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Retentive Drug Delivery Systems Based on Shape Memory Materials

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Abstract

Retentive drug delivery systems are intended for prolonged residence and release inside hollow organs of the body, in pursuit of either local or systemic therapeutic goals. Because of the relatively long-lasting period of time they could cover during operation, a primary advantage arising from their use would lie in reduced dosing frequency, thereby improving the overall adherence of patients to prescribed medication regimens. The treatment of numerous pathologies that affect the urinary bladder and the stomach could especially benefit from viability of such delivery technologies. Moreover, by making use of effective gastroretentive dosage forms, the bioavailability of drugs that are preferably absorbed from the upper gastrointestinal tract could be increased. Expansion of devices following administration is often exploited for retention purposes, and several formulation strategies have been proposed in this respect. Innovative applications of shape memory materials have also been explored, highlighting the great inherent potential for facing the challenges involved.

Introduction

In pharmaceutical care, the lack of adherence to prescribed administration regimens is widely known to negatively impact on the therapeutic outcome, having unfavorable repercussions on risk to benefit ratio and healthcare costs. Among therapy-related factors, the dosing frequency represents one of the main determinants of poor patient compliance[1]. This would particularly apply to chronic disease conditions involving lifelong medication or inconvenient modes and routes of administration, which will increasingly be the case in view of population aging and ever more numerous treatments based on biological drugs having unfavorable biopharmaceutical and pharmacokinetic properties. Thus, there is a strong rationale behind all efforts made to reduce the degree of complexity of dosing schedules.

Drug delivery sciences are primarily concerned with supplying the patients' body with the right amount of the indicated bioactive molecules according to the most appropriate spatial and temporal patterns for meeting therapeutic needs that are being faced. Since its earliest days, research in this field has been endeavoring to tackle the issues raised by frequent dosing. As a result, prolonged-release dosage forms, able to make the bioactive molecule slowly available for absorption over an extended period of time, have been proposed in a large number and variety during the last fifty years, mainly with the aim of counteracting drug elimination half-lives that would bind to more closely repeated administration. In several instances, such delivery systems, mostly intended for peroral or parenteral dosing, have been proved highly successful in lessening the burden brought about by pharmacological therapy. Particularly, advanced formulations meant for the oral route have led to once- or twice-daily dosing of bioactive compounds that would involve frequent daylong intake when given as immediate-release dosage forms, thereby impacting heavily on living habits and posing a serious threat to adherence[2]. On the other hand, the use of injectable and implantable systems for prolonged drug release, which are not affected by the limited gastrointestinal residence time, has made infradian time spans between successive doses even possible, thus helping reduce dropouts due to pain and discomfort associated with invasive dosage.

However, while prolongation of drug release over time through proper formulation strategies is invariably required for a reduced dosing frequency, it may alone be insufficient to address such issues. For instance, this might occur when it is necessary to establish persisting effective drug concentrations within a specific compartment of the body, often because a local action is sought and systemic exposure is deliberately prevented[3]. Otherwise, preferential entryways to

the systemic circulation, such as absorption windows in the upper gastrointestinal tract, may need to be exploited. In all of these cases, extended residence of the drug delivery system at the site of action or absorption would also be necessary. Accordingly, a more complex approach based on combined strategies or technologies has to be pursued in order to consistently slow down release of the bioactive compound(s) irrespective of the physiological variables encountered (volume, pH, ionic strength, composition and hydrodynamics of the medium, presence of enzymes, mucus *etc*.) and concomitantly maintain the delivery system in the desired anatomical position throughout a sufficiently long-lasting period of time. The intervals during which the resulting formulation would slowly deliver the active ingredient and reside inside the target compartment should roughly overlap. Moreover, they would have to cover the therapeutic time frame as completely as possible, or else be as extended as possible when chronic treatments are dealt with.

Interestingly, such a combination approach may especially be beneficial to improve delivery of drugs to hollow muscular organs in the body. These are in the form of a sac made up of overlaid tissue layers, wherein a leaky inner cavity contains an aqueous biological fluid varying in volume and composition. The cavity is connected with the outer environment through single or multiple passageway ducts that fulfill diverse physiological functions and may be blocked up by sphincteric contraction. It ensues that, because the drug would fast be cleared from the interior of the sac as a solution or a dispersion, either by continuous or periodic emptying depending on sphincter activity, administration of simple immediate-release dosage forms would largely fail to provide the desired local concentrations during the time frame concerned. As a result, frequent and/or systemic dosing modes would have to be used to overcome the drug loss due to continuous washout.

Regardless of how freely the cavities of hollow organs can be accessed for medication, the key point in the design and formulation of a system aimed at *in situ* delivery is that sizes differing from one another would be required for safe entry into and effective retention within them, respectively. On the one hand, a sufficiently small-sized conformation would indeed be needed for administration and positioning of the drug-loaded device inside the cavity, whereas, on the other, a larger spatial encumbrance would be mandatory for its untimely emptying to be prevented. Importantly, the bulky conformation could serve the purpose only if it were reached promptly after dosing and subsequently maintained over time also in spite of physical stresses undergone due to smooth muscle contractions. The dosage unit would thus be expected to

possess adequate mechanical resistance characteristics when taking on the cumbersome retentive configuration. Evolution from a smaller to a larger size may result from differing physical phenomena, such as water-swelling occurring on glass-rubber transition, osmotically-induced water uptake or return to an originally bulkier shape, *e.g.* because of unfolding and/or elastic behavior upon discontinuation of a compressive external force, or else in view of inherent shape memory properties of component materials[3–7].

While a properly-designed intra-organ delivery system would help reduce the frequency of administration, thereby promoting the overall patient compliance, it is understood that it should not negatively impact on the latter when dosed to, retained in or retrieved from the release site. To this end, a number of additional requirements, strictly associated with regulatory safety prerequisites, have to be satisfied beyond the basic concepts of enduring residence and prolonged release performance within the organ of interest. Firstly, the delivery device should be suitable for painless and convenient administration modes. Moreover, every hazard that may arise from long-term location in the host body part needs to be ruled out. On operation, it is thus expected not to cause any harmful reactions, interfere with the physiological functions performed by the organ, bring about damages to the mucosa or the other tissues the wall is formed from, either at the micro- or macroscale level, alter motility patterns, ease microbial infection and proliferation, obstruct connection canals or orifice sphincters. Also, it should possibly be subject to spontaneous elimination processes after exhaustion, *e.g*. by dissolving, disintegrating, undergoing chemical degradation or collapsing. Otherwise, it should involve no painful and uncomfortable removal procedures. The total residence should be well characterized and consistent in duration, to overcome risks of longer-lasting contact of the organ with the foreign unit or even of accumulation thereof.

The above-depicted scenario typically relates to hollow organs of the digestive and genitourinary systems, namely the stomach and the urinary bladder. In this respect, a wide range of tasks need to be accomplished by drug delivery sciences to properly face the many issues pending. The particular challenges posed by intragastric and intravesical administration of drugs have been identified and broadly discussed in the last decades, as major medical needs were being highlighted. Such aspects are reviewed hereby, along with those design strategies that leverage shape memory materials. These are endowed with the ability to retain memory of a permanent original shape and, after deformation into substantially different temporary shapes, recover it upon exposure to appropriate non-mechanical environmental *stimuli*[8,9]. Thanks to the

unique potential they hold, the use of shape memory materials for sophisticated biomedical and pharmaceutical applications is currently at the forefront of healthcare research and has opened up deeply innovative prospects in the field of retentive drug delivery devices[10].

Intravesical Delivery Systems

The urinary bladder is a hollow muscular organ responsible for storage and disposal of urine coming from the kidneys via the ureters, which drains waste substances cleared from the systemic circulation[11]. The urethra connects the bladder cavity with the external urinary meatus. Shape, dimensions and relative position of the bladder vary as a function of the filling state and on the adjacent organs. It stretches and contracts continually as urine is collected and emptied, respectively. Capacity is reported to be of 400-600 mL and, under maximum filling conditions, pseudospherical shape is reached. The wall comprises a mucosal, a smooth muscle, i.e. the detrusor, and a serous layer. The mucosa epithelium, known as urothelium, is interfaced with the urinary fluid and, independent of the filling state, performs a critical function as an impermeable barrier, which is also enabled by the urothelial glycosaminoglycan (GAG) layer covering the typical umbrella cells. Physiological functionality of the urinary bladder may be impaired by aging and/or various disease states. Among them, recurrent microbial infections, interstitial cystitis/painful bladder syndrome, atonic or hyperactive bladder, urinary incontinence and cancer are prevalent debilitating pathologies that may have severe repercussions on homeostasis of the entire body and on life quality of the patients, also associated with medication[5]. Both systemic and topical pharmacological treatments are often involved, the latter offering clear advantages in terms of tolerability and efficacy due to direct administration of the bioactive ingredient(s) to the diseased site. This especially applies to the therapy of interstitial cystitis/painful bladder syndrome and cancer, which is currently carried out through instillation of aqueous formulations, either solutions or dispersions, via transurethral catheters reaching the vesical cavity from the outside[3,4,11]. The drug instilled, however, is progressively diluted because of urine collection. Besides, it is periodically washed out when urge to urinate can no longer be deferred in spite of the bladder being voided just before treatment and of concomitant restrictions on fluid intake that are generally recommended. The difficulties in maintaining therapeutic concentrations of bioactive substances within the bladder are coupled with their poor spread throughout the overlaid layers of the wall due to the impermeable barrier provided by the urothelium. The chances of drug

penetration are also limited by strict solubility, ionization, partition and molecular mass constraints. Furthermore, repeated and permanent use of catheters is frequently connected with bacterial colonization of the urinary tract and may also lead to mucosal damage, thus bringing about complications that would worsen the overall symptomatology and threaten the outcome of the therapy. Importantly, the discomfort caused by catheterization, owing to its invasive nature and all the drawbacks involved, is reflected in therapeutic adherence issues[12,13]. High dropout rates are indeed reported, with evil consequences especially in the case of bladder cancer[14]. This has a deep impact on healthcare costs, which is added to the burden associated with the dosing procedures often requiring to be performed by trained personnel. Hence, there is a strong rationale behind the efforts to have the residence time of drugs inside the bladder prolonged and improve the relevant penetration across the wall[3–5,11]. To these ends, several formulations approaches, also in combination with chemical or physical methods, have been explored. The most prominent strategies described in the literature range from smart hydrogel carriers, liposomes and nanoparticles, optionally endowed with tumor cell targeting properties, up to implantable indwelling devices. The latter substantially differ from therapeutic systems dosed as liquids via instillation in that they have own shape and macroscale dimensions. Moreover, once inserted into the bladder cavity, they can be retained there mainly because of spatial encumbrance attributes that hamper the relevant leakage with urine[3,5,15]. Interestingly, indwelling systems hold potential for yielding extended intra-organ residence and drug delivery over time lapses in the order of few to several days. Depending on whether or not biodegradable and/or bioerodible materials are used for fabrication, their elimination may either occur spontaneously or need to be accomplished by manual withdrawal after exhaustion[16]. The systems may alternatively be conceived in a modular form, so that smaller component units able to cross the urethra would be set free at the end of the drug release process[17]. To enable retention, an increase in size taking place after administration of the device, i.e. when the step of passing through the urethra and the bladder neck is fulfilled, has particularly been pursued. For instance, this has been attained by post-dose filling from the outside in the case of UROS oxybutynin infusion pump (Situs Co., US-CA) that was in clinical development for overactive bladder therapy[3,18]. More recently, the use of shape memory materials has been proposed as an attractive option to be seized[4]. A lidocaine-releasing intravesical system (LiRIS®, TARIS Biomedical Inc., US-MA) has been developed for improved local treatment of interstitial cystitis/painful bladder syndrome[19]. The indwelling device is a small-sized osmotic pump

consisting in a two-hollow water-permeable silicone tube. One of the cavities, provided with a laser-drilled orifice for release, is loaded with lidocaine hydrochloride crystals, whereas the other one houses a wire made of superelastic nickel-titanium (nitinol) alloy. The delivery system is inserted into the bladder by cystoscopy while it is in an elongated shape imposed by the transurethral catheter. Inside the cavity, the nitinol wire switches back to a lower-energy coiled conformation with no sharp edges possibly harmful to the wall tissues. Shape recovery prevents the system from being emptied until it is non-surgically retrieved via a reverse cystoscopy procedure. In both female volunteers and patients, LiRIS® has been successfully retained and well tolerated, also when administered to the healthy subjects in a *placebo* form that would rule out potentially misleading effects of the anesthetic drug[20]. Enduring pain relief, reduced voiding urgency and frequency as well as signs of bladder healing have been reported after a two-week treatment. With the aim of circumventing invasive removal of exhausted devices, the use of shape memory polymers having water solubility properties has recently been proposed[21]. Particularly, poly(vinyl alcohol) (PVA) has been selected because of its availability in pharmaceutical grades and water-induced shape memory effect, which could be actuated at body temperature. Moreover, it is a thermoplastic polymer suited for hot-processing via hot-melt extrusion (HME) and fused deposition modeling (FDM) 3D printing[22]. Based on experience previously built in the relevant use, mainly for oral delivery targets, such techniques have been employed in view of the versatility they would grant in terms of achievable shapes and sizes for the intravesical device as well as of the interesting overall applications they may offer[23–26]. Among these, the potential of HME for continuous manufacturing and the rapid prototyping ability of FDM, along with its prospective use as a tool for therapy customization, have drawn special attention[27,28]. Notably, the presence of shape memory components, allowing morphology changes to occur upon exposure to proper external *stimuli* after the 3D printing process, has provided the basis for 4D printing, the fourth dimension lying in the time frame during which the programmed shape modifications would take place[29,30]. Prototypes conceived in simple original shapes have been obtained by both techniques[21]. Deformed to differing temporary shapes and immersed in distilled water at 37 °C, they have shown shape recovery as a function of the thermo-mechanical characteristics of the starting formulations, while releasing the drug tracer loaded. Feasibility of the propounded 4D printing approach to fabrication of a retentive delivery system has thereby been demonstrated. However, many issues are still to be

met, primarily including the time course of release, and extensive investigation is needed to this end.

Gastroretentive Delivery Systems

The stomach is a hollow muscular organ in the gastrointestinal tract, located between the esophagus and the small intestine. The pyloric sphincter regulates the passage of gastric contents (chyme) into the duodenum. The stomach is especially involved in dietary protein breakdown, secreting pepsinogen and hydrochloric acid that provides the acidic pH required for enzyme activation[31,32]. Fat digestion and absorption of certain substances, in addition to water and electrolytes, are also performed. The gastric wall consists of overlaid layers, *i.e.* mucosa, submucosa, muscularis externa and serosa, and is distensible to adapt to the contents that result from food and beverage ingestion as well as mucosal secretion. Accordingly, the stomach changes in volume from approximately 50 mL up to 1500 mL in the fasted and fed state, respectively[6].

Sustaining the release of drugs into the stomach has been a major goal in the field of oral delivery for almost five decades. Indeed, there are several compelling rationales either in maintaining effective gastric concentrations of therapeutic agents, for improved treatment of local disease conditions such as peptic ulcer, gastroesophageal reflux, Helicobacter pylori infection and gastritis, or in slowly supplying downstream areas of the gut with the needed amounts of bioactive compounds intended for systemic therapy of a range of high-prevalence chronic pathologies[33,34]. Particularly, this would apply to drug molecules that present oral bioavailability limitations because of a narrow upper intestinal absorption window, *e.g.* due to exploitation of carrier-mediated transport mechanisms mainly in the duodenum and jejunum. In addition, drugs that would poorly be stable at neutral to alkaline pH values, or may be degraded by intestinal digestive enzymes, may benefit from such a delivery mode. Extended gastric release could also provide a ploy to circumvent hurdles encountered with formulation of drug substances that, on account of a short elimination half-life and/or issues of peak-to-trough fluctuations in their plasma levels, would constitute ideal candidates for administration as oral prolonged-release dosage forms, yet fail to meet the basic requirement of distal intestinal absorption. The stomach, however, poses harsh and extremely variable conditions, owing to the highly acidic pH and the presence of digestive enzymes as well as of food, source of possible detrimental drug interactions[6,32]. Active substances that do not present adequate solubility and

stability characteristics in the gastric environment, or may cause damage to the mucosal lining, such as typically anti-inflammatory drugs, would not be eligible for release into the stomach.

The differing formulation strategies that have been attempted are all aimed at extended gastric residence of prolonged-release dosage forms, mainly encompassing mucoadhesion, floatation in the gastric fluid thanks to low-density or effervescence properties, high density-induced sinking to the bottom of the stomach and expansion in volume to gain greater spatial encumbrance[34–39]. Although some have been translated into commercially-available drug products, particularly relying on buoyancy, each of these strategies is challenged by specific physiological constraints, such as mucus turnover, variable volume and viscosity of the contents, fluid displacement due to the subject moving and changing position, and destructive forces exerted by smooth muscle activity[7]. Overall, the above-mentioned factors strongly limit the possibility of achieving multi-hour gastric residence, which the organ would naturally be committed to prevent. This particularly relates to the fasted state, when the volume of contents is reduced. Even more important, rapidly successive peristaltic contractions (housekeeper waves) of peak intensity that come with the interdigestive migrating myoelectric complex, along with maximum dilation of the pyloric sphincter, lead to extensive clearance of stomach[37].

Expandable dosage forms have been recognized to offer more reliable retention chances in view of a greater likelihood of withstanding evacuation regardless of fasted or fed conditions, and of the type and amount of food ingested[6,7,37]. Such systems are designed to present a relatively small-sized initial configuration suitable for easy swallowing, and then acquire, once they have entered the stomach, sufficient spatial encumbrance to hamper passage through the wide-open pylorus. In this respect, although a broad range of dimensions have been reported, a cutoff of approximately 13 mm has frequently been quoted. The cumbersome configuration should be maintained over time to ensure retention as programmed. Finally, it should be cast off when drug release has been completed, to enable uncomplicated gastric emptying. Basically, the increase in size needed for retention has been pursued either through swelling of polymer components, *e.g.* superporous hydrogels, or unfolding of a forcedly coiled, bent or contracted structure. There are plenty of examples of how these concepts have been implemented, including proprietary Acuform® (Assertio Therapeutics Inc, US-IL, formerly Depomed Inc., US-CA) and Accordion Pill™ (IntecPharma Inc., US-NY) technologies, respectively, that have yielded drug products in the marketplace or in late-stage development. Expansion-dependent retention tools also underlie a number of cutting-edge engineered devices, and related

construction materials, aimed at gastric residence times beyond 24 h up to several weeks[7]. Star-shaped and spherical fenestrated structures, subject to *in situ* reversible expansion due to elastic unfolding, and a pufferfish-like hydrogel system having high-speed, high-ratio and durable water swelling have been described[40–44]. All of these would notably match the "Ultra-long-acting oral formulation" category of FDA's Emerging Technology Program, which has been launched by the agency to endorse adoption of innovative pharmaceutical design and manufacturing schemes entailing purposely set regulatory evaluation approaches[45]. Interestingly, protracting gastric retention and release over many days or weeks would broaden the range of oral delivery possibilities that normally have to cope with gut transit-related temporal limitations[7]. In such cases, the dosage unit, resembling an intragastric implantable depot rather than a peroral modified-release formulation, could help boost adherence to chronic drug therapies involving multi-dose daily regimens, thus bringing social and pharmacoeconomic benefits, *e.g.* in typically non-compliant patient populations or resource-constrained settings.

The latest advances in the field have also relied on the use of shape memory materials, which hold potential for fully innovating research in the area of expandable gastroretentive delivery systems. Taking advantage of the superleastic properties of nitinol, previously exploited for LiRIS® development, a device in the form of a cylindrical coil has been proposed with the aim of addressing compliance issues involved by long-term multi-gram daily dosing of anti-tubercular drugs, which also raise serious drug resistance concerns[46,47]. Such a device is intended for nasogastric administration and retrieval in a straight temporary shape, as well as for recovery of the coiled conformation within few seconds since ejection from the dosing tube[47]. Magnets placed on either end of the metal coil would allow the system to be detected inside the gastric cavity and intercepted for removal after the operation time lapse. Drug formulations consisting in pierced vinylpolysiloxane matrix beads, containing polyethylene glycol as a water-soluble pore former and provided with a Eudragit® RS or polycaprolactone coating to reduce burst effect, have been threaded on a central nitinol wire and kept in position by a retainer unit. Safe retention of a doxycycline hyclate-loaded prototype and sustained serum concentrations of the antibiotic have been demonstrated in a large swine animal model over a one-month period, consistent with prolonged-release *in vitro* results. Subsequently, nitinol has also been utilized for blooming flower-inspired design of an intra-esophageal device meant for convenient swallowing, elastic deployment within the organ cavity and consequent drug release

into the mucosa through millineedles applied onto the outer surface of petal-like polycaprolactone arms[43]. Closure into a smaller-sized conformation, suitable for safe passage through the pylorus and intestinal tract, has been achieved by thermal triggering of shape-memory nitinol springs upon intake of a limited volume of warm water (55 °C).

Finally, PVA of pharmaceutical grade has been proposed for HME and FDM 3D printing of protoype devices having, on the one hand, a temporary configuration fitting into 00el size hard-gelatin capsules and, on the other, a possibly retentive original shape to be recovered in the gastric fluid following water-induced activation of the polymer shape memory response[48,49]. Permanent shapes incorporating wide void volumes, such as S- or atom-like ones and cylindrical or conical coils, have been conceived and explored. Special templates, obtained by FDM, have been employed for manual deformation of the extruded samples to have them take on their temporary shapes with reduced dimensions. Irrespective of their original configuration and manufacturing technique, the prototypes have been shown to rapidly undergo shape modification in 0.1 N hydrochloric acid at 37 °C and meanwhile start releasing a drug tracer. Although preliminary in scope and outcome, this study has paved the way for future work, particularly aimed at improving the drug load and the duration of release. Thanks to the versatile approach used, such goals could be pursued through changes in the overall surface/volume ratio of the device, increased length of extruded or printed rods, application of a release-controlling coating and/or selection of different polymer components.

Conclusions

While so many clinical needs still fail to be met by pharmacological therapy, poor adherence to existing treatments of proven efficacy represents a serious hurdle to the benefits these would provide. Over the last decades, patient compliance issues have extensively been addressed by pharmaceutical formulation and drug delivery sciences, leveraging either more consolidated or emerging technologies. In this respect, shape memory materials are currently the subject of growing research interest because of the broad spectrum of exciting opportunities offered. Recently, their successful application to the design of drug-eluting retentive devices has been described, highlighting major related advantages and disclosing novel possibilities to seize. Thanks to the peculiar shape recovery behavior, devices based on such materials would possess the ability to withstand emptying from hollow organs of the body for period of times of even considerable duration and meanwhile release the conveyed drug in a sustained mode. The

urinary bladder and the stomach represent chief targets for retentive delivery systems in view of inherent physio-anatomic characteristics and pathological conditions they may be affected by. In these instances, although critical aspects associated with safety, convenience of administration and removal as well as duration of residence and release still require in-depth investigation, special benefits could be anticipated from effective combination of prolonged-retention and prolonged-release performance. Site-selective treatments could indeed be performed, with a positive outcome in terms of efficacy and tolerability. In the case of intragastric delivery, intestinal absorption windows could also be exploited for systemic therapeutic purposes. Finally, medication regimens with reduced dosing frequency would be viable, thus prompting patient compliance in high-prevalence disease states involving direct and indirect costs for the healthcare systems.

References

1. Ingersoll, K. S.; Cohen, J. *J. Behav. Med.* **2008**, *31*, 213.
2. Paquin, A. M.; Zimmerman, K. M.; Kostas, T. R.; Pelletier, L.; Hwang, A.; Simone, M.; Skarf, L. M.; Rudolph, J. L. *Expert Opin. Drug Saf.* **2013**, *12*, 829.
3. Cima, M. J.; Lee, H.; Daniel, K.; Tanenbaum, L. M.; Mantzavinou, A.; Spencer, K. C.; Ong, Q.; Sy, J. C.; Santini, J.; Schoellhammer, C. M.; Blankschtein, D.; Langer, R. S. *J. Control. Release* **2014**, *190*, 157.
4. Farokhzad, O. C.; Dimitrakov, J. D.; Karp, J. M.; Khademhosseini, A.; Freeman, M. R.; Langer, R. *Urology* **2006**, *68*, 463.
5. Zacchè, M. M.; Srikrishna, S.; Cardozo, L. *Res. reports Urol.* **2015**, *7*, 169.
6. Klausner, E. A.; Lavy, E.; Friedman, M.; Hoffman, A. *J. Control. Release* **2003**, *90*, 143.
7. Altreuter, D. H.; Kirtane, A. R.; Grant, T.; Kruger, C.; Traverso, G.; Bellinger, A. M. *Expert Opin. Drug Deliv.* **2018**, *15*, 1189.
8. Lendlein, A. *Science (80-.).* **2009**, *1673*, 1673.
9. Wischke, C.; Lendlein, A. *Pharm. Res.* **2010**, *27*, 527.
10. Wischke, C.; Neffe, A. T.; Steuer, S.; Lendlein, A. *J. Control. Release* **2009**, *138*, 243.
11. GuhaSarkar, S.; Banerjee, R. *J. Control. Release* **2010**, *148*, 147.
12. Tapiero, S.; Helfand, A.; Kedar, D.; Yossepowitch, O.; Nadu, A.; Baniel, J.; Lifshitz, D.; Margel, D. *Urology* **2018**, *118*, 107.
13. Serretta, V.; Gesolfo, C. S.; Alonge, V.; Cicero, G.; Moschini, M.; Colombo, R. *Urol. Int.* **2016**, *96*, 20.
14. Recchia, A.; Gerace, C.; Era, S.; Doria, S.; Di Ponzio, G.; Teruzzi, C. *Int. J. Technol. Assess.*

Health Care **2017**, *33*, 208.
15. Lee, S. H.; Choy, Y. Bin *Int. Neurourol. J.* **2016**, *20*, 101.
16. Tobias, I. S.; Lee, H.; Engelmayr, G. C.; Macaya, D.; Bettinger, C. J.; Cima, M. J. *J. Control. Release* **2010**, *146*, 356.
17. Haupt, M.; Thommes, M.; Heidenreich, A.; Breitkreutz, J. *J. Control. Release* **2013**, *170*, 161.
18. Fraser, M. O.; Lavelle, J. P.; Sacks, M. S.; Chancellor, M. B. *Rev. Urol.* **2002**, *4*, 1.
19. Lee, H.; Cima, M. J. *J. Control. Release* **2011**, *149*, 133.
20. Nickel, J. C.; Jain, P.; Shore, N.; Anderson, J.; Giesing, D.; Lee, H.; Kim, G.; Daniel, K.; White, S.; Larrivee-Elkins, C.; Lekstrom-Himes, J.; Cima, M. *Sci. Transl. Med.* **2012**, *4*, 143ra100.
21. Melocchi, A.; Inverardi, N.; Uboldi, M.; Baldi, F.; Maroni, A.; Pandini, S.; Briatico-Vangosa, F.; Zema, L.; Gazzaniga, A. *Int. J. Pharm.* **2019**, *559*, 299.
22. Melocchi, A.; Parietti, F.; Maroni, A.; Foppoli, A.; Gazzaniga, A.; Zema, L. *Int. J. Pharm.* **2016**, *509*, 255.
23. Loreti, G.; Maroni, A.; Del Curto, M. D.; Melocchi, A.; Gazzaniga, A.; Zema, L. *Eur. J. Pharm. Sci.* **2014**, *52*, 77.
24. Melocchi, A.; Parietti, F.; Loreti, G.; Maroni, A.; Gazzaniga, A.; Zema, L. *J. Drug Deliv. Sci. Technol.* **2015**, *30*, 360.
25. Maroni, A.; Melocchi, A.; Parietti, F.; Foppoli, A.; Zema, L.; Gazzaniga, A. *J. Control. Release* **2017**, *268*, 10.
26. Melocchi, A.; Parietti, F.; Maccagnan, S.; Ortenzi, M. A.; Antenucci, S.; Briatico-Vangosa, F.; Maroni, A.; Gazzaniga, A.; Zema, L. *AAPS PharmSciTech* **2018**, *19*, 3343.
27. Melocchi, A.; Loreti, G.; Del Curto, M. D.; Maroni, A.; Gazzaniga, A.; Zema, L. *J. Pharm. Sci.* **2015**, *104*, 1971.
28. Zema, L.; Melocchi, A.; Maroni, A.; Gazzaniga, A. *J. Pharm. Sci.* **2017**, *106*, 1697–1705.
29. Yang, G. H.; Yeo, M.; Koo, Y. W.; Kim, G. H. *Macromol. Biosci.* **2019**, *19*, 1.
30. Lee, A. Y.; An, J.; Chua, C. K. *Engineering* **2017**, *3*, 663.
31. Koziolek, M.; Garbacz, G.; Neumann, M.; Weitschies, W. *Mol. Pharm.* **2013**, *10*, 1610.
32. Baxevanis, F.; Kuiper, J.; Fotaki, N. *Eur. J. Pharm. Biopharm.* **2016**, *107*, 234.
33. Hoffman, A.; Stepensky, D.; Lavy, E.; Eyal, S.; Klausner, E.; Friedman, M. *Int. J. Pharm.* **2004**, *277*, 141.
34. Lopes, C. M.; Bettencourt, C.; Rossi, A.; Buttini, F.; Barata, P. *Int. J. Pharm.* **2016**, *510*, 144.
35. Moes, A. J. *Crit. Rev. Ther. Drug Carrier Syst.* **1993**, *10*, 143.
36. Hwang, S. J.; Park, H.; Park, K. *Crit. Rev. Ther. Drug Carrier Syst.* **1998**, *15*, 243.
37. Streubel A., Siepmann J., B. R. *Expert Opin. Drug Deliv.* **2006**, *3*, 217.

38. Prinderre, P.; Sauzet, C.; Fuxen, C. *Expert Opin. Drug Deliv.* **2011**, *8*, 1189.
39. Pawar, V. K.; Kansal, S.; Asthana, S.; Chourasia, M. K. *Expert Opin. Drug Deliv.* **2012**, *9*, 551.
40. Zhang, S.; Bellinger, A. M.; Glettig, D. L.; Barman, R.; Lee, Y. A. L.; Zhu, J.; Cleveland, C.; Montgomery, V. A.; Gu, L.; Nash, L. D.; Maitland, D. J.; Langer, R.; Traverso, G. *Nat. Mater.* **2015**, *14*, 1065.
41. Bellinger, A. M.; Jafari, M.; Grant, T. M.; Zhang, S.; Slater, H. C.; Wenger, E. A.; Mo, S.; Lee, Y. A. L.; Mazdiyasni, H.; Kogan, L.; Barman, R.; Cleveland, C.; Booth, L.; Bensel, T.; Minahan, D.; Hurowitz, H. M.; Tai, T.; Daily, J.; Nikolic, B.; Wood, L.; Eckhoff, P. A.; Langer, R.; Traverso, G. *Sci. Transl. Med.* **2016**, *8*, 365ra157.
42. Kirtane, A. R.; Abouzid, O.; Minahan, D.; Bensel, T.; Hill, A. L.; Selinger, C.; Bershteyn, A.; Craig, M.; Mo, S. S.; Mazdiyasni, H.; Cleveland, C.; Rogner, J.; Lee, Y. A. L.; Booth, L.; Javid, F.; Wu, S. J.; Grant, T.; Bellinger, A. M.; Nikolic, B.; Hayward, A.; Wood, L.; Eckhoff, P. A.; Nowak, M. A.; Langer, R.; Traverso, G. *Nat. Commun.* **2018**, *9*.
43. Babaee, S.; Pajovic, S.; Kirtane, A. R.; Shi, J.; Caffarel-Salvador, E.; Hess, K.; Collins, J. E.; Tamang, S.; Wahane, A. V.; Hayward, A. M.; Mazdiyasni, H.; Langer, R.; Traverso, G. *Sci. Transl. Med.* **2019**, *11*, eaau8581.
44. Liu, X.; Steiger, C.; Lin, S.; Parada, G. A.; Liu, J.; Chan, H. F.; Yuk, H.; Phan, N. V.; Collins, J.; Tamang, S.; Traverso, G.; Zhao, X. *Nat. Commun.* **2019**, *10*, 493.
45. U.S. Food & Drug Administration Emerging Technology Program _ FDA. https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program.
46. Verma, M.; Furin, J.; Langer, R.; Traverso, G. *BMJ Glob. Heal.* **2019**, *4*, e001323.
47. Verma, M.; Vishwanath, K.; Eweje, F.; Roxhed, N.; Grant, T.; Castaneda, M.; Steiger, C.; Mazdiyasni, H.; Bensel, T.; Minahan, D.; Soares, V.; Salama, J. A. F.; Lopes, A.; Hess, K.; Cleveland, C.; Fulop, D. J.; Hayward, A.; Collins, J.; Tamang, S. M.; Hua, T.; Ikeanyi, C.; Zeidman, G.; Mule, E.; Boominathan, S.; Popova, E.; Miller, J. B.; Bellinger, A. M.; Collins, D.; Leibowitz, D.; Batra, S.; Ahuja, S.; Bajiya, M.; Batra, S.; Sarin, R.; Agarwal, U.; Khaparde, S. D.; Gupta, N. K.; Gupta, D.; Bhatnagar, A. K.; Chopra, K. K.; Sharma, N.; Khanna, A.; Chowdhury, J.; Stoner, R.; Slocum, A. H.; Cima, M. J.; Furin, J.; Langer, R.; Traverso, G. *Sci. Transl. Med.* **2019**, *11*, eaau6267.
48. Melocchi, A.; Uboldi, M.; Inverardi, N.; Baldi, F.; Maroni, A.; Pandini, S.; Briatico-Vangosa, F.; Scalet, G.; Zema, L.; Gazzaniga, A. *CRS Annual Meeting & Exposition*, July 21-24, Valencia (S).
49. Melocchi, A.; Uboldi, M.; Inverardi, N.; Briatico-Vangosa, F.; Baldi, F.; Pandini, S.; Scalet, G.; Auricchio, F.; Cerea, M.; F.oppoli, A.; Maroni, A.; Zema, L.; Gazzaniga, A. *Int. J. Pharm.*

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