Methods and Materials for Drug Eluting Urinary Stents Design and Fabrication

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Irene Carmagnola, Giulia Giuntoli, and Gianluca Ciardelli

1 Introduction

After urinary stenting, patients often suffer from mid- and long-term complications, such as infections, bacterial colonization, encrustations, or stent obstruction which are related to the design, materials and surface properties of the stent.

Drug eluting stents (DES) is an advance technology that can reduce the morbidity associated with stenting, by locally releasing loaded drugs in a time-controlled manner.

The first DES were introduced in the earlies'00 for cardiovascular applications to address the problems of restenosis associated with bare metal stents after coronary angioplasty [1]. In urology, DES could potentially solve or reduce a variety of stent-related and time-dependent complications, such as infections and obstruction, which are often related to encrustation and biofilm formation and which can dramatically result in stent failure [2]. Moreover, they could also find application for the management of cancer therapies [3] (Fig. 1).

Common stents are made of "inert" materials to minimize the foreign body reaction. Nonetheless, these stents are affected by several clinical problems. For instance, encrustation is caused by the deposition of urine constituents (such as

I. Carmagnola (✉) · G. Giuntoli
Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

PolitoBIOMed Lab, Politecnico di Torino, Turin, Italy
e-mail: irene.carmagnola@polito.it; giulia.giuntoli@polito.it

G. Ciardelli
Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

PolitoBIOMed Lab, Politecnico di Torino, Turin, Italy

Department for Materials and Devices of the National Research Council, Institute for the Chemical and Physical Processes (CNR-IPCF), Pisa, Italy
e-mail: gianluca.ciardelli@polito.it

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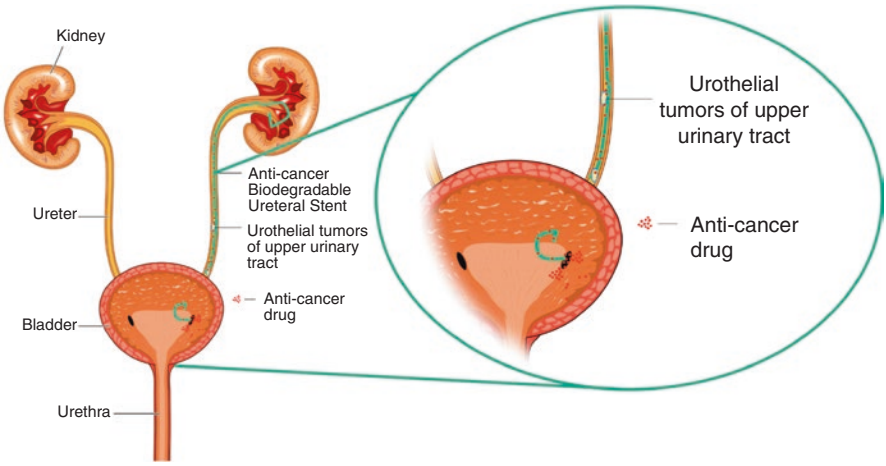

Fig. 1 Scheme of the concept of anti-cancer drug eluting biodegradable ureteral stent as a potential drug delivery system

proteins, ions and minerals) over the stent's surface [4]. This phenomenon occurs due to the physico-chemical characteristics of patient's urine, such as urine pH, composition and flow dynamics, as well as stent's constitutive materials or surface characteristics. Encrustation not only compromises stent drainage potential but also favor bacterial colonization and biofilm formation [5].

Different strategies can be applied to feature the stent with drug delivery systems able to reduce the incidence of encrustation and biofilm development by increasing the drug effectiveness and limiting any side effect associated with systemic delivery.

In this chapter is firstly reported an overview of the materials and manufacturing methods for conventional urinary stents, then are discussed the engineered strategies for the design and fabrication of drug eluting stents. These strategies can be divided into two main categories which are discussed in more detail in the next paragraphs: (1) DES obtained by surface functionalization and coating techniques, or (2) direct manufacturing.

2 Conventional Urinary Stents

2.1 Urinary Stent Materials

The constitutive materials of urinary stents have great influence on their performances and durability. Materials are selected based on several requirements such as biocompatibility, mechanical strength and flexibility, surface properties, ease processability and cost-effectiveness.

Non-biodegradable polymeric and metallic materials are the main constitutive materials used for urinary stenting. The first ureteral stent, described by Herdman in 1949, was made of polyethylene due to its desirable properties such as flexibility, strength, hydrophobicity and bio-inertness [6]. However, it was soon abandoned due to the occurrence of encrustations and the high risk of fracturing. Today, the most common polymeric non-biodegradable materials include silicones, polyurethanes, and other proprietary materials [7]. Between them, silicones have shown better performances in terms of encrustation resistance and ions deposition hindering [8].

Compared to polymeric stents, metallic stents made of titanium, nickel–titanium alloys (e.g. nitinol), or stainless steel have superior mechanical properties, and are often chosen to treat severe conditions, such as malignant ureteric strictures, or when long indwelling times are required [9]. Metallic stents suffer from encrustation as the polymeric ones but have higher migration rates and production costs.

More recently, biodegradable and/or bioresorbable stents have been introduced as novel class of temporary stents which can be dissolved or absorbed in the body [10]. These stents have the advantage of decreasing patient discomfort, eliciting fewer complications—for instance they are less prone to encrustation-, and reducing the healthcare costs (e.g. secondary procedures for stent replacement or removal). Biodegradable polymers include poly(L-lactide) acid (PLLA), polyglycolide (PGA) and polycaprolactone (PCL), whereas biodegradable metals include magnesium and its alloys [11]. Although very promising, no biodegradable nor bioresorbable stents have yet the U.S. Food and Drug Administration (FDA) regulatory approval for urological applications.

2.2 Conventional Stent Manufacturing

Extrusion is the most common technique for manufacturing polymeric hollow tubes from thermoplastic materials. Plastic materials, in the form of pellets, granules, flakes or powders, are fed from a hopper into the barrel of the extruder machine; the molten polymer is forced by a rotating screw into a die, which confers to the product its final shape. To obtain a hollow section, a pin or a mandrel is placed within the die, while, to prevent the tube from collapsing, a positive or negative pressure can be applied to the internal lumen or to the outside diameter of the tube, respectively. For tubes with multiple lumens, more than one pin can be inserted into the die.

Coextrusion is typically used to produce a multilayered tube by extruding simultaneously two or more discrete layers of different materials using the same die. This technique can be exploited, for instance, to encapsulate non-medical materials between two medical-material layers. Blow molding and die drawing are other hot process techniques employed for fabricating polymeric tubes. In the former, blown air expand the polymeric tube against a mold, while the latter, similarly to extrusion, forces the polymer through a conical die.

Metal based stents are obtained by extrusion or die casting, followed by surface treatments such as chemical or plasma etching, plasma treatment micro-electro discharge machining, and laser cutting [12]. Laser cutting is a rapid prototyping technique that ensures a high-precision, burr-free cut, reliability and flexibility of the design.

3 Drug Eluting Stents

Drug eluting stent is an effective means for local drug delivery to the urinary tract. It can potentially solve a variety of upper urinary tract problems, such as stent-related urinary tract infections and discomfort, ureteral stricture, and neoplastic diseases. There are many strategies for loading drugs, including: (1) hot melt extrusion; (2) soaking the polymers into drug solution (dipping); (3) CO_2 impregnation; (4) nanofibers; (5) nanoparticles. However, the release of drug elutes on the surface of biostable stents is often unsustainable and uncontrollable.

Some previous researches had coated drugs to the surface of biostable stents, and the results were not satisfactory due to the uncontrolled drug release. Alternatively, drugs or active agents can be continuously released in a controlled manner from a drug-eluting biodegradable stents (BUS), when the stent degrades. BUS are potentially a powerful tool to contrast the most frequent adverse effects reported by patients experiencing that are pain and difficulties in urinary tract.

Several surface engineering strategies have been applied to minimize encrustation and bacterial adherence over the stent surface, through antimicrobial (bactericidal), anti-fouling (bacteriostatic), lubricating or drug eluting coatings [13].

Natural antibacterial coatings include glycosaminoglycans and heparin—natural components of the urine that were found to delay encrustation; hydrophilic coatings such as phosphoryl-choline or hydrogels demonstrated the ability to inhibit biofilm formation thanks to the hydrophilic environment that hinders proteins adsorption, thus bacterial adhesion; similarly, chitosan is used for its intrinsic antibacterial properties. Other coatings, like diamond-like carbon or polytetrafluoroethylene, diminish the surface friction, facilitating stent insertion and placement while lowering patient discomfort.

3.1 Coating Strategies

Stents surface can be directly coated with active agents by several methods, such as impregnation by dipping or supercritical fluid technology [3], crystallization, spray-coating, or layer-by-layer techniques. The first are most traditional and used, instead layer-by-layer technique is quite innovative in the urinary stent fields.

Drugs immobilization by impregnation is a two-step procedure: first, a conventional polymeric or metallic stent is fully immersed into a solution containing the drug; subsequently the solvent evaporates leaving the surface coated with the drug.

Antibacterial agents/drugs can also be directly spray-coated onto the surface of the stent [14]. For example, Nasongkla et al. deposited chlorhexidine-loaded nanospheres on the surface by high-pressure emulsification-solvent evaporation technique. In detail nanosphere suspension was perpendicularly sprayed to the spinning silicone tubes for 10 s by air pump spray gun with the flow rate of 0.2 mL/s. Then silicone tubes were drained under air flow. The drug release ability of the coated silicone tubes were tested in artificial urine and the chlorhexidine was sustained release for 2 weeks. Additionally, nanoparticles based coating showed antibacterial activity against common bacteria causing urinary tract infections up to 15 days.

Similarly, direct crystallization allows to crystallize drug onto a substrate through temperature-dependent or microdrop spray, ensuring a slower release than amorphous drug layers due to lower dissolution rate and at the same time limiting the loaded drug amount [15]. However the direct crystallization method is characterized by burst drug release kinetics.

With solvent-based polymer spraying, a drug-eluting coating can be obtained with few steps, including [16]: drugs incorporation into the polymeric solution by mixing, drug/polymer formulation spraying onto the surface; solvent evaporation. Coating characteristics, such as thickness, can be easily tailored by controlling solvent evaporation kinetics or spaying parameters. DES with prolonged antibiotic action have been obtained by spray coating drug-loaded nanospheres solutions, obtaining a smooth and homogeneous coating after several spray cycles; a sustained drug release up to 30 days occurs after the initial burst release of the loaded drug [14].

Layer-by-layer technique was firstly proposed by Decher et al. in the beginning of 1990s and it based on the alternating exposure of a charged substrate to solutions of molecules with opposite charges. After each deposition step, the substrate is washed to avoid cross-contamination of the polyelectrolyte solutions and eliminate the excess polyelectrolytes. The LBL technique allows to obtain homogeneous coating with precise and tunable architecture. It is also applicable to substrates of any shape and dimension, it is environmentally friendly and all the deposition processes can be carried out in mild conditions with low-cost manufacturing. The coating features are easily tunable by adjusting the experimental parameters, such as pH, ionic strength and polyelectrolyte concentration [15–17]. Tzanov and coworkers proposed the layer-by-layer technique to modify the surface of silicone urinary catheters to achieve infection-preventive coatings, as summarized on Fig. 2. Aminocellulose nanospheres positively charged were combined with the hyaluronic acid (HA) polyanion to build a layer-by-layer construct on silicone surfaces. Silicone supports were previously functionalized by polymerizing 3-(aminopropyl) triethoxysilane, ensuring the deposition of the first negatively charged HA layer, the multilayer coating was build-up employing a multi-vessel automated dip coater system to obtain 5, 10 and 100 bilayers. LbL coating antibiofilm activity was tested against *P. aeruginosa*. The inhibition of biofilm formation was already

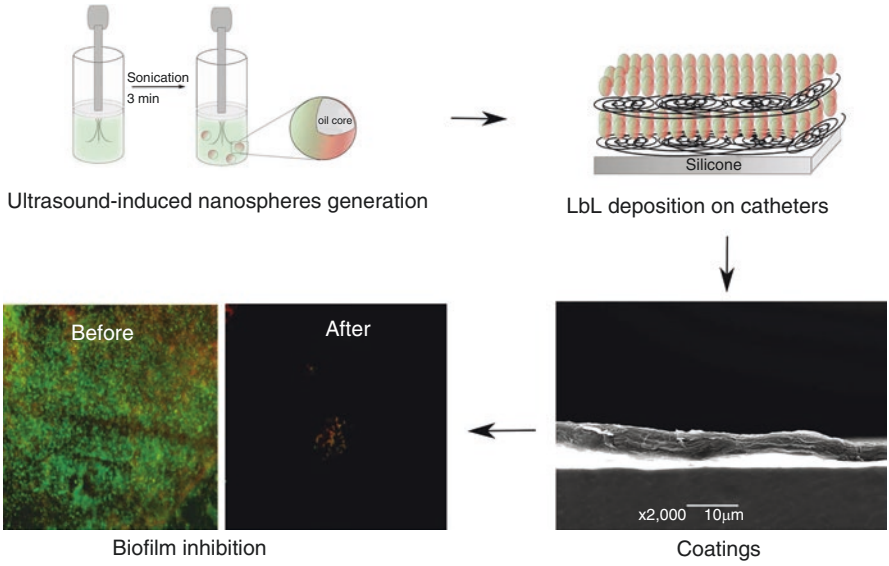

Fig. 2 Scheme of the antibacterial surfaces fabrication exploiting LbL techniques on silicone based surface. (From [18])

demonstrated with 5 bilayers coating. The antibiofilm efficiency of 10 bilayer multilayer coating on a Foley catheter was additionally validated under dynamic conditions using a model of the catheterized bladder in which the biofilm was grown during 7 days.

Although the manufacturing process is quite simple, DES obtained by direct coating methods are short term solutions and do not ensure sustained drug delivery. In fact, due to the rapid drug elution times, 90% of the drug is released within 2 days via burst release; once the thin biodegradable coatings are fully degraded or the drug content completely eluted, DES can be compared to conventional stents. To delay the complete depletion of the drug, additional coatings can be used for drug protection, among which the most common are hydrogels. Solutions employing drug delivery systems overcome the limited effectiveness of delivery observed for DES obtained by direct coating methods and provide the stent with sustained and controlled drug release over few weeks. The approach of using polymer coating layers has several functions: (1) delay the complete depletion of the active agent; (2) operate as drug loading system; (3) control drug release kinetics; (4) act as biocompatible coating after drug depletion.

Stents with a hydrophilic hydrogel coatings are currently commercially available (e.g., Universa® Soft Ureteral Stent-COOK® Medical). Hydrogel based coatings are design to reduce surface friction upon deployment which facilitates the placement of the stent and lowers patient discomfort and to be exploited for the controlled release of drugs and other biologically active compounds. For instance, antiproliferative drugs can be spray-coated onto the surface of the stent and be further

covered with an additional hydrogel layer to protect them upon stent insertion and further prevent a burst release [19]. Similarly, hydrogel or other polymeric materials can also work as a carrier due to a direct or indirect incorporation of the targeted drug into the polymeric matrix. Indirect incorporation includes the use of nanospheres/nanoparticles in which the drug can be loaded [20].

Drug-loaded nanoparticles can be prepared by several encapsulation methods which are reviewed by Pinto Reis et al., and others [21, 22]. Most of these procedures are simple and have industrial scale-up applicability, besides high encapsulation efficacy and improved pharmacokinetics and pharmacodynamics.

3.2 DES Direct Manufacturing

Drug eluting stents may be fabricated in a single process using direct manufacturing techniques. Drug delivery is a typical application of multilayered extruded tubes obtained by coextrusion [23]. In detail reservoir implants contain a drug loaded core encased in a rate controlling sheath. Co-extrusion to produce a core-sheath or multiple layer system requires multiple single screw extruders: centering and process adjustments to control dimensions can be difficult. The materials in the layers should stick together; generally chemical similarity predicts adhesion.

In the last decades additive manufacturing techniques have been emerged as alternative tool for the fabrication of drug-eluting implants combining the advantages of a targeted local drug therapy over longer periods of time with a manufacturing technique that easily allows modifications of the implant shape to comply with the individual needs of each patient [24]. Research until now has been focused on several aspects of this topic such as 3D-printing with different materials or printing techniques to achieve implants with different shapes, mechanical properties or release profiles.

3.3 DES Bioabsorbable Urinary Stents

Drug-eluting technologies can be successfully combined with completely biodegradable devices. A biodegradable stent would eliminate the need for the patient to undergo a stent removal procedure, the problems of chronic indwelling stents (encrustation, stone, formation, infection), as well as the complication feared by urologists knows as the forgotten stent.

Biodegradable urinary stents (BUS) include both bioabsorbable natural or synthetic polymers, or metals. Polymeric BUS are not yet in available for urological applications but represent an important area of investigation.

BUS present several benefits such as higher resistance to encrustation and elimination of stent removal/replacement procedures, with an overall reduction

of healthcare costs. The most used biodegradable polymer is PLA. Polylactic acid (PLA) belongs to the family of aliphatic polyesters commonly made from α-hydroxy acids. It is both biocompatible and biodegradable and it is one of the most promising polymers in various applications, including biomedical field, due to its mechanical, thermoplastic and biological properties. PLA is a biodegradable polymer, which degrade in physiological environment by macromolecular scission into smaller fragments, and then into stable end-products. It is possible to produce PLA textile structures, by different techniques, such as extrusion of the polymer into mono- and multifilaments, which may be achieved by melt, dry, dry-wet-jet spinning or electrospinning.

Different techniques can be used to incorporate drugs/active agents on BUS. Freeze-casting has been proposed as a new fabrication method to obtain biodegradable porous stents with increased urine drainage and reduced risk of reflux [25]. This simple technique involves few steps: (1) preparation of a stable suspension or polymeric solution (usually water-based); (2) injection into a mold; (3) solidification by freezing within the mold; (4) solvent removal by sublimation (freeze-drying). Porous biodegradable DES could be further obtained by dispersing the selected drug in the polymeric solution using impregnation techniques. A method for obtaining drug-eluting BUS is supercritical CO_2-impregnation, reported by Barros et al. [26]. This technique has several advantages over conventional water- or solvent-based impregnation, since supercritical CO_2 shows high diffusivity and low viscosity, resulting in a fast diffusion of the solute molecules into the polymer matrix (Fig. 3). Moreover, CO_2 is chemically inert in a wide range of conditions, has low toxicity, environmental sustainability, besides being ready available and low-cost [27].

Nowadays, nanotechnologies are widely used in many fields, including biomedical applications. Among nanotechnologies, electrospinning (ES) is rapidly emerging as a simple, versatile, and cost-effective method for the fabrication of smooth non-woven fibers with controllable morphology and tunable porosity, from a charged polymer solution or melt. Electrospinning process involves the application of a high electric field to produce micro and nanofibers. The features of the end fibers depend both on solution properties, such as polymer molecular weight, concentration and conductivity, and operating parameters, such as flow-rate, applied voltage and tip-collector distance.

ES has high encapsulation efficiency for drug loading, controlled residence time, desirable delivery of encapsulated drug at a predictable rate, better stability, high surface contact area, degradability, and satisfactory softness and flexibility.

Chew et al. reported many studies about the fabrication of biodegradable eluting ureteral stent by using double-needle electrospinning [28, 29]. To address the main

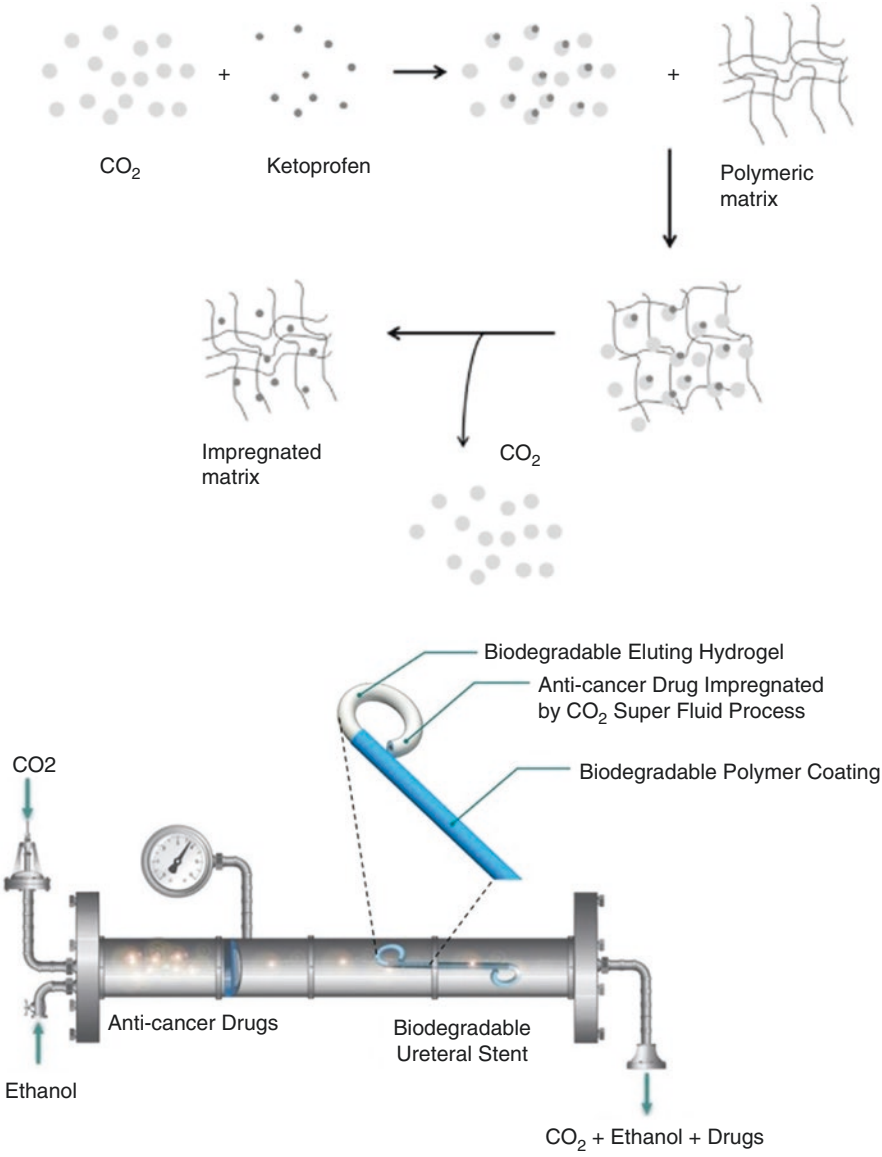

Fig. 3 Supercritical CO_2-impregnation process of ketoprofen into a polymeric matrix. (From [26])

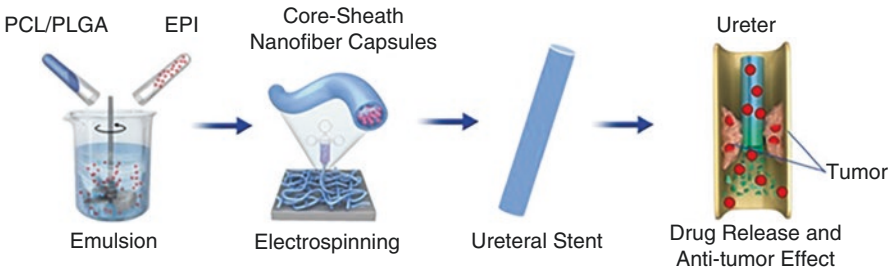

Fig. 4 Schematic illustration of preparation and antitumor effect of EPI-loaded PCL/PLGA electrospun fibers

challenges of BUS, PLGA degrading within 8 weeks was selected as stent basic material in combination with polycaprolactone (PCL) which degrades over 6 months. By using the technique of double nozzle electrospinning, researchers were able to produce a ureteral stent with different mass ratios of PCL/PLGA that degrade gradually from proximal end to the distal end.

PCL/PLGA based nanofibers can be exploited to have a controlled drug release. Ding et al. developed a biodegradable drug-loaded ureteral scaffolds able to maintain long-term effective drug concentrations in the lesion sites [30]. Epirubicin delivery was assessed on different ration PCL/PLGA electrospun fibers. Emulsion-electrospinning technology was used to fabricate a core–sheath structured EPI-loaded PCL/PLGA nanofiber capsules, displaying a sustained EPI release and controlled degradation *in vitro* and *in vivo* (Fig. 4).

4 Conclusions

Drug eluting ureteral stents, and in general urinary stents, were introduced to performed a drug delivery aiming to obtain a local treatment as well as to overcomes the main issues related to urinary stenting implantation. Drugs and/or active agents can be directly loaded in the stent structure or can be introduced through a surface coating. Although very simple, DES obtained by direct coating methods are short term solutions; once the thin biodegradable coatings are fully degraded or the drug content completely eluted, DES can be compared to conventional stents.

Drug-eluting technologies can then be combined with biodegradable bioabsorbable stents in order to eliminate the need for stent removal procedure. However some disadvantages remain still unsolved. In the last decades innovative manufacturing approaches and methods, such as nanotechnologies and additive manufacturing techniques, provide to scientists new tools for the design and fabrication on smart and custom-made urinary stents, able to go towards perfectly to patient needs.

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