic regimen.

Administration of drugs in the upper GI tract by injection through the mucosa was recently proposed to *i)* overcome the limitations associated with passive absorption, *ii)* mitigate the first-pass metabolism of drugs and *iii)* effectively deliver biologics or other poorly-stable highly-sensitive active ingredients, which could be damaged by an enzyme and bacteria-rich environment and by pH variations [31,61]. By way of example, this strategy could be suitable for insulin, monoclonal antibodies, nucleic acids (*e.g.* antisense oligonucleotides, siRNA, mRNA), enzymes, and hormones but also for other macromolecular drugs that do not fit subdermal injection due to local skin reactions, such as oligonucleotides and certain tumor necrosis factor- α inhibitors. Indeed, these type of molecules cannot be orally administered and currently require delivery through parenteral routes. Several approaches have been pursued to enable their absorption upon oral intake, including co-administration with enzyme inhibitors, chemical modifications and formulation in polymeric micro- and nano-carriers [62,63]. Moreover, release into the colon was targeted [64-71]. Indeed, this region has broadly been described for the increased chances of absorption if compared with the small bowel, in view of the relatively long transit time, the lower concentration of proteolytic enzymes in the lumen, the brush-border membrane and the higher responsiveness of the mucosa to permeation enhancers. More recently, systems able to develop a high surface in close contact with the small intestine epithelium, thus creating a local environment of high concentration and reducing the chance of macromolecule degradation into the lumen, have also been proposed [72]. However, besides entailing the development of broadly new drug-containing formulations, these approaches were generally characterized by reduced bioavailability compared with dosing *via* the parenteral routes. [31,61]. In this respect, the possibility of combining the advantages associated with injection to those relevant to oral administration, thus start working on the development of piercing DDSs, seemed a promising alternative to bypass the natural barriers present in the GI tract for biologics. These DDSs would in principle require minimal reformulation of the active molecule, thus potentially becoming a high-versatile and easy-to-use delivery platform, to be employed for the local delivery in different regions of the GI tract. In this respect, piercing DDSs may represent a step forward in traditional drug

delivery to simplify dosing regimens and maximize therapeutic effects through the sustained release of drugs at the upper GI tract. Notably, complex release kinetics could even be attained with these systems by fine-tuning the characteristics of the formulations deposited by injection, *e.g.* composed of micro- and nano-vectors.

3. Strategies for targeting the upper GI tract

Over the years, various strategies have been proposed to target the release of drugs in the upper GI tract.

Traditionally, this goal was pursued through the development of GR DDSs, *i.e.* characterized by a prolonged gastric residence time [1,28]. The latter, although very variable, can be reduced in the fasted state to less than 2-3 h at most, due to the physiological emptying of the stomach caused by its peristaltic activity. For ensuring retention inside this organ, the following approaches were leveraged, involving *i)* high-density, *ii)* floating, *iii)* adhesion/anchoring, or *iv)* encumbrance of the DDS [7,18,51,73]. As a step forward, GR DDSs combining two or more of the above mentioned features were also developed, with the main idea of overcoming the limitations potentially entailed by systems relying on a single strategy.

For high-density GR DDSs, the starting formulation generally contains inert materials that increase the weight/volume ratio of the device. Therefore, they should settle on the bottom of the stomach, generally below the level of the pylorus. This way, it is reported as less likely that the systems would be eliminated during gastric emptying.

Being characterized by a lower density than that of stomach fluids, floating DDSs are instead designed to float on the gastric contents, thus in principle prolonging their residence time.

In the case of mucoadhesive systems, the presence of a component that enhances adhesion of the device to the epithelial surface of the stomach is described to promote their long-lasting retention.

Various researchers have worked on the above mentioned approaches, which are probably among those mostly investigated in the scientific literature so far. In this respect, both single- and multiple-

unit DDSs were described [30,74,75]. Taking advantage of less common anchoring strategies, relatively unusual approaches to stomach retention have also been proposed [76-81]. By way of example, these were based on the presence of microneedles onto the DDSs surface, to transiently fix the latter to the stomach mucosa, and on the addition of a small magnet in the device formulation. With respect to those previously described, magnetic DDSs need an active action from the patients taking the device. Indeed, upon oral administration, a second magnet has to be externally placed on the subjects' abdomen. This way, the resulting attractive force between the two magnets would be responsible for keeping the item at the site of interest for the desired time period.

Finally, expandable GR systems are characterized by the capability to take up a relatively bigger volume after swallowing [28]. More into detail, when in the stomach, they gain a spatial encumbrance greater than the dimensions of the sphincter potentially responsible for their elimination. By way of example, as the average diameter of the wide open pylorus is in the 13-17 mm range, almost two of the main dimensions achieved by these DDSs should be around 20 mm [51]. This encumbrance is generally reached thanks to swelling or unfolding processes [28]. While the former is a rather known mechanism in the drug delivery field, that based on unfolding could be considered relatively new. Moreover, the expanded configuration of swelling-based devices results from volume increase following water absorption, so the shape could neither easily nor necessarily be controlled. Conversely, systems relying on unfolding entail the contemporary development of specific collapsed and expanded configurations. Indeed, both of them have to be taken into account to ensure appropriate administration and safe expansion, especially because the evolution between the two strictly depends on the selected geometry. For this reason, increasingly complex shapes/configurations have been described over years for expandable DDSs relying on unfolding.

More recently, attempts to provide the GR DDSs with advanced sensing components were also pursued [82]. Biomedical electronics allowing advanced diagnostic and therapeutic functionalities represent a new frontier in research especially in view of the application potential towards personalized medicine and treatment customization [83-85]. Except for those electronics that can be

worn as accessories (*i.e.* wearable devices), these systems generally require invasive procedures for implantation and specialized receivers for communication. In this respect, electronics to be orally administered can benefit from a non-invasive administration mode and, in view of the required long-term retention, from the space available within the GI tract, which is also a relatively immune-tolerant environment [82]. In particular, the development of electronic systems whose design and composition is intended to guarantee long-lasting retention into the stomach were deemed particularly interesting, as this organ is characterized by a quite large holding volume (of approximately 1.5 L) and has relatively higher tolerance for foreign materials.

A very new strategy for the administration of drugs through the mucosa of the GI tract is that based on physical modes borrowed from transdermal drug delivery, *i.e.* piercing, jetting, ultrasound, iontophoresis, and involving disruption or perturbation of the epithelial cell layer [31]. Particularly, drawing inspiration from other fields and even from nature (*e.g.* self-righting tortoise, skin of scaly animals), piercing DDSs were conceived to remain in the lumen of hollow organs (*e.g.* esophagus, stomach, small intestine, blood vessels, trachea) the time required to locally perform an injection into the tissue. This approach seemed also to innovate some of the GR strategies previously described. By way of example, piercing DDSs able to self-orient themselves to always have the injection mechanism facing towards the tissue were attained through the implementation of a high-density component into their structure (*i.e.* SOMA and L-SOMA systems) [86,87]. In other applications, injection of the formulations conveyed was obtained upon either a change in geometry/encumbrance of the system (*i.e.* Kirigami-inspired stent, flower-like system) or expulsion from a capsule-like structure followed by expansion (*i.e.* LUMI system) [88-90]. Moreover, the working mechanism of these DDSs was generally based on the use of springs undergoing mechanical/elastic deployment, the latter needing to be properly activated.

3.1 Smart devices: graphical discussion

Among the strategies so far proposed in the literature for the administration of drugs in the upper GI tract, GR DDSs relying on unfolding-based expandable mechanisms and piercing systems were found to have the highest degree of complexity in terms of design, working mechanism, type/number of starting materials and manufacturing steps, thus being defined as smart devices. In the following chapters, we have made an effort to identify for each of them *i)* the administration mode, *ii)* the strategy for targeting the site of release, for delivering their content and eventually remain in the target area as well as for being definitely removed from it (*i.e.* elimination), and *iii)* the main design, formulation, manufacturing and performance features. All the above mentioned aspects were described in detail making use of graphics (Figures 1-8). Indeed, this approach would allow the readers to have an immediate and clear understanding of the complexity of the applications proposed and the variety of the solutions identified.

3.1.1 Unfolding-based expandable GR DDSs

GR DDSs based on unfolding, *i.e.* characterized by an expansion in the volume occupied at the target site, are provided with two different configurations, able to shift from one to the other upon administration [28]. The former is the collapsed shape intended to make the system suitable for oral intake, mainly by having the patient autonomously swallowing it. In this respect, to further favor swallowing from the psychological point of view or to help maintaining the DDSs in their collapsed state, they are generally conveyed into already available hard capsules, which are widely used in the formulation of immediate release dosage forms. Once at the site of interest, they expand assuming the cumbersome configuration responsible for retention and release in the targeted organ. After complete deployment and having released the drug conveyed, to be truly efficient and perceived as poorly hazardous, the device should reduce its dimensions - spontaneously or upon external intervention - in order to ease restarting of its transit along the GI tract or to be removed. In this respect, elimination ways proposed so far for these systems were characterized by different degree of

invasiveness from the patient perspective. Overall, the transition from the collapsed to the unfolded expanded shape is expected to occur in the shortest possible time and mainly relies on mechanical/elastic deployment (Figures 1-3), shape memory effect (Figure 4) or superelasticity (Figure 5). The different mechanisms of shape shifting result from the use of excipients/materials with specific properties, combined with a thorough and focused design phase, to identify the proper geometry for the DDSs.

Systems capable to gain the expanded shape only when the mechanical constraint that forces them to remain into the collapsed configuration is removed, for instance following the dissolution of the capsule in which they were inserted to enable oral administration, were further classified on the basis of the geometry in which they were manufactured and that they assume by deployment.

Various scientists worked independently on expandable GR DDSs in a similar film-like structure [41,91-98]. This largely represented the most investigated geometry at the research level, probably for its design simplicity. Even the limited complexity of the manufacturing process involved, based on single or multi-step casting, played a pivotal role in the widespread of film-like systems. These entailed either a single drug-containing layer (Figure 1) or multiple layers (Figure 2). In the latter case, they were variously located (*e.g.* externally, as a frame) to control the release performance, to provide the whole system with sufficient mechanical resistance or to ease its unfolding [41,91,93,94,96]. To further favoring the latter process, in a few applications the external surfaces of the film were sprayed with a powder layer, composed of antiadherent and/or effervescent excipients [41,92-96,98]. Moreover, taking advantage of the relatively large surface the film-like systems are generally characterized of, they were often improved with mucoadhesion ability [41,47]. Retention of these DDSs into the stomach ranged from very few to 48 hours in the best case scenario and was demonstrated dependent not only from dimensions but also from rigidity of the films. Following progressive dissolution, the films would lose their mechanical strength, making the overall systems less resistant to stomach contraction. This way, they would pass through the pylorus in pieces or folded. Among the film-like systems, the Accordion Pill[®] developed from Intec Pharma is one of the

earliest proposed and also one of the most advanced in terms of development and possible commercialization [41,42,99,100]. Indeed, it is currently in clinical phase III for the treatment of Parkinson.

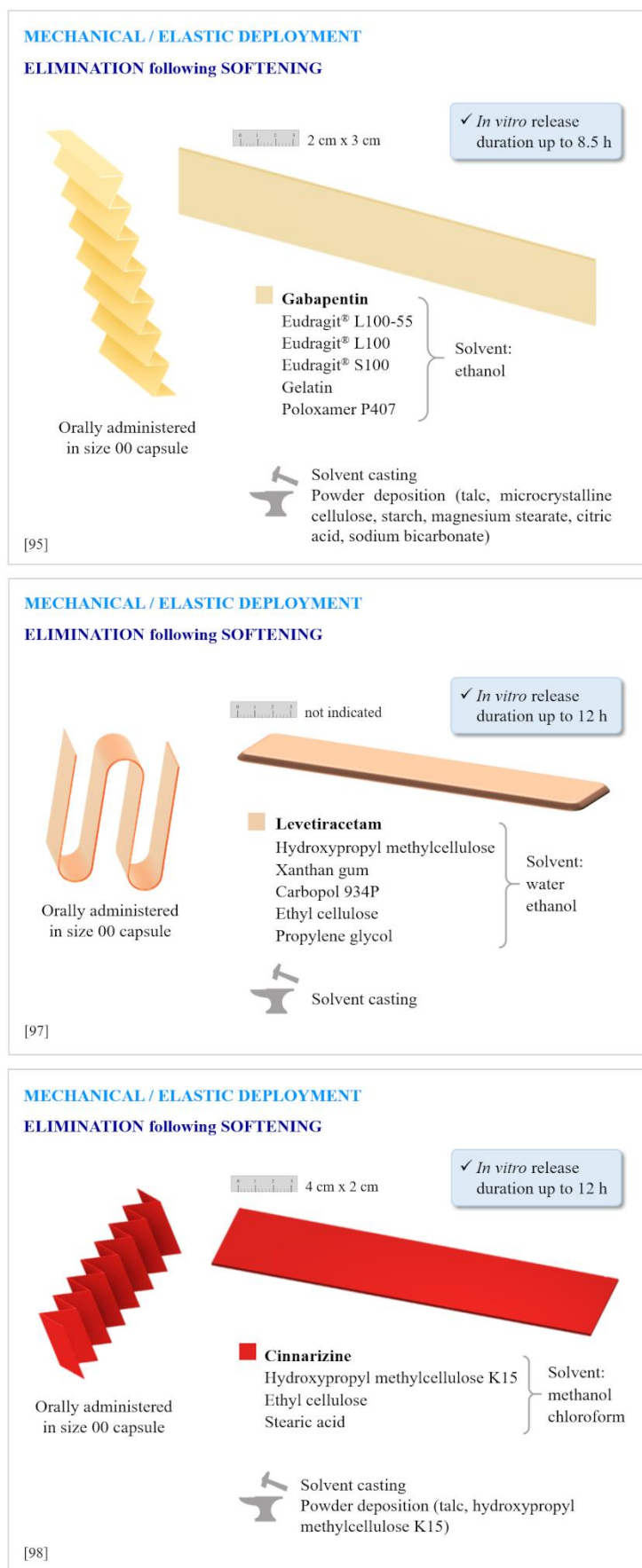


Figure 1: Outline of expandable GR DDSs the unfolding behavior of which is based on mechanical/elastic deployment: single film-like structures

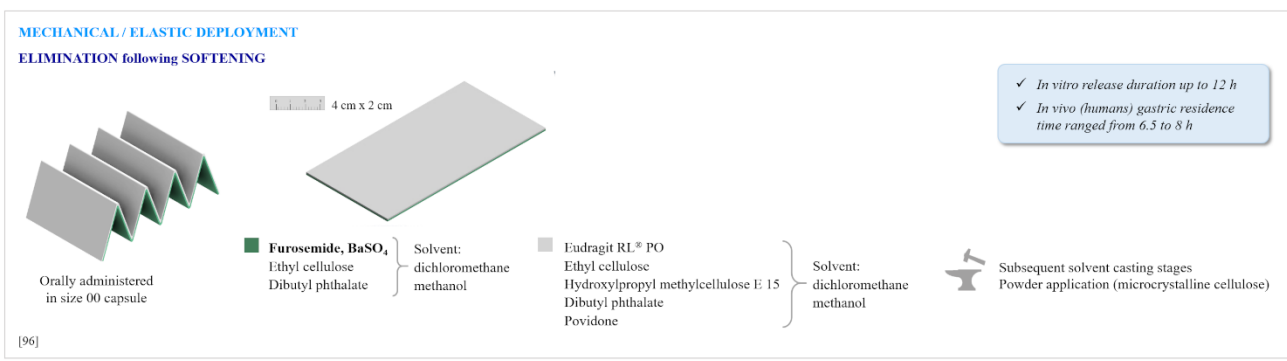
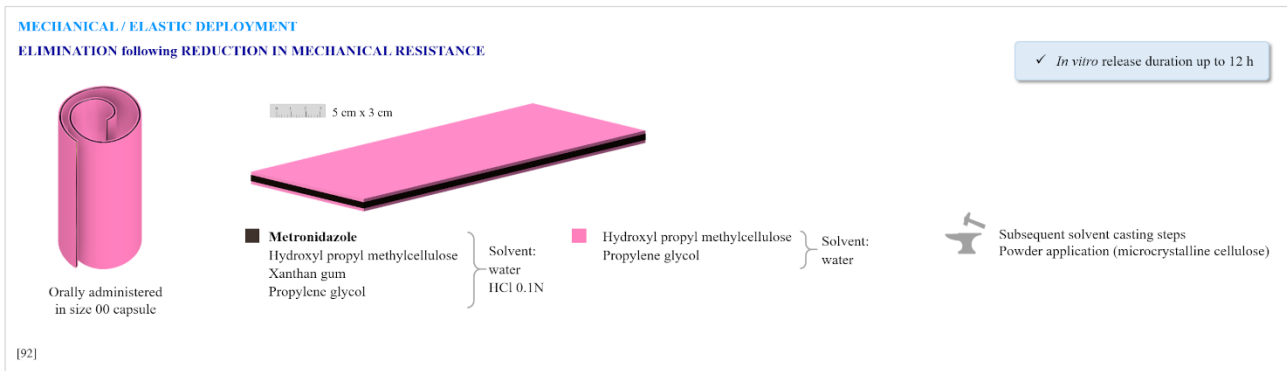
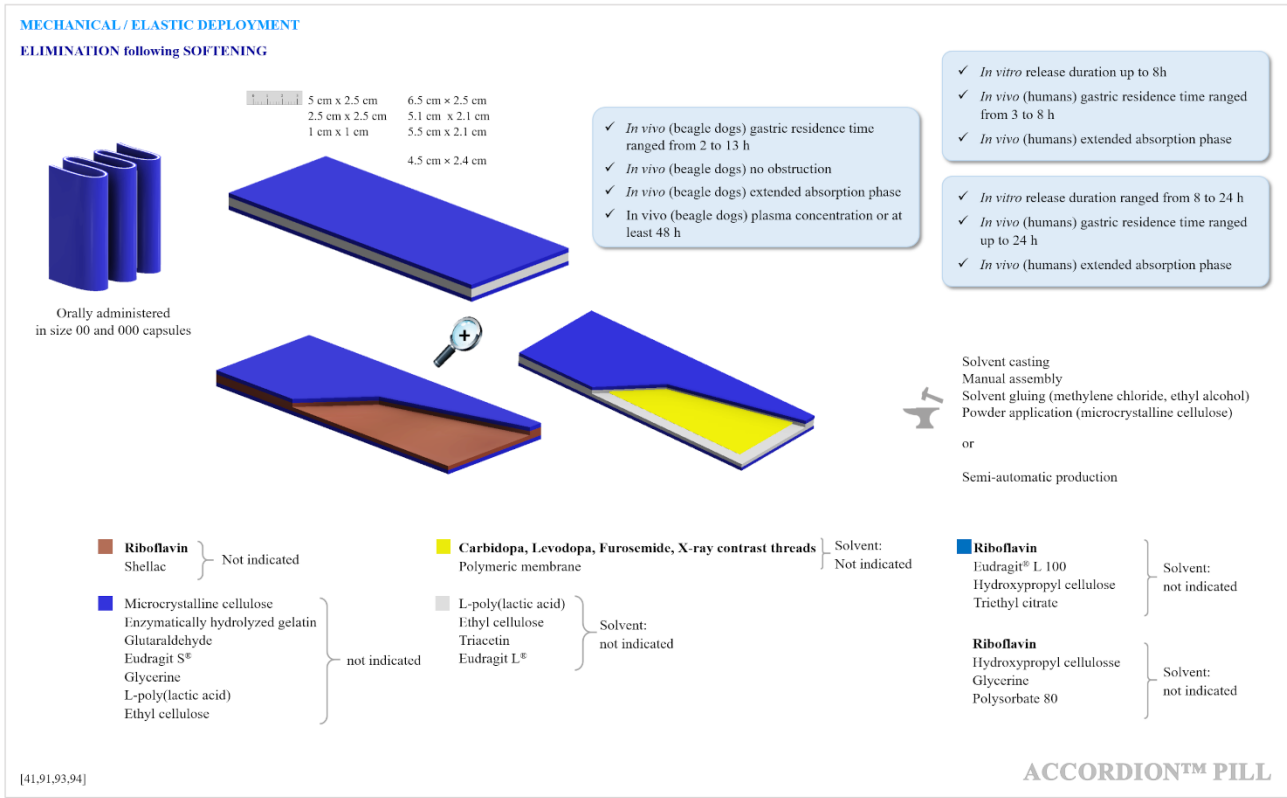


Figure 2: Outline of expandable GR DDSs the unfolding behavior of which is based on mechanical/elastic deployment: multiple film-like structures.

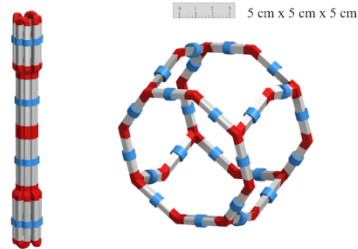
Many other geometries for unfolded GR DDSs were also considered and systems characterized by different shape, size and flexibility were devised. These were mainly attained following assembly of components and parts purposely designed and formulated to perform different functions (Figure 3a). Tetrahedron-, ring-, sphere-, star-shaped devices were described [53,54,59,60,89,101-104]. These entailed at least the following components: matrix portions (*e.g.* arms or arcs), generally responsible for the prolong release of the conveyed drugs, and connecting elements having different design and features, for instance provided with elastic properties, thus capable of fostering the folding of the system and its expansion. The possible presence of additional parts capable to progressively disassemble, brake up or dissolve would finally guarantee the reduction in size of the DDSs, thus enabling their passage through the pylorus. The presence, quite generalized in these systems, of different drug-containing parts, numerous and variously assembled, would make them particularly suitable for polypharmacy applications. The overall complexity in terms of number of different parts and relevant function, which necessarily relied on their specific shape, physico-technological characteristics and composition, was also reflected in the manufacturing of the final DDSs. Indeed, a multi-step process was generally devised to fabricate the single components of the devices and to assemble them. Production of negative molds to be used for casting and melting, hot melt extrusion, 3D printing and milling were concurrently employed and a final manual assembly phase was included in these early stages studies, which were mainly focused on appropriate development and evaluation of the finale system.

In a further evolution, unfolding-based expandable GR DDSs were also implemented with electronics, to improve the treatment efficacy and the clinical outcomes [82]. The gastric resident electronic (GRE) system, in particular, combined sensor elements, capable to directly interface with portable consumer personal electronics, with drug delivery modules, thus enabling a rapid, automated and even on-demand release of active substances (Figure 3b). The idea of making it compatible with personal electronics *via* bluetooth, thus avoiding the need for specialized equipment, would ease remote health management and monitoring, as well as the collection of personal and large population

data for clinical studies. To combine oral administration, stomach retention, drug delivery and sensing, the latter entailing wireless electronics, a power system and an antenna, a 3D heterogeneous design was developed and attained by a multimaterials fused deposition modeling (FDM) 3D printing process. Beside the possibility to combine different materials, each with specific properties and a well-defined spatial localization into the final device, this technique would enable on-demand manufacturing at the point of care being the tool for implementing next-generation personalized treatment strategies. Moreover, the breakup performance of the device and its release kinetic could be wirelessly and electronically controlled by adding other specific components to the GRE, such as elements to be electrochemically corroded by shifting the electrochemical potential (*e.g.* gold membranes, electroactive adhesives).

MECHANICAL / ELASTIC DEPLOYMENT

ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS



Directly delivered into the stomach through an orogastric tube

MATRIX
 Carbamazepine, Moxifloxacin, BaSO₄
 Polycaprolactone
 Polyethylene glycol
 Kolliphor P407
 Carbothane thermoplastic polyurethane
 Eudragit® E PO

COATING
 Polycaprolactone } Solvent: acetone
 Eudragit® E PO }

- Polyurethane
- Polycaprolactone mixed with polycarbonate-based polyurethane

- Hot melt extrusion
Injection molding
Coating by dipping
- Hot melt extrusion
Molding
- Molding

■ Molding
Manual assembly

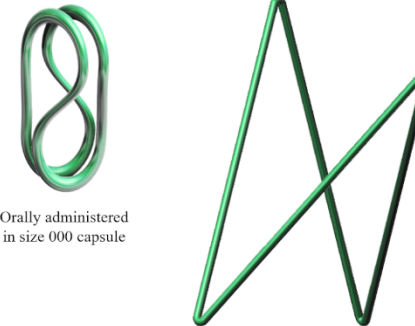
- ✓ *In vitro* release duration over 14 days
- ✓ *In vivo* (pigs) gastric residence time up to 14 days
- ✓ *In vivo* (pigs) release duration up to 14 days

[89]

MECHANICAL / ELASTIC DEPLOYMENT

ELIMINATION not indicated

2 cm x 2 cm x 2 cm
 1.5 cm x 1.5 cm x 1.5 cm x 1.5 cm



Orally administered in size 000 capsule

■ BaSO₄
 Indium-111-oxine
 Low-density polyethylene
 Ethylene-vinyl acetate

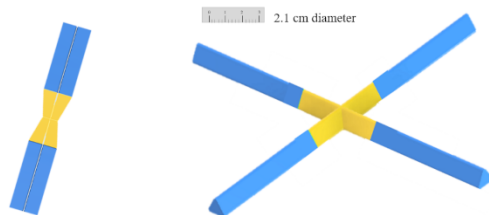
■ Hot melt extrusion
Injection molding

- ✓ *In vivo* (beagle dogs) gastric residence time up to 24 h
- ✓ *In vivo* (humans) gastric residence time up to 24 h

[101,102]

MECHANICAL / ELASTIC DEPLOYMENT

ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS



Directly delivered into the stomach through an orogastric tube

■ Meloxicam, steel ball bearings
 Polycaprolactone

■ Purposely synthesized cross-linked polycaprolactone-based polyurethane
 Polyurethane

- Hot melt extrusion
Injection molding
- Melting
Cutting
- Molding
Manual assembly

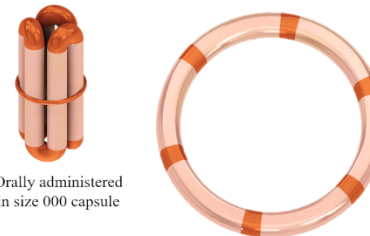
- ✓ *In vitro* prolonged release
- ✓ *In vivo* (rabbits) gastric residence time at least of 3 days

[103]

MECHANICAL / ELASTIC DEPLOYMENT

ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS

0.2 cm width
 0.2 cm depth
 3.2 cm diameter



Orally administered in size 000 capsule

■ Polycaprolactone

■ Purposely synthesized enteric elastomer composed of poly(acryloyl 6-aminocaproic acid) and poly(methacrylic acid-co-ethyl acrylate)

■ Molding
Cutting
Manual assembly

- ✓ *In vitro* disassembly in 12 h
- ✓ *In vivo* (pigs) gastric residence time ranged from 2 to 5 days

[104]

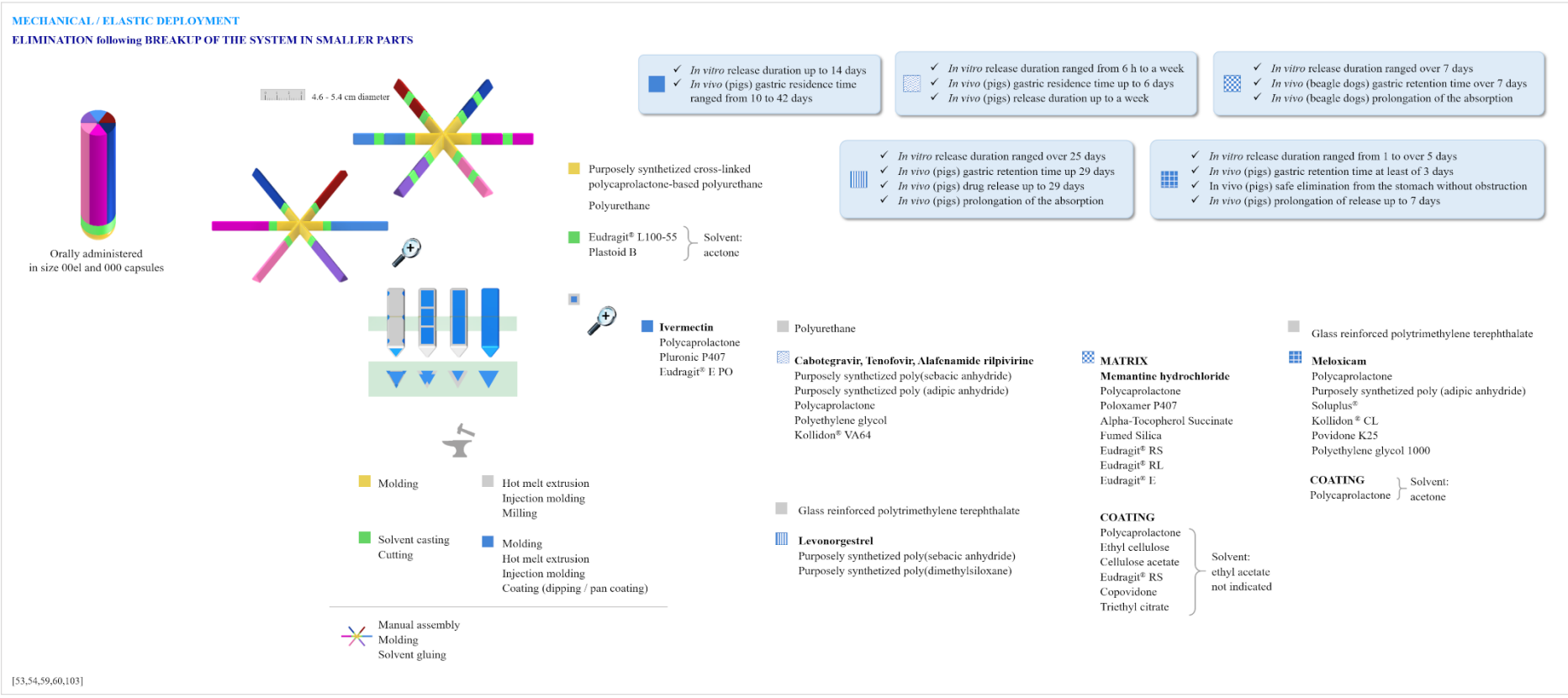
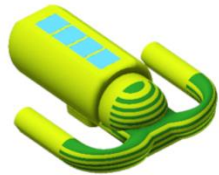


Figure 3a: Outline of expandable GR DDSs the unfolding behavior of which is based on mechanical/elastic deployment: systems of various 3D geometries.

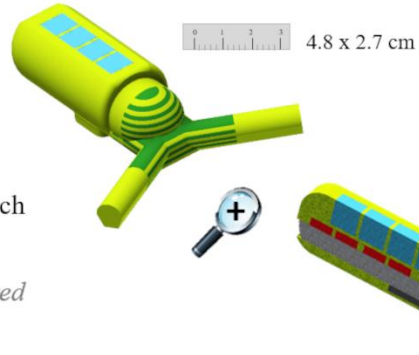
MECHANICAL / ELASTIC DEPLOYMENT

ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS










Directly delivered into the stomach
through an orogastric tube




*Designed to be orally administered
in size 000 capsules*



- ✓ *In vitro* size increasing in 50 s
- ✓ *In vitro* prolonged release over 1 week
- ✓ *In vitro* broadcasting lifetime of 20 days
- ✓ *In vivo* (pigs) gastric residence up to 36 days
- ✓ *In vivo* (pigs) wireless communication up to 15 days
- ✓ *In vivo* (pigs) disassembly

-  **Doxycycline hyclate**
Polycaprolactone
-  **Stainless steel beads**
Polylactic acid
Epoxy conductive traces
-  Polyurethane
-  Coin cell batteries
-  Antenna
-  Radio-frequency chipset
-  **Levonorgestrel**
Poly(dimethylsiloxane)



-  Melting
3D printing
-  3D printing
-  3D printing



- Molding
- Manual assembly

[82]

Figure 3b: Outline of expandable GR DDSs the unfolding behavior of which is based on mechanical/elastic deployment: systems implemented with electronics.

Other unfolding-based expandable GR DDSs are those entailing the use of smart materials having unique properties. In particular, shape memory materials, including both polymers and alloys, which has recently drawn a special interest in many industrial fields, were considered [105-109]. Their most interesting feature is probably the relevant ability to experience shape variations under the application of an appropriate external *stimulus* of a non-mechanical nature. These include changes in temperature, light, magnetic field or contact with water. In particular, prototypes are fabricated with a specific geometry, called original shape. Subsequently, they can be forced under defined conditions, involving for instance mechanical stress and heat, to assume a different temporary shape. At this point, the products remain in the given temporary configuration until the triggering *stimulus* would cause the recovery of the original shape (*i.e.* shape memory effect).

Focusing on system based on shape memory polymers, only very recently feasibility studies, and some preliminary data on the development, of a retentive delivery platform for the administration of drugs into hollow muscular organs and particularly into the stomach were presented (Figure 4) [110,111]. For this application, a pharmaceutical-grade hydrophilic swellable soluble polymer was employed to fabricate *via* hot-melt extrusion and FDM some prototypes of prolonged-release systems, which represent one of the first examples of 4D printing in the relevant literature. They were also equipped with an external permeable coating film able to improve the duration of the release performance beyond 12-18 hours [112]. Original simple expanded shapes were obtained under manufacturing and programmed to different temporary collapsed configurations suitable for oral intake inside commercially-available capsules. The physiological shape shifting is expected to be triggered by contact with aqueous fluids at body temperature and, interestingly, during *in vitro* testing, the shape memory behavior turned out not to be affected by the presence of the coating. Novel characterization methods and the set-up of dedicated constitutive models as well as related computational methods to be employed in the relevant development were proposed [113]. The properties of the starting materials bode well for a safe and complete elimination of the exhausted system.

SHAPE MEMORY EFFECT

ELIMINATION following REDUCTION IN MECHANICAL RESISTANCE

✓ *In vitro* release ranged from to more than 24 h



Orally administered in size 00 and AA DB capsules



15 mm height 25 mm height
17 mm diameter 27 mm diameter

25 mm height
36 mm in base diameter
10 mm top diameter

25 mm x 25 mm x 21 mm



■ **Allopurinol**
Poly(vinyl alcohol)
Glycerol

COATING

Eudragit® RS } Solvent:
Eudragit® RL } ethanol
Triethyl citrate }

Eudragit® NE } Solvent:
water }



Hot melt extrusion
3D printing
Coating

[111,112,113]

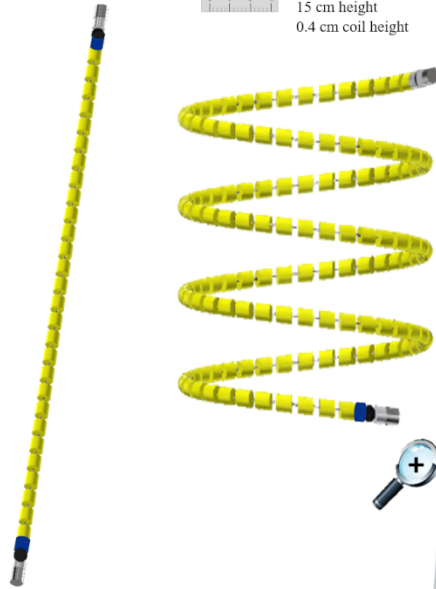
Figure 4: Outline of an expandable GR DDSs, the unfolding behavior of which is based on shape memory effect.

In the case of alloys provided with shape memory effect, nitinol represents the material of choice in view of its well-established use in the biomedical field and its proved safety-profile [114-116]. However, researchers developing GR expandable DDSs took mainly advantage of its superplastic behavior rather than its shape memory effect (Figure 5) [46,50]. Indeed, superelasticity is the ability of the material to immediately undergo a shape change upon removal of an external stress, which cannot be controlled nor programmed and typically occurs at room temperature. The device consists of a nitinol wire representing its skeleton, on which several prolonged release matrices, having a central hollow, are inserted. The ends of wire are closed by a locking system equipped with a magnet. In this respect, customization in terms of type/strengths of drugs to be delivered and/or duration of the release would be attained by increasing the length of the nitinol wire, the number of matrices inserted and their formulation. In a further evolution of the DDSs, the end containing the magnet could also be provided with a range of sensors (*e.g.* for ethanol and temperature) to be connected *via* bluetooth with mobile phones to enable monitoring of the patients and improve their engagement into the therapy. The administration of the spring-like system took place by elongating and forcing it into a nasogastric tube. The latter, upon insertion into the nasal cavity, could reach the stomach through the esophagus. Once in the target organ and coming out of the nasogastric tube, the nitinol wire would regain its helix-configuration due to superelasticity within 1 min. Being characterized by a sufficient spatial encumbrance, this would prevent the system to be emptied through the pylorus. At the end of release, the device would be recovered through the same nasogastric tube used for administration, but equipped with a sensor and a magnet. This way, it would be possible to track the position of the device in the stomach and to bind, by attraction, the magnet at the end of the nitinol wire, thus favoring the device removal.

SUPERELASTIC DEPLOYMENT

MANUAL REMOVAL

10.4 cm diameter
15 cm height
0.4 cm coil height



Directly delivered into the stomach through a nasogastric tube

MATRIX
Doxycycline hyclate, Isoniazid, Ethambutol, Pyrazinamide, Moxifloxacin, Rifampicin
Vinylpolysiloxane
Polyethylene glycol 400
Polyethylene glycol 3500

COATING
Eudragit® RS 100
Polycaprolactone
Talc
Triethyl citrate

Solvent:
acetone
isopropanol

- Nitinol wire
- Polycaprolactone
- Retainer
- Glue
- Magnet
- Tube

MATRIX
Sofosbuvir, Daclatasvir, Ledipasvir, Ribavirin
Vinylpolysiloxane
Polycaprolactone of different molecular weight
Pluronic P407
Poly(ethylene glycol)

COATING
Polycaprolactone

Solvent:
not indicated

- Nitinol wire
- Battery
- Bluetooth and temperature sensor
- Ethanol sensor
- Glue
- Magnet
- Protective membrane

- ✓ *In vivo* drug release duration up to 30 days
- ✓ *In vivo* (pigs) gastric residence time over 28 days
- ✓ *In vivo* (pigs) drug release duration over 28 days

- ✓ *In vitro* release duration up to 30 days
- ✓ *In vitro* sensing capabilities for 30 days
- ✓ *Ex vivo* (pigs) sensing capabilities
- ✓ *In vivo* (pigs) gastric residence time up to 30 days
- ✓ *In vivo* (pigs) release duration up to 30 days



- Casting
- Molding
- Cutting
- Punching
- Coating
- Molding
- Wrapping
- Heating
- Quenching



[46,50]

Figure 5: Outline of expandable GR DDSs, the unfolding behavior of which is based on superelastic deployment.

3.1.2 Piercing DDSs

The proof of concept for microneedle-based delivery into the upper GI tract might be dated back to less than 10 years ago, with the researchers trying to address the challenge associated with oral administration of biologics [61]. As a first step towards the development of piercing DDSs, a placebo microneedle capsule-like structure was studied *in vivo* on pigs by radiographs, upon relevant stomach positioning *via* an overtube. Any evidence of obstruction, perforation or tissue damage was discarded, thus supporting the possibility for this system to undergo safe elimination through the GI tract. Such a conclusion was even strengthened considering that the device was retained for 7 days. In parallel, serial injections of insulin were performed on the gastric, duodenal and colonic mucosa of the same animal model, and resulted more effective (improved pharmacokinetics and a more robust hypoglycemic effect) than subcutaneously administered ones taken as a reference standard. Given the rather large diameter and the number of metallic needles employed, the safe passage observed with this prototype reassured and further highlighted the potential of this administration method for safe oral delivery of macromolecules.

These initial studies prompted the subsequent research and several works have been published on the topic since then, proposing more advanced and increasingly complex piercing systems and specific target areas for injection, from mouth to esophagus, stomach and small intestine as well [86-90]. The most recent evolution in this respect involved either the achievement of different release kinetics or the development of devices characterized by high versatility (*e.g.* type and dose of active molecules and of formulations to be loaded). This step forward was probably taken to match the needs of the rapidly growing concept of precision medicine and to ease the availability of therapies based on nucleic acids, which raised a lot of attention during the recent Covid-19 emergency.

So far, systems proposed in the scientific literature entailed both hollow and solid microneedles. In this respect, the former would deliver the active molecule from an inner reservoir, that could even be potentially compressed and activated by the peristaltic contraction. On the other hand, solid microneedles would contain the drug into their formulation so as, upon injection, they could break

off from the overall system and penetrate into the tissue, thus having them releasing the drug in a controlled manner.

Design and development of piercing DDSs necessarily involved a multi-disciplinary approach, also entailing simulation modeling to perfectly tune the devices to work as expected before producing the actual prototypes to be tested. By way of example, the size/composition and the possibility for the system to broke in many small pieces needed to be accurately studied to ensure safe passage through the GI tract [86]. In this respect, the size of the OROS system (9 mm in diameter and 15 mm in length; 12 mm in diameter and 5 mm in length) was often used as a threshold reference value in the development of orally administered piercing DDSs. Indeed, this is a non-degrading drug delivery device already approved by the Food and Drug Administration based on the limited risk to cause GI obstruction (approximately 1 in 39 million or less). Also the actuation mechanism of the systems has become progressively more articulated, for instance decoupling the movement of the needles from the actual delivery of the loaded drugs, proposing solutions to ensure a controlled injection when or where it was more appropriate to happen and evaluating the possibility to exert different pressures on the pierced tissue. Overall, the reviewed piercing DDSs were fabricated using many different techniques, involving both subtractive and additive processes, and relying on final manual assembly. Although manufacturing methods compatible with mass-production started to be identified, feasibility of these DDSs - generally characterized by high design complexity and composed of multiple parts to be assembled - by automated large-scale process still needs to be validated. In addition, further research would also be required to determine chronic effects caused by daily GI injections, foreign body response and local therapeutic agent exposure.

Piercing DDSs intended to deliver active molecules into the esophagus, the stomach or in the small intestine are graphically described in the following Figures 6-8.

Injection into the esophageal submucosa can be attained with systems that, upon insertion into the hollow organ with an endoscope or an orogastric tube, could be activated to perform piercing and then removed rapidly and safely. A DDSs combining expandable and piercing capabilities was

conceived drawing inspiration from a blooming flower [89]. It is composed of four arms connected through elastic L-beam-shaped recoil elements to a central core. Upon the recoil elements relieving the elastic energy trapped during folding the flower would open (unfolded cumbersome configuration) and the microneedles connected to the external surface of the arms penetrate the esophageal mucosa, enabling drug delivery. On the other hand, the shape memory effect of four nitinol springs added to the bottom surface of the arms, triggered by a local temperature increase attained by spraying of warm fluids, was used to promote the flower closure. This way, the system could be safely removed, reducing risks of tissue perforation during the extraction phase. In a second application, a drug-depositing stent inspired by Kirigami, the Japanese paper art of folding and cutting, and by the skin of scaly animals was developed [90]. This is neither intended to be ingested nor implanted, but is placed *in situ* and activated by fluid pressure to enable piercing and delivery of the payload before being removed. The system entailed an external surface, showing periodic array of denticle-like needles, integrated with a pneumatic soft actuator. Thanks to fluid transfer via a syringe connected to the inner actuator, radial expansion of the overall stent could occur. This stretching caused a change in needle orientation (*i.e.* from planar to perpendicular to the stent body surface), enabling submucosal injections of drug-loaded degradable microparticles. Given the promising results obtained and the possibility of manufacturing the stent in different sizes, this DDSs could have an interesting application potential for drug delivery in other tubular organs, such as arteries and airways.

Moving forward along the GI tract, different piercing systems intended for oral administration were developed, thus avoiding the need for an invasive administration mode to be performed by trained personnel. Resembling expandable unfolding strategies based on mechanical/elastic deployment, the LUMI (*i.e.* luminal unfolding microneedle injector) system was described for the intestinal delivery of biologics [88]. It is provided with 3 separated arms equipped with degradable microneedles, able to ensure multiple points of contact with the intestinal tissue in both axial and parallel orientation. Moreover, to avoid dissolution of the microneedles before piercing, the LUMI device was inserted

into a custom-made capsule-like shell. This way, the drug-containing parts can stay separated from the gastric and intestinal fluids until seconds before actuation. Indeed, once at the site of interest, the folded device is propelled out of the capsule thanks to the mechanical actuation of an inner spring, the latter being triggered by the dissolution of an enteric coating applied to only one end of the external shell. Notably, the coating composition could be modified to attain different duration of its dissolution phase, thus in principle having the microneedle-containing device released earlier or later. Free from the external constraint, the latter would gain its expanded piercing configuration thanks to the mechanical/elastic deployment of the core. In this respect, the system would be able to control the time of release by promoting piercing in different areas of the small intestine. Once emptied, the capsule broke apart into different pieces and the arms underwent dissolution to prevent GI blockage. The metal components of the LUMI system could represent an issue at this regard, for instance in view of possible interference with imaging machines. However, other polymeric material could be used to replace these parts in further development stages.

Keeping the idea of developing an easily ingestible system, a self-orienting millimeter-scale applicator (SOMA), able to autonomously insert drug-loaded milliposts into the gastric mucosa was described [86,87,117]. In fact, being characterized by a wall thickness in the 4-6 mm range, a quick regeneration capability and a mucous barrier that could temporary seals defects in the lining, the stomach would be characterized by less risk of tissue perforation. Mimicking the behavior of leopard tortoise, the SOMA system was optimized for rapid self-orientation regardless of external conditions (*e.g.* peristaltic contractions, presence of food). Based on its design and composition, the system was able to always assume a preferred orientation in the stomach, thus only exposing the needle towards the tissue to be punctured. Indeed, the coming out of the needle was attained by a spring-based actuation mechanism, *i.e.* a compressed spring encapsulated into a mixture of soluble materials able to hold it in this configuration until complete dissolution following contact with biological fluids. In a further evolution (L-SOMA), the system was also engineered to *i)* increase the dosing sizes, *ii)* ensure a fast action, thus broadening the release pattern over the delayed or prolonged kinetics

previously pursued, and *iii*) decouple the needle insertion from the drug injection process. As a consequence, the entire dose can be delivered directly into the tissue, thus in principle avoiding contact of the drug with the gastric fluids and possible degradation phenomena. Notably, this was attained by implementing the device with a multi-spring actuation system. The liquid formulations to be loaded would mimic the pre-approved and pre-tested parenteral ones, thus potentially reducing the time to-market of the new device. A version capable of retracting the needle after injection was also designed. More recently, the possibility to effectively deliver nucleic acids through the SOMA system was also investigated, studying the transfection of dosed mRNA in cells and in animal models [117]. The nucleic acids were formulated in nanoparticles starting from purposely-synthesized polymers. These were demonstrated successful to improve stability, to convey clinical relevant doses (up to 150 µg) and to achieve efficient *in vivo* transfection/translation by limiting relevant degradation upon injection. The piercing DDSs that can be considered at the most advanced stage of development is the robotic capsule RaniPill™ from Rani Therapeutics, intended for the delivery in the small intestine [118-125]. It entails a hydroxypropyl methylcellulose-based capsule coated with a gastroresistant film and containing a microsyringe. The latter was equipped with a dissolvable drug-containing needle and was attached to a self-inflating polyethylene balloon, the latter being properly folded to fit into the capsule. Upon contact with intestinal fluids, the balloon spontaneously inflated, as a result of the development of carbon dioxide produced by the contact between the effervescent adjuvants it contained, thus being able to direct the microsyringe toward the intestinal walls (*i.e.* perpendicular to the long axis of the small intestine) and activate the plunger. This caused injection of the drug-filled needle directly into the tissue where its external shell dissolved within 15 minutes while releasing the drug contained. Finally, the balloon deflated and the system could safely pass through the rest of the GI.

The RaniPill™ proof-of-concept was attained using insulin, while a phase I study was successfully completed in 2019 with octreotide, demonstrating safety, tolerability and effectiveness of the device, which was able to achieve high reliability and bioavailability [126,127]. Interestingly, no incidence

of pain or discomfort associated during both deployment and needle delivery was reported. Being considered particularly promising, the system was also envisaged for the delivery of other biologics, such as tumor necrosis factor α inhibitors, parathyroid hormone, human growth hormone, and glucagon-like peptide. However, the RaniPill™ still has some criticalities that would need to be thoroughly considered, such as the lack of predictability of the drug delivery time, due to the inherent variability in stomach emptying and the drug payload it can accommodate, which is currently defined by the capacity of the single needle (*i.e.* approximately 3.5 mg).

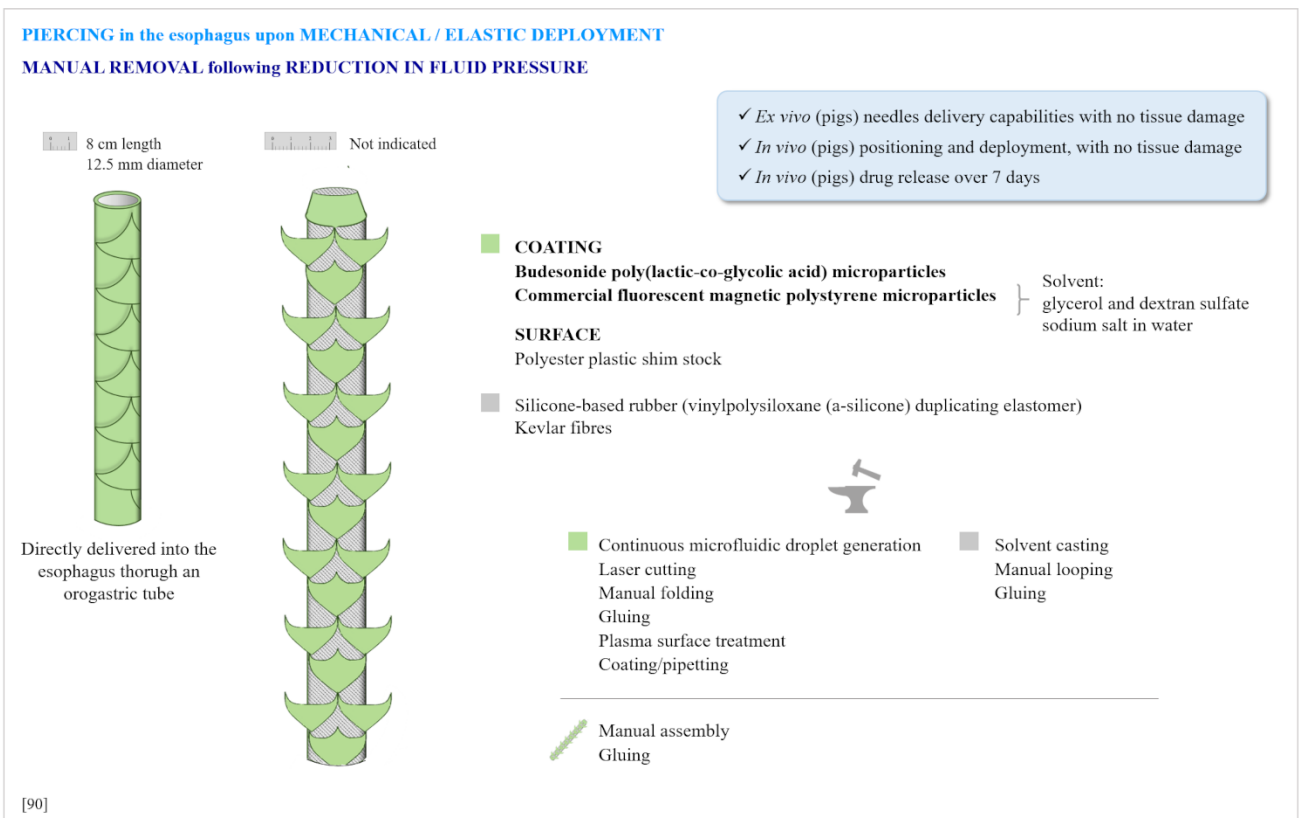
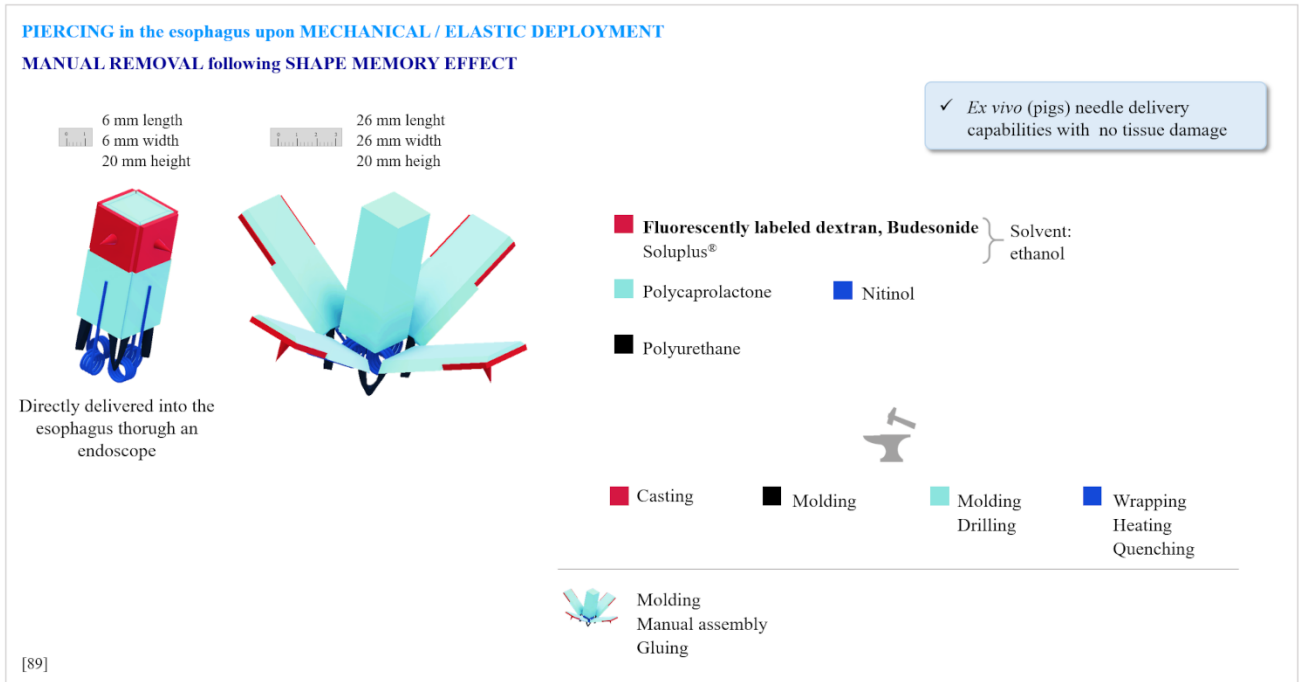
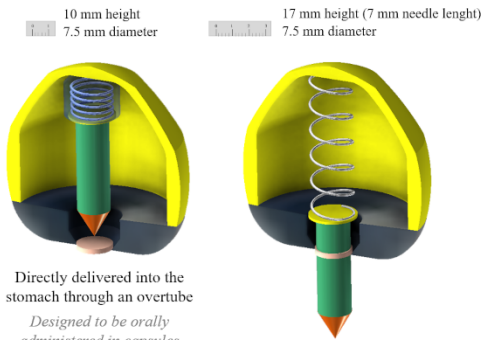


Figure 6: Outline of piercing DDSs for the release of drugs in the esophagus.

PIERCING in the stomach upon MECHANICAL/ ELASTIC DEPLOYMENT
ELIMINATION of the ENTIRE SYSTEM



Directly delivered into the stomach through an overtube
 Designed to be orally administered in capsules

- Human insulin, lysozyme, glucose-6-phosphate dehydrogenase, steel washer, BaSO₄
Poly(ethylene) oxide 200,000
- Poly(ethylene) oxide 200,000
Hydroxy propyl cellulose
- 316L stainless steel
Field's metal
- Two-component silicone rubber
- Polycaprolactone
Dense polypropylene
- Stainless steel
- Sucrose
Isomalt

- ✓ *In vitro* (media having diverse viscosities) self-orientation capabilities
- ✓ *In vitro* resistance to outside motion
- ✓ *In vitro* drug dissolution in 60 min
- ✓ *In vitro* enzymatic activity
- ✓ *Ex vivo* (pigs) self-orientation capabilities and persistence of mucosal engagement
- ✓ *In vivo* (pigs) self-orientation capabilities and persistence of mucosal engagement
- ✓ *In vivo* (pigs) needle delivery capabilities, with no tissue damage
- ✓ *In vivo* (pigs) prolonged release for at least 30 h
- ✓ *In vivo* (pigs) gastric retention up to 9 days
- ✓ *In vivo* (pigs) safe elimination

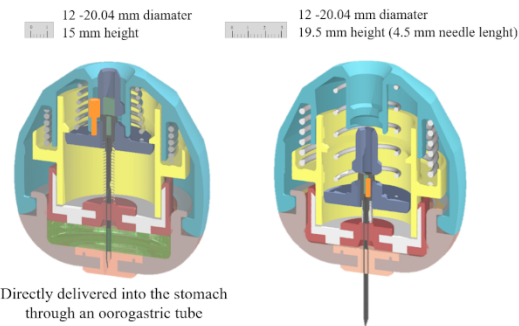
- Molding Compression
- Milling
- Molding Compression
- Molding
- Casting Cutting
- Molding

- Manual assembly
Compression
Melting

[86]

SOMA system

PIERCING in the stomach upon MECHANICAL/ ELASTIC DEPLOYMENT
ELIMINATION of the ENTIRE SYSTEM



Directly delivered into the stomach through an oro-gastric tube
 Designed to be orally administered in capsules

- Adalimumab, Insulin, Glucagon-like peptide-1 receptor agonist, Epinephrine
 - Branched and branched hybrid nanoparticles containing
 - purposely synthesized poly(b-amino esters)
 - mRNA / plasmid DNA
 - sucrose
- Solvent: water and serum-free medium
- 304 stainless steel
 - VisiJet SL Flex ink
Pro Black 10 ink
 - Silicone
 - Polyoxymethylene
 - Thermoplastic elastomers
 - 18-8 stainless steel
 - Polyphenylene ether
 - Thermoplastic elastomers
 - Stainless steel
 - Isomalt

- ✓ *Ex vivo* (pigs, dogs) self-orientation and injection capabilities with no tissue damage
- ✓ *Ex vivo* (pigs) retraction capabilities
- ✓ *In vivo* (pigs) needle delivery capabilities, with no main tissue damage
- ✓ *In vivo* (pigs) capabilities to deliver larger drug doses
- ✓ *In vivo* (pigs) prolonged drug level for at least 3 days

- ✓ *In vitro* (cells) transfection and translation
- ✓ *In vivo* (mice) systemic uptake, transfection and translation upon stomach injection
- ✓ *In vivo* (pigs) needle delivery capabilities, with no main tissue damage
- ✓ *In vivo* (pigs) transfection and translation need to be confirmed

- Not indicated
- Milling
- Casting
- Dissolution/dispersion
Mixing by pipetting
Lyophilization
Reconstitution
- Injection molding
- Not indicated
- Injection molding
- Milling
- Injection molding
- Compression
- 3D printing
Curing
- Injection molding

- Manual assembly
Compression
Melting

[87,117]

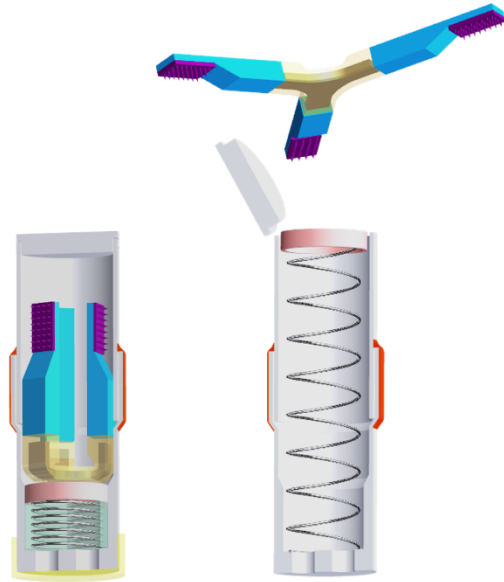
SOMA and L-SOMA systems

Figure 7: Outline of piercing DDSs for the release of drugs in the small intestine.

PIERCING in the small intestine upon MECHANICAL / ELASTIC DEPLOYMENT
ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS

9 mm diameter
 30 mm length
 1mm height and 0.4 mm base diameter of

23-25 mm arm length
 12 mm core diameter
 1.5 mm core height
 1.5 x arm length = triangle height



Directly delivered into the stomach through an orogastric tube
 Designed to be orally administered

- ✓ *In vitro* actuation and modulation of the working mechanism
- ✓ *In vitro* disassembly
- ✓ *In vitro* arm degradation in 24 h
- ✓ *Ex vivo* (pigs, humans) needles delivery capabilities, with no tissue damage
- ✓ *In vivo* (pigs) deployment
- ✓ *In vivo* (pigs) needles delivery capabilities, with no tissue damage
- ✓ *In vivo* (pigs) elimination
- ✓ *In vivo* (pigs) arm degradation in 24 h

- Insulin, lysozyme, α -glucosidase, BaSO₄, tissue marking dye
 Polyvinylpyrrolidone 58,000
 Sorbitol } Water
- Stainless steel
 Mediprene elastomer
- Polyethylene oxide 100,000 - 200,000 Soluplus®
- Eudragit® S100 } Solvent: Water, Acetone, Isopropanol
 Triethyl citrate
 Talc
- Eudragit® L100 } Solvent: Water, Acetone, Isopropanol
 Triethyl citrate
 Talc
- Polyethylene glycol 3,000 - 35,000
- Metal Polycaprolactone
- Not indicated
- Not indicated

- Powder deposition in molds
- Liquid binding
- Centrifugation
- Drying
- Sanding
- Coating
- Milling
- Molding
- Hot melt extrusion
- Molding
- Spray coating (airbrush)
- Spray coating (airbrush)
- Melting
- Trimming
- Cutting
- Compression
- Coating
- Printing
- Not indicated

- Tying (SparkFun conductive thread)
- Heating
- Manual assembly

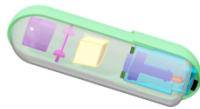
[88]

LUMI system

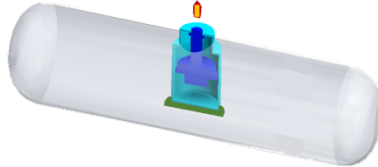
PIERCING in the small intestine upon GAS INDUCED DEPLOYMENT
ELIMINATION following DEFLATION

2.61 cm length
 1 cm diameter

7.3 - 7.7 cm length (5.1 ± 0.13 mm needle length)
 2.1 - 2.5 mm diameter



Orally administered in size 000 capsule



- ✓ *In vivo* (humans) safety and tolerability
- ✓ *In vivo* (humans) needle delivery capabilities, with no tissue damage or pain
- ✓ *In vivo* (humans) high release reliability and drug bioavailability

- Insulin
- Octreotide
- BaSO₄
- Polyethylene glycol
- Polyethylene oxide
- Polyethylene
- Eudragit® L30-D55
- Plasacyl™ HTP20
- Hydroxypropyl methylcellulose
- Polyethylene
- Citric acid
- Potassium bicarbonate
- Polyethylene
- Bismuth
- Liophilization
- Tableting
- Tableting
- Coating (pan coating)
- Tableting

- Manual assembly

[119,120]

RANIPILL™ system

Figure 8: Outline of piercing DDSs for the release of drugs in the stomach

Highlights and conclusions

A comprehensive literature review was performed focusing on the specific goals of drug delivery in the upper GI tract, upon oral intake, and on the systems proposed so far to achieve them. In this respect, few release strategies have been more thoroughly investigated in the scientific literature and are currently recognized as more established, encompassing low-density, adhesive and swellable expandable GR DDSs. However, the more creative and complex systems, even devised for implementation with electronics, were deepened taking advantage of graphic representations. This way, it was highlighted their *i)* administration mode, *ii)* mechanism for reaching/being maintained at the site of release as well as for undergoing safe removal and *iii)* main design, formulation, manufacturing and performance characteristics. The smart devices reviewed at this stage encompassed mainly GR DDSs relying on unfolding, and piercing systems targeting different regions of the upper GI tract, from the esophagus to the small intestine. In the pharmaceutical field, they might enable real innovations in terms of achievable therapeutic goals, such as ultra-long release over days, development of combination products, even personalized, effective and safe oral delivery of biologics. The main criticalities that were more or less common to the different smart devices reviewed and still need to be adequately addressed in order to find viable solutions were represented by:

- i)* the complexity of the manufacturing approach pursued, that needs to be streamlined and potentially automated. Indeed, it was often a multi-step process, involving the use of solvents as well as purposely synthesized materials, and encompassing different parts to be fabricated and assembled. Moreover, it was partially performed manually, thus impacting on product reproducibility;
- ii)* the residence time at the site of interest, which in some cases needed to be improved;
- iii)* the stability over time of mechanical/technological properties and release performance;
- iv)* the safety of use and long-terms effects associated with relatively invasive administration and delivery modes (*e.g.* orogastric tubes, endoscopes, repeated piercing of the mucosa to

inject the drug) as well as removal procedures, which may lead to possible infection and inflammation.

None of the systems described are currently on the market but some of them are at an advanced stage of development. In this respect, the solutions proposed so far for enabling administration, activation, release or removal of the DDSs could represent useful insights for promoting further development in the field, leading to a faster achievement of the therapeutic targets pursued and of the recently-identified objectives of precision medicine.

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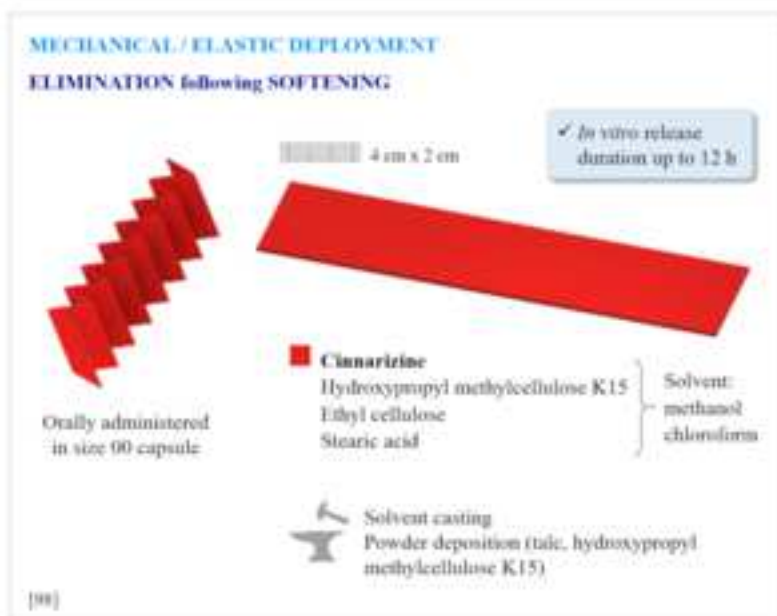
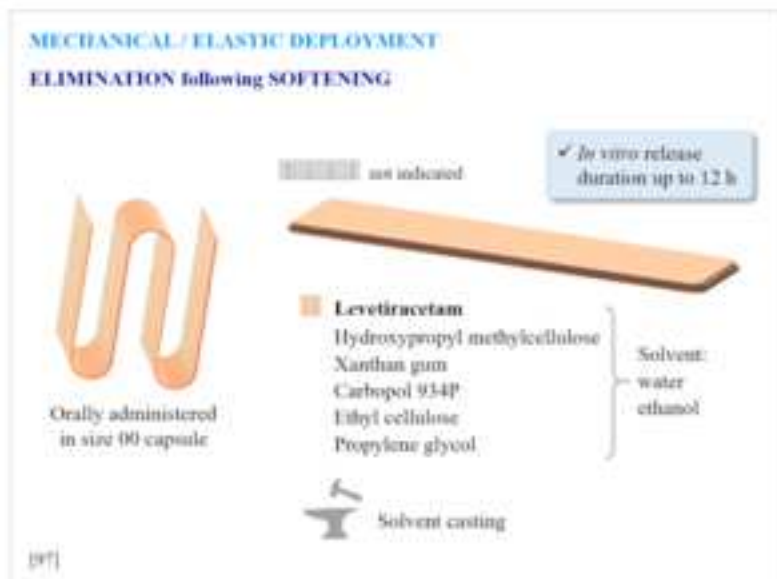
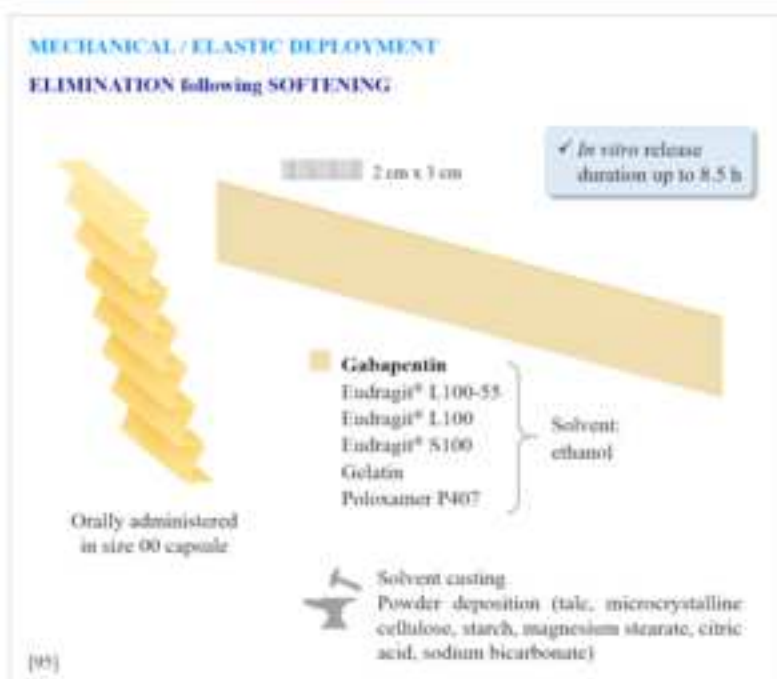
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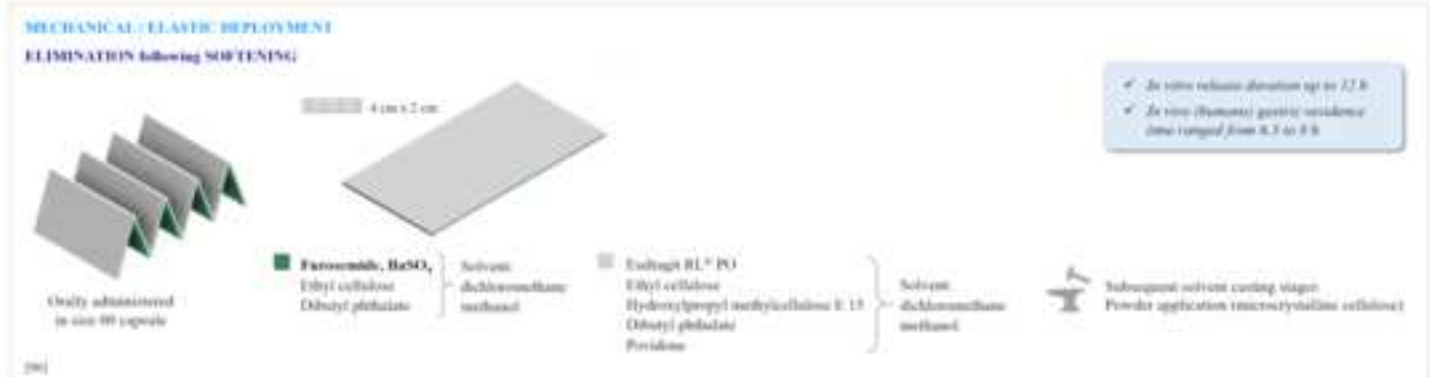
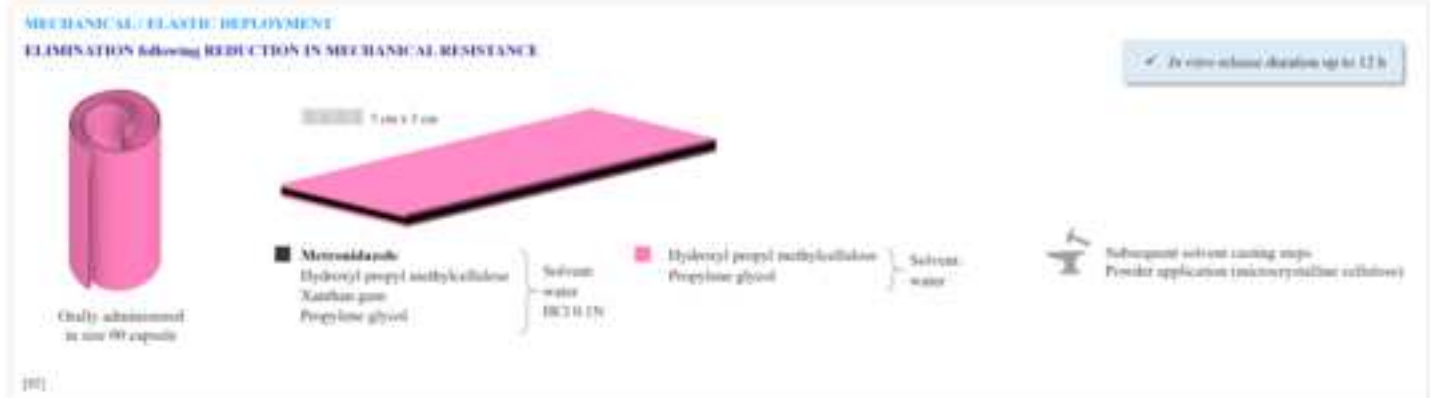
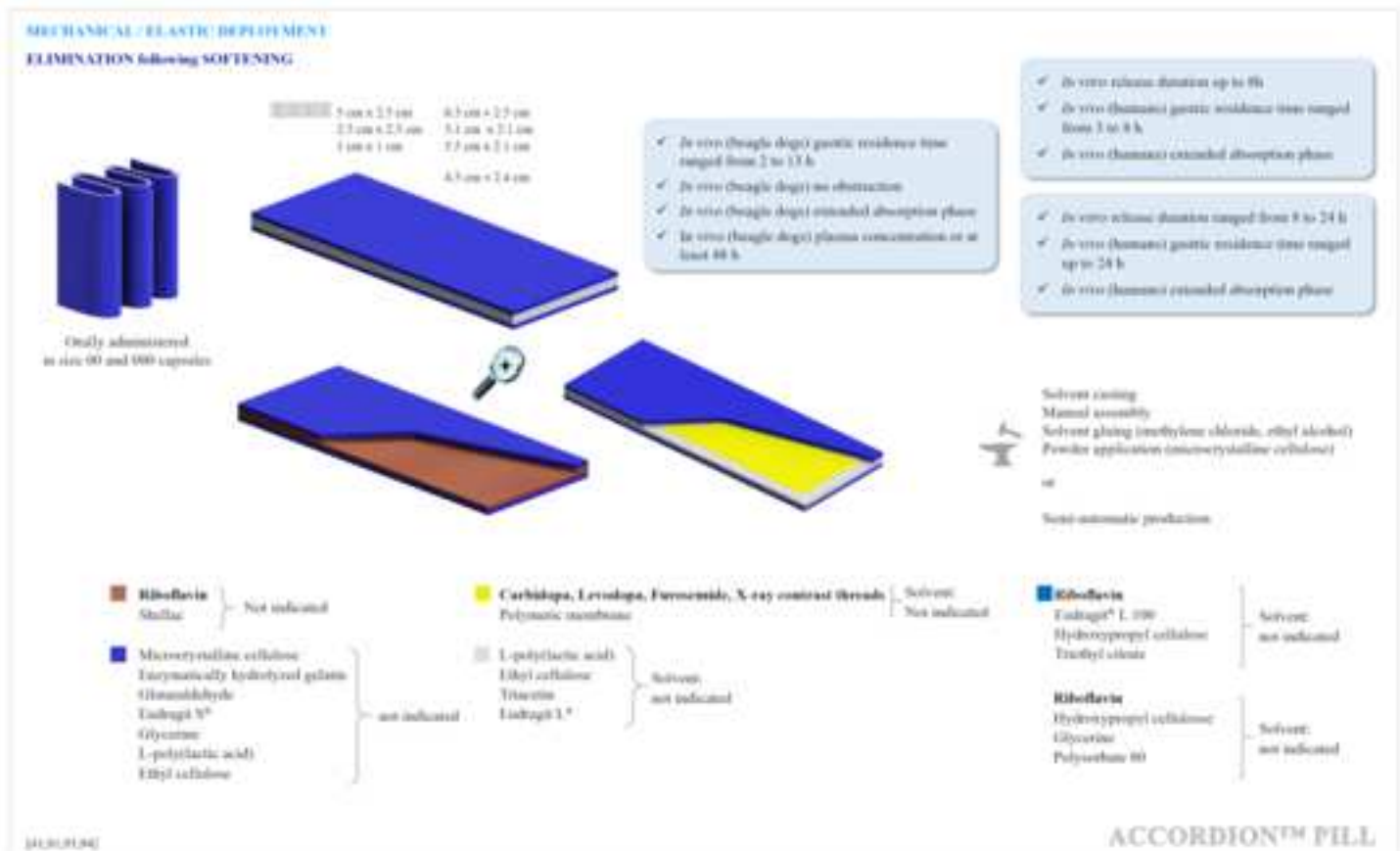
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Uboldi et al., Figure 2.tif




MECHANICAL / ELASTIC DEPLOYMENT**ELIMINATION following BREAKUP OF THE SYSTEM IN SMALLER PARTS**

Directly delivered into the stomach
through an orogastric tube.


*Designed to be orally administered
in size 000 capsules*



- ✓ *In vitro* size increasing in 50 s
- ✓ *In vitro* prolonged release over 1 week
- ✓ *In vitro* broadcasting lifetime of 20 days
- ✓ *In vivo* (pigs) gastric residence up to 36 days
- ✓ *In vivo* (pigs) wireless communication up to 15 days
- ✓ *In vivo* (pigs) disassembly

 **Doxycycline hyclate**
Polycaprolactone

Levonorgestrel
Poly(dimethylsiloxane)

 **Stainless steel beads**
Polylactic acid
Epoxy conductive traces


 Polyurethane

 Coin cell batteries

 Antenna

 Radio-frequency chipset



 Melting
3D printing

 3D printing

 3D printing



Molding
Manual assembly

SHAPE MEMORY EFFECT

ELIMINATION following REDUCTION IN MECHANICAL RESISTANCE

✓ *In vitro* release ranged from to more than 24 h



Orally administered in size 00 and AA DB capsules

- 15 mm height 25 mm height
- 17 mm diameter 27 mm diameter
- 25 mm height
- 36 mm in base diameter
- 10 mm top diameter
- 25 mm x 25 mm x 21 mm



- **Allopurinol**
- Poly(vinyl alcohol)
- Glycerol

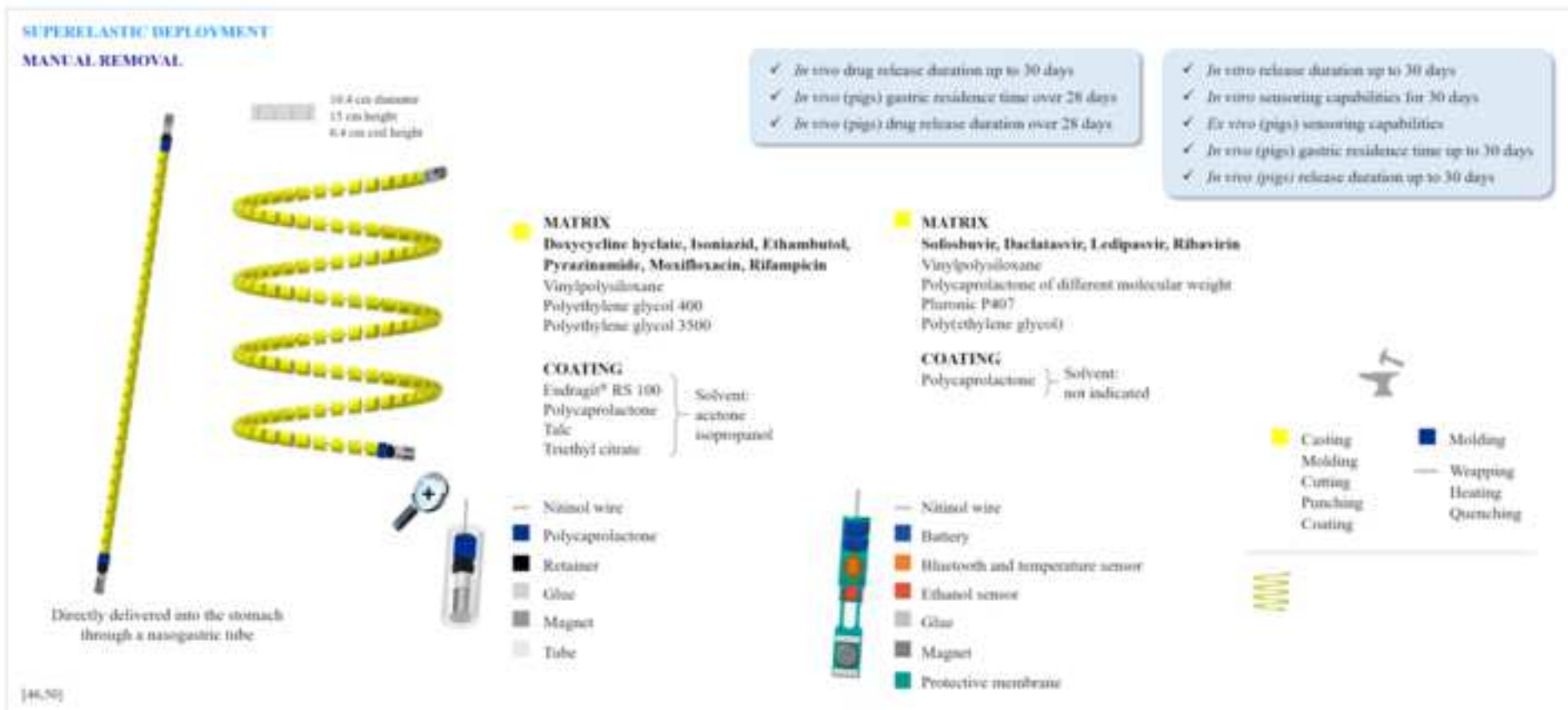
COATING

- Eudragit® RS
 - Eudragit® RL
 - Triethyl citrate
- } Solvent: ethanol

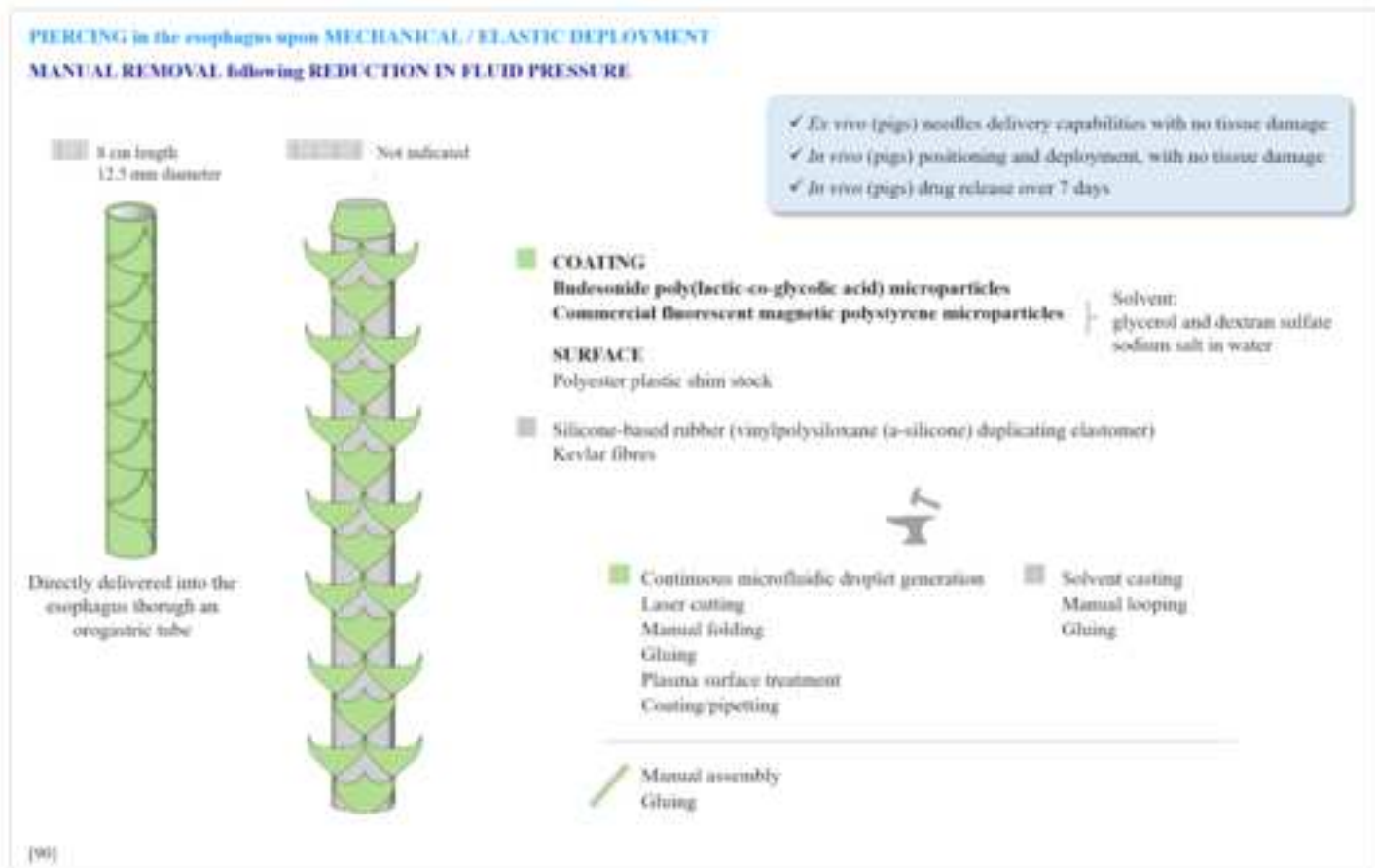
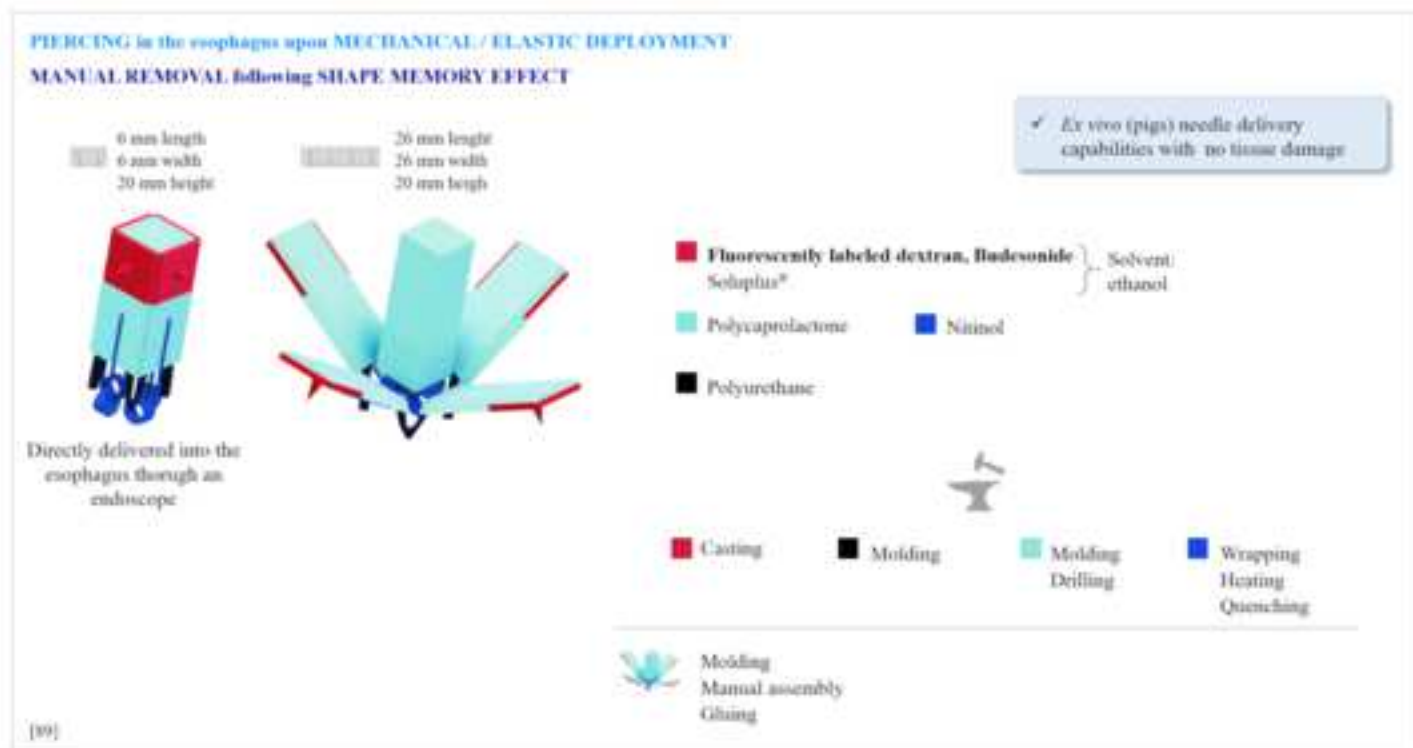
- Eudragit® NE
- } Solvent: water

- Hot melt extrusion
- 3D printing
- Coating

[111,112,113]



Uboldi et al., Figure 6.tif



Uboldi et al., Figure 7.tif

