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## DRUG DELIVERY SYSTEMS IN UROLOGY – GETTING “SMARTER”

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### Introduction

Urology holds the most enviable position in the medical firmament. Unique among specialties in bringing the surgeon in contact with human beings throughout the spectrum of human life – from newborn to geriatric patients – urologists need to be adept at both medical and surgical therapies alike. In this context, drug delivery in urology has had a long, and sometimes far from illustrious, history. Traditionally, many genito-urinary (GU) conditions have been treated with medications administered via an oral route, which requires larger doses with concomitant side effects. The popularity of localized delivery systems, on the other hand, has been determined by the easiness of system implantation, objective treatment efficacy, patient-reported treatment satisfaction and observed side effects.

The GU tract presents a unique opportunity for local drug delivery. The kidney, bladder and prostate are easily accessible for minimally invasive interventions. Nanoparticles, microparticles or small-scale implants can simply be deployed and retrieved using percutaneous or endoscopic systems in outpatient settings with minimal patient discomfort and maximal therapeutic benefit. This review describes GU therapies of the past, present, and future with particular emphasis on the emerging state-of-the-art biopolymer and drug delivery systems in urology and their potential to shape the future of urologic science and practice.

### Limitations of Current Therapeutic Approaches

#### Intravesical Treatments

Molecular weight, polarity, concentration, exposure time and urothelial surface alterations have been proposed as the major factors determining the rate of transurothelial drug absorption.<sup>1</sup> The ideal intravesical agent has been postulated to have negligible ionization between pH 6 and 7, a molecular weight greater than 200, and a partition coefficient in the critical ranges of

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either  $-0.4$  to  $-0.2$ , or  $-7.5$  to  $-8.0$ .<sup>2</sup> The importance of these factors is underscored by the results of a recent phase III randomized clinical trial for intravesical mitomycin. Eliminating the residual volume, overnight fasting, doubling the mitomycin concentration to 40 mg in 20 mL, and urinary alkalization using oral bicarbonate (to reduce mitomycin degradation) resulted in doubling of the durable tumor-free rate at 5 years.<sup>3</sup>

In addition to intravesical mitomycin, acidic urinary pH is also the limiting factor in intravesical doxorubicin and epirubicin therapy. Alkalinization with gamma linolenic acid has been shown to increase epirubicin efficacy. Further enhancement has been reported following verapamil administration.

Another major determinant of therapeutic success is the degree of drug lipophilicity, which allows penetration through cell membranes. For example, paclitaxel, a highly lipophilic compound, achieves higher intraurothelial concentrations than either mitomycin or doxorubicin. However, its poor urine solubility presents unique challenges for intravesical administration. Moreover, Cremophor® (polyoxyethylated castor oil), a stabilizing agent used in the FDA-approved formulation (Taxol®), reduces the paclitaxel free fraction by entrapping it in micelles and lowering drug penetration in bladder tissue. Paclitaxel bioavailability can be increased by using surface-active agents (e.g., DMSO)<sup>4</sup> to release the agent from the micelles, by employing glyceryl monooleate bioadhesive drug delivery system or nanoparticle encapsulation.

Gemcitabine is an attractive candidate for the ideal intravesical agent. Its molecular weight of 300 allows optimal urothelial penetration and minimal systemic absorption. Gemcitabine has a pKa of 3.6 and its reconstitution results in a solution with a pH of 2.7–3.2. This favors negligible drug ionization at the usual urinary pH of 6.0–7.0 and enhances drug activity. A recent phase II clinical trial of 2000 mg gemcitabine administered once a week for 6 weeks showed lack of side effects in 81.3% of the patients with a disease-free rate of 74.6% at 12 months.<sup>5</sup>

### Intraprostatic Treatments

Intraprostatic drug administration has long been considered an attractive alternative for treating prostatic diseases ranging from infection to cancer. Although Brodie first recommended “puncture of the prostate” through the perineum in the treatment of prostatic abscess, Stoll is credited with performing the first intraprostatic injection in 1877. A detailed discussion of intraprostatic drug kinetics and distribution is beyond the scope of the present article and the reader is referred to an excellent recent review.<sup>6</sup> It is, however, important to emphasize that the easy accessibility of the prostate, coupled with its slow perfusion rate (16 mL/minute/100 g) favors drug entrapment and ensures high concentrations inside the gland following direct intraprostatic delivery. According to the model, proposed by Partin and Rodriguez,<sup>7</sup> intraprostatic drug penetration is dependent on drug lipophilicity and nonionic diffusion through cellular membranes. Once the agent reaches the acidic prostatic fluid, it becomes protonated and acquires a more positive charge with charged drugs becoming relatively trapped within the prostatic secretions. Therefore, the major determining factors for successful penetration are the pKa, protein-binding ability of the drug and pH of the prostatic secretions. The pH of human prostatic secretions varies greatly from 6 to 8, with a mean value of 6.6. Prostatic inflammation presents a special therapeutic challenge since the pH tends to be 7 or greater. Thus, antibacterial agents which show in vitro activity, might be inactive in the alkaline prostatic milieu.<sup>7</sup>

## Novel Drug Delivery Approaches

Recent advances in materials science, biomaterial development and tissue engineering are changing the face of medicine.<sup>8</sup> Biopolymers and drug delivery systems provide the conceptual framework for improving the efficacy of existing drug formulations and developing new treatments.<sup>8,9</sup> Specifically, there has been extensive research in the area of biodegradable materials for controlled release of drugs, which obviates the need for removal of non-degradable drug-depleted devices. Many biodegradable polymers have been evaluated for their suitability as a matrix for drugs including polyesters, polycarbonates, natural and synthetic polyamides, polyphosphate esters, polyphosphazenes and polyanhydrides. These polymers may be used in a variety of devices including biodegradable polymer shape-memory stents, “smart” hydrogel-based systems, nanoparticle-aptamer conjugates, or miniaturized drug delivery devices.

### Biodegradable shape-memory polymers (BSMPs)

The advent of BSMPs ushered in the new era of unlimited endoscopic possibilities.<sup>10,11</sup> BSMPs possess the ability to “memorize” a permanent shape that can differ substantially from their initial temporary shape. Thus, bulky devices can be introduced endoscopically in a compressed temporary shape (e.g. a “coil”), which can then be expanded on demand into a permanent shape (e.g. a “rod”, Fig. 1). Additionally, these polymers can be engineered into sutures that possess the ability to tie themselves (Supplementary Video) on demand as a result of a temperature shift (e.g., from room to body temperature).

In urology, these materials hold the promise for developing degradable drug-eluting stents.<sup>12</sup> Initially at room temperature, a shape-memory stent could be delivered endoscopically in a compressed state; when the temperature is raised to that of the human body (i.e. above the switching transition temperature of the polymer), the stent expands into a coil.<sup>10</sup> Biodegradable stents obviate the need of repeat interventions for removal<sup>13</sup> and can serve as reservoirs of active agents (e.g. antibiotics, alkalizing agents) which can bulk the device and be released from the surface.

### “Smart gels”

Histrelin-eluting hydrogel implants have been shown to effectively suppress testosterone in prostate cancer patients for over a year.<sup>14</sup> Furthermore, hydrogels have been employed as oligonucleotide-releasing vehicles in the kidney<sup>15</sup>. During the past two decades, hydrogels have been developed as “smart” carriers in controlled drug delivery systems.<sup>16</sup> Their physical and chemical properties have been engineered at the molecular level to optimize their properties, such as permeability (e.g. sustained release applications), enviro-responsive nature (e.g. pulsatile release applications), surface functionality (e.g. PEG coatings for stealth release), biodegradability (e.g. bioresorbable applications), and surface biorecognition sites (e.g. targeted release and bioadhesion applications).

Environmentally-responsive hydrogels have been employed for a variety of controlled drug delivery applications. The “smart” component of these systems allows for release of drugs in response to changes in the surrounding environment. For example, thermo-responsive hydrogels have been used for sustained intravesical drug delivery.<sup>17,18</sup> pH-responsive hydrogels composed of polyethylene-glycol(PEG)-containing ionic networks have been employed for protein delivery, e.g. insulin.<sup>19</sup> Furthermore, through exhibiting control over cross linking and swelling properties, hydrogels can be programmed to trigger drug release.<sup>20</sup> These properties have been used in both poly(vinyl alcohol) and PEG systems where the density and degree of network cross linking can be regulated through modifying the polymer chain length, polymer composition and initiation concentration amongst other factors.<sup>21</sup>

Drug delivery systems responsive to biological analytes can be developed by incorporating enzymes within environmentally-responsive hydrogels, e.g. glucose-responsive hydrogels incorporating glucose.<sup>22</sup> Their release kinetics makes them useful as “smart” materials for diabetes applications or, in the case of incontinence, these gels can provide “remote control” and ongoing re-adjustment of implants.

## Targeted nanoparticles

One approach aimed at minimizing the adverse effects of current chemotherapeutic agents and enhancing the survival of patients with metastatic cancer involves drug targeting to cancer cells through tumor-specific antigens (such as PSMA) and direct intracellular cytotoxic agent release over an extended period of time.<sup>23,24</sup> This goal can be achieved through combining controlled-release technology and targeted drug delivery approaches. With advances in nanotechnology, it is now possible to develop highly selective and effective cancer therapeutics by combining specialized biomaterials with available chemotherapeutic agents.<sup>25</sup> An emerging promising strategy involves the delivery of drug-laden nanoparticles conjugated to targeting moieties.<sup>23,24</sup> (Fig. 2) One major clinical advantage of such nanoparticle-drug conjugates over conventional drugs is the specific delivery of large amounts of chemotherapeutic agents per recognition event. In choosing effective targeting moieties one must consider their ability to exhibit high specificity and affinity for the target molecule.

A recent genomics-based approach for identifying cancer-specific antigens suitable for targeted therapy demonstrated high levels of E-selectin expression in prostatic cancer epithelium. Based on this finding, an E-selectin-targeting antibody drug conjugate was constructed which showed great potential in a mouse prostate cancer model.<sup>26</sup>

Antibodies-based treatment strategies against several target antigens, e.g. Her-2/neu, the EGF receptor, PSMA have successfully been employed in urology.<sup>27</sup> A recent phase I trial of <sup>177</sup>Lutetium-labeled J591, a monoclonal antibody to PSMA in patients with androgen-independent prostate cancer, demonstrated the efficacy of this treatment approach.<sup>28</sup> Another promising approach is the use of MLN2704, a de-immunized, PSMA-targeted monoclonal antibody conjugated to drug maytansinoid 1 (DM1), a microtubule-depolymerizing compound.<sup>29</sup> Additionally, drug targeting can be accomplished through conjugation of molecules (such as antibodies or peptides) to nanoparticles. Although peptide-based molecules may be an effective mode of delivery, a potential disadvantage of this approach lies in the challenges involved in monoclonal antibody production. For example, the target antigen may not be well tolerated by the animal used to produce the antibodies or the target molecules may be inherently less immunogenic making it difficult to raise antibodies against such targets (although this problem is overcome with the use of phage display libraries).<sup>30,31</sup>

A strategy that aims to overcome some of these limitations is the use of aptamers for the delivery of controlled-release polymer systems. Nucleic acid ligands (aptamers) are a novel class of ligands<sup>32,33</sup> that have the potential to rival current antibody-based targeting approaches.<sup>34,35</sup> Aptamers are short, single-stranded DNA or RNA oligonucleotides that have been selected in vitro from a large number of random sequences ( $\sim 10^{14}$ – $10^{15}$ ) and have a molecular weight of 10–15 kD which is one order of magnitude lower than that of antibodies (150kD).<sup>36</sup> Aptamers bind to their targets with high affinity and specificity, have a high inhibitory potential, are not toxic or immunogenic, and can be produced synthetically. They can discriminate between closely related isoforms or different conformational states of the same target, and can recognize murine and human protein targets with equal affinities, making them suitable for both preclinical and clinical development. In contrast to antibodies, aptamers bind to functional domains of the target protein, e.g., substrate binding pockets or allosteric sites, thereby modulating the biological function of the molecule. Aptamers usually retain their

binding and inhibitory behavior even after immobilization on carrier material, delivery into animals, labeling with various functional groups, or when expressed within cells. Aptamers are derived from an *in vitro* iterative protocol (*in vitro* selection<sup>32</sup> or systematic evolution of ligands by exponential enrichment (SELEX)).<sup>33</sup> In addition, any specific targeting aptamer may be tailor-made, provided that a small quantity of pure target is available. Although the total number of targets is largely unknown, the SELEX system may be successfully modified using a variety of approaches to overcome these limitations. For example, it is possible to incorporate selection by intact biological entities such as cancer cells or tissues to identify an array of highly specific aptamers.<sup>37,38</sup>

A major limitation of current loss-of-function technologies (gene knockout, antisense oligonucleotides, or RNA interference), is their dependence on genetic inactivation at the genomic or transcriptional level. The use of antibodies as target validation tools is limited to extracellular targets since the reducing intracellular environment hampers the application of antibodies inside the cells. In this respect, aptamers offer a unique advantage since they have low molecular weight, can be used for intracellular studies and can be labeled with fluorophores or nanoparticles for localization experiments. Furthermore, aptamers inhibit their targets by competitive and noncompetitive mechanisms. This unique property allows the study of different inhibitory mechanisms or posttranslational conformations of target proteins in protein networks without altering the proteomic status of the model system.

We have recently demonstrated *in vitro* a proof of concept for nanoparticle-aptamer bioconjugates which target PSMA on the surface of prostate cancer cells and get taken up by cells which express the PSMA protein specifically and efficiently.<sup>23</sup> We have also shown, using a microfluidic system, that these aptamers are suitable for targeted drug delivery<sup>24</sup> and have recently demonstrated the *in vivo* efficacy of nanoparticle-aptamer conjugates using a xenograft prostate cancer mouse model.<sup>39</sup>

## Miniaturized Drug Delivery Devices

Microscale and nanoscale devices are attractive platforms for urologic therapies. Microscale approaches, such as microfluidics, microdevices and micropatterning, provide a particularly useful method of delivering molecules to various tissues of the body.<sup>40,41</sup> These technologies, known as MEMS (for micro-electro-mechanical systems), originated in the semiconductor and microelectronics industry in microchip fabrication. MEMS technology has been used in sensing chemicals, performing microsurgery, and delivering drugs. To create MEMS devices capable of releasing drugs, typically top-down nano- and microfabrication methods such as photolithography or soft lithography have been employed.

In photolithography, a mask is aligned above a thin film of a photo-responsive material, termed photoresist. Microstructures can then be generated by shining the UV light on particular regions of a substrate.<sup>42</sup> Although photolithography has been widely used in microelectronics, it has a number of disadvantages such as high costs associated with photolithographic equipment (aligners and spinners) and clean room usage, as well as the chemically harsh conditions that are not compatible with biomolecules. To alleviate these challenges, a set of alternative techniques collectively known as soft lithography has been developed to fabricate functional structures with dimensions in the range of tens of nanometers to hundreds of micrometers.<sup>42</sup> Soft lithographic approaches commonly utilize a microstructured surface made with elastomeric polymers such as poly(dimethylsiloxane) (PDMS). PDMS is optically transparent, permeable to gases, elastomeric, and durable which makes it also suitable for cell applications. By utilizing a micromolding process soft lithographic approaches minimize the amount of clean room time and equipment.

MEMS technology has great potential in various urological diagnostic applications as such as pressure sensors and micropumps.<sup>43</sup> The seminal research on the use of MEMS technology for drug delivery was performed by using microchips that were designed to release complex profiles of multiple drugs. These systems exist in both a non-degradable “active”<sup>40,41,44</sup> (Fig. 3) and a degradable “passive” format (Fig. 4).<sup>45,46</sup>

The active format (Fig. 3) is constructed from a silicon wafer containing multiple microscale reservoirs that can be opened to release drugs through electrochemical dissolution of a thin gold membrane (anode) which covers the micro-reservoirs. The release of the drug, which can be stored in either solid, liquid or gel form, is initiated by applying an electric potential of approximately 1 V between the anode membrane and the cathode to any individual reservoir. The cathode remains intact during this process, but the anode dissolves due to a reaction between it and the salt solution it is immersed in.

Alternatively, the passive format (Fig. 4) is made from poly(lactic acid) and is fully resorbable with reservoirs covered with thin biodegradable membranes. Through using various types of polymers or co-polymers with a variety of molecular weights, the microchip systems can be programmed to degrade at set times after implantation. Current development in the use of this technology is to incorporate control elements such as pumps and sensors that can release drugs in response to external stimuli. It is envisioned that through their capability to deliver multiple drugs at desired doses, microchip drug delivery devices will provide useful vehicles that can be either implanted or injected for urological applications.

Microfabricated technologies have also been developed for delivering drugs to a target site by using microfabricated silicon or biodegradable microneedles. Although the main application of these delivery vehicles has been for transdermal delivery, it is envisioned that by using microfabricated techniques it is possible to generate self-contained devices that can be deposited cystoscopically into the bladder and be used as drug delivery reservoirs. A similar approach has been developed by creating asymmetric microfabricated vehicles.<sup>47</sup> These have been extensively used as bioadhesives and may be used for localized drug delivery inside bladder, e.g. for paclitaxel.

Another mode of drug delivery that may be suitable for urological application is through the fabrication of micropumps for intrarenal and intraprostatic delivery. Micropumps may be used to deliver medication for treating diseases such as uric acid nephrolithiasis. Most of the existing methods of delivering fluids today are based on silicon technology.<sup>48</sup> While silicon has the added benefit of being well-studied, it is rigid and may not be suitable for some delivery applications. Therefore, the use of flexible microchannels made from novel materials (such as parylene) can be employed to fabricate flexible probes and delivery tools for specific urological applications.<sup>49,50</sup> These flexible microfluidics can transfer fluids within the body along a narrow path without the damaging effects of a rigid object.

## Conclusions

Advances in material science are shaping the future of urologic clinical practice. With the drug delivery technology maturing, the application of nanodevices in urology will provide methods of addressing current clinical challenges, ultimately leading to mainstream therapies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

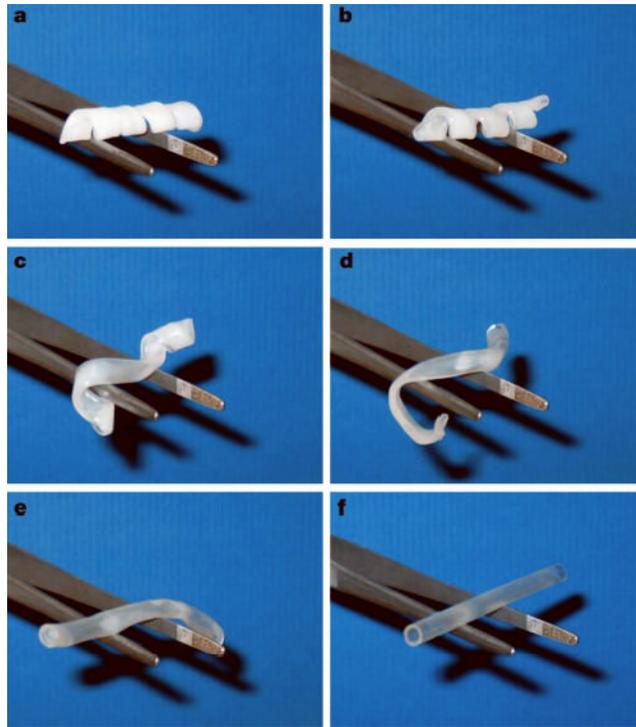
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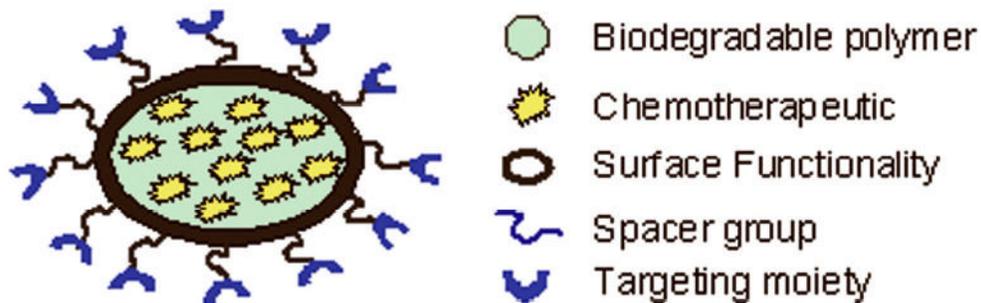
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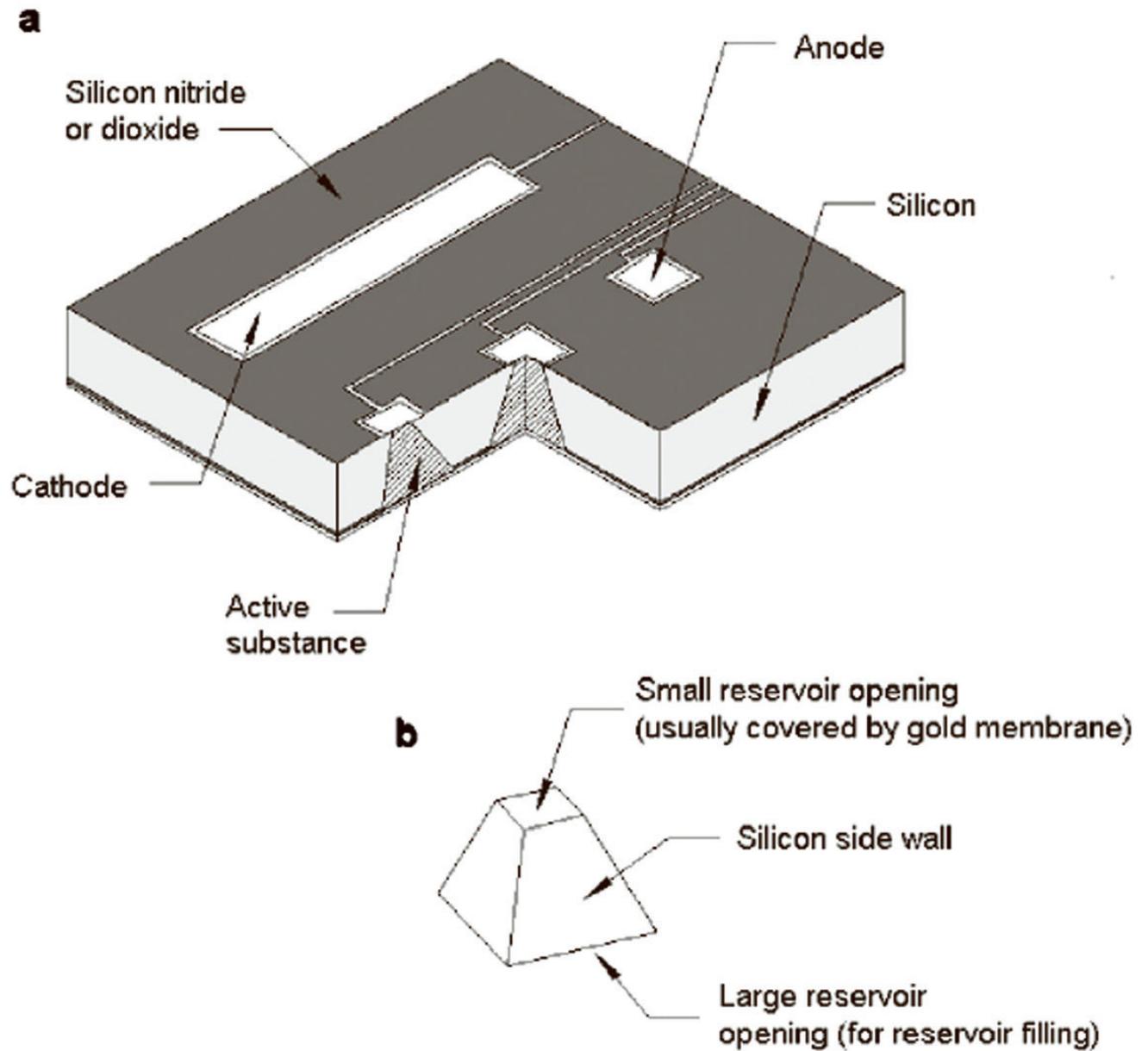


**Figure 1.** Time series of photographs showing recovery of a shape-memory tube. a–f, Start to finish of the process; total time, 10 seconds at 50°C. The tube was made of a poly(epsilon-caprolactone) dimethacrylate polymer network that had been programmed to form a flat helix. (Reproduced with permission from Langer and Tirrell<sup>8</sup>)

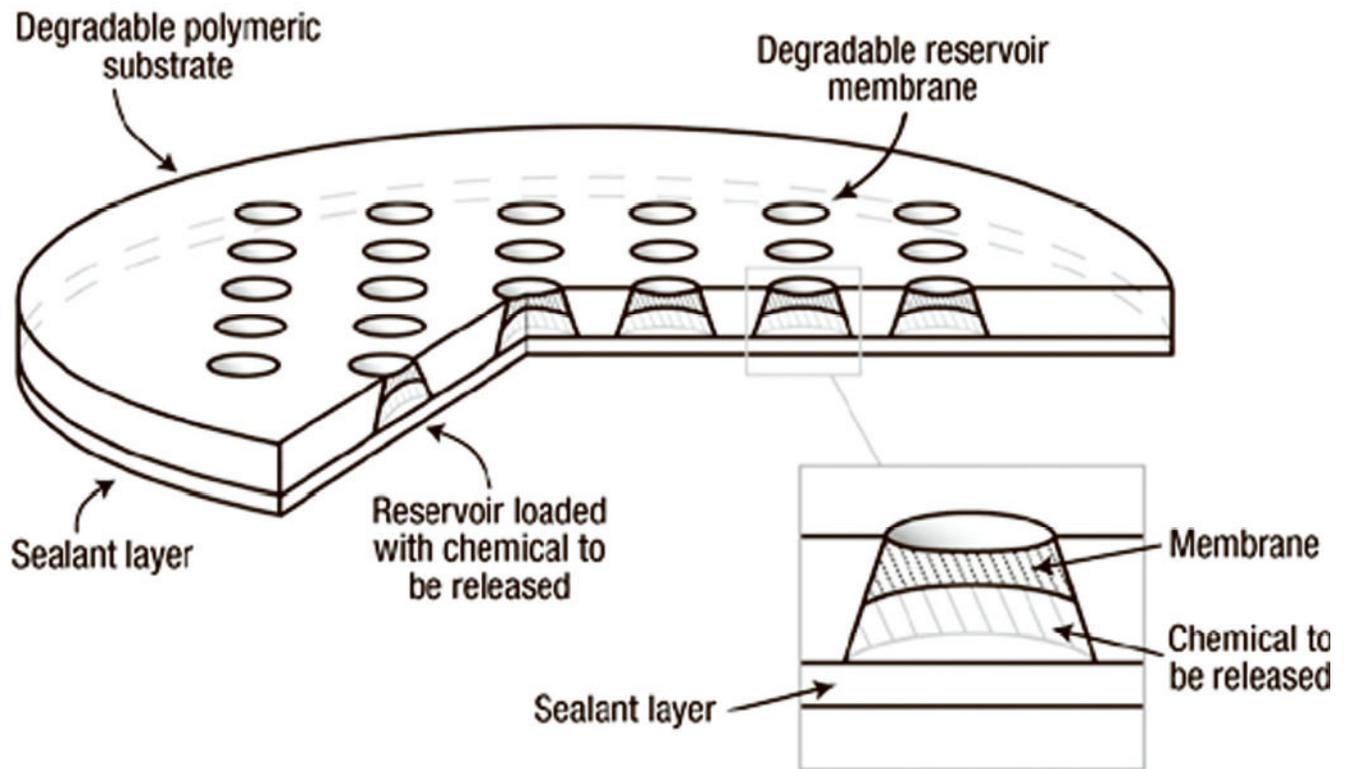


**Figure 2.**

Design of nanoparticle-drug conjugates involves combining drug laden materials, such as biodegradable polymers, with a targeting moiety. The polymer should have functional groups for the attachment of targeting moieties (which may be bound directly to the surface or through a spacer group) and of molecules to enhance the half-life in circulation (i.e. poly(ethylene glycol)).



**Figure 3.** Non-Degradable microchip device for pulsatile release of multiple substances (Reproduced with permission from Santini et al<sup>40</sup>)



**Figure 4.** Degradable microchip device for pulsatile release of multiple substances. (Reproduced with permission from Richards et al<sup>46</sup>)