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Advanced Drug Delivery Reviews 58 (2006) 387–401
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Mechanisms of controlled drug release from drug-eluting stents☆

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Received 2 November 2004; accepted 31 January 2006
Available online 6 March 2006

Abstract

The clinical importance of drug-eluting stents (DESs) has been demonstrated by their unparalleled success in preventing restenosis after stenting procedures. The magnitude of success is historic despite their short history. The current DESs deliver a single drug aiming to prevent or minimize proliferation of smooth muscle cells. Since the restenosis process involves several different biological responses, the ability to deliver the right drugs at the right times is critical for further development of the second generation of DESs. As the type of drugs that can be delivered from DESs varies, it is imperative to understand the drug delivery mechanisms and the approaches available for drug coating on the stents. The drug delivery mechanisms of current DESs that have been used clinically and under clinical trials are explained.

Keywords: Drug-eluting stents; Restenosis; Controlled drug delivery; Stent coating; Biocompatibility

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Drug-Eluting Stents: an Innovative Multidisciplinary Drug Delivery Platform", Vol. 58/3, 2006.

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doi:10.1016/j.addr.2006.01.016

1. Introduction

A stent is a small, expandable wire mesh in a tube form that is used to maintain an artery open after balloon angioplasty. Stent implantation, however, tends to cause injury to the blood vessel resulting in neointimal proliferation, known as in-stent restenosis, which continues to hamper initial procedural success in 10% to 50% of patients undergoing coronary intervention [1–3]. Recently, the concept of using coronary stents for localized delivery of antiproliferative drugs with programmed pharmacokinetics has emerged as an appealing solution to overcome the restenosis problem [4–6]. The aim of such localized drug delivery is to control, or reduce, smooth muscle cell growth and migration as well as to prevent inflammatory response, which are the predominant causes of neointimal proliferation and in-stent restenosis [7].

Localized drug delivery from drug-eluting stents (DESs) has been shown to be quite effective and accepted as one of the most promising treatment methods for preventing restenosis after stenting procedures. DESs ensure maximum delivery of the pharmacological agent directly to the target site, since they are in immediate contract with the coronary artery wall [8]. The DES approach has several advantages. Biologically active agents can be directly delivered to the target site, resulting in therapeutically effective drug concentrations in the surrounding tissues with the minimal systemic release of the drug and thus, negligible risk of systemic toxicity [9,10].

Despite its relatively short history, DESs have already made seminal impacts in the interventional cardiology. While a few DESs are clinically available, many more DESs are expected to be developed in the near future. Currently, only two drugs, sirolimus and paclitaxel, are used in DESs approved by the Food and Drug Administration. There are many other drugs that are potentially useful for treating restenosis. Selection of a controlled drug delivery technology suitable for each drug depends on many factors, including physicochemical properties of the drug, duration of release and the release profiles. It is important to understand the currently available drug delivery technologies and how they can be applied to optimize the existing DESs and to develop new DESs. This article reviews the current DES formulations and their drug release kinetics, so that it can serve as a useful source of information for those who are involved in the DES area.

2. Drug delivery mechanisms

To appreciate the technologies associated with the current DESs and to develop new formulations, it would be beneficial to briefly review the drug delivery technologies. The controlled release technologies have been advanced during the last four decades. As a result, hundreds of commercial products have been developed based on the controlled drug delivery technologies. Despite such a large number of clinical products, there are only several distinct mechanisms for controlled drug release. Many excellent reviews are available on controlled drug delivery technologies [11–16].

Table 1 lists the types of controlled release mechanisms commonly used in the currently available controlled release dosage forms. The controlled release mechanisms can be broadly classified into physical and chemical mechanisms. The physical mechanisms include diffusion of drug molecules through a polymer layer, dissolution or degradation of polymer matrix controlling the drug release rate, osmotic pressure for drug release, and use of ion exchange for ionized drugs. One of the main advantages of using physical mechanisms is that the drug release kinetics can be controlled by the drug delivery system itself. Each drug delivery system has predetermined drug release kinetics that can be adjusted by varying simple parameters, e.g., thickness of the polymer membrane, type of a polymer used, and surface area. The chemical mechanisms are based on breaking of covalent bonds that connect drug molecules to a delivery vehicle, such as polymer chains, by either chemical or enzymatic degradation. The main disadvantage of using the chemical mechanisms is that drug molecules have to be chemically modified for grafting to the delivery vehicle, and this results in new chemical entities which are called prodrugs. For this reason, the physical mechanisms have been used most widely. They are simple to use and yet highly effective in controlling the drug release kinetics.

2.1. Diffusion-controlled drug release

Diffusion-controlled drug release can occur in two different formulations. In the reservoir devices, the drug reservoir is covered with a thin polymer layer which functions as a rate-controlling membrane. At the steady state, the drug release rate remains constant to result in a zero-order release. In the matrix (or monolithic) devices, a drug is usually dispersed inside the polymer matrix, and the drug is released into the environment without any rate-controlling barrier layer. Since the drug molecules away from the surface have to migrate longer distances, the drug release rate decreases over time, resulting in non-zero-order release.

In the early days of developing controlled drug delivery technologies, it was thought that the zero-order release would be more desirable than other forms of drug release profiles. The drug delivery systems, however, can be equally effective regardless of their release kinetics as long as the drug concentration in the blood is maintained between the maximum safe concentration (C_{max}) and the minimum effective concentration (C_{min}). The ratio of C_{max}/C_{min} is known as the therapeutic index (TI) and the TI values vary from very low (e.g., less than 2 for digitoxin) to very high (e.g., 2000 for diphenhydramine and 20,000 for triphenylamine). For many drugs with high TI values, the drug release kinetics does not matter much, but for those drugs with low TI values, maintaining a certain drug release kinetics throughout the lifespan of the device is critical. Proper uses of controlled drug delivery systems can increase the C_{max}, and thus TI, by minimizing the side effect.

2.2. Dissolution/Degradation-controlled drug release

Dissolution/degradation-controlled drug release is based on dissolution or degradation of a polymer membrane encapsulating the drug reservoir or a drug-containing polymer matrix itself. Since most water-soluble polymers dissolve rather quickly, they may not be a good option for developing DESs. Biodegradable polymers, such as poly(glycolic acid),

Table 1
Mechanisms of controlled drug release

1. Diffusion
A. Reservoir system
B. Matrix system
2. Dissolution or degradation
A. Reservoir system
B. Matrix system
3. Ion exchange
4. Osmosis
5. Prodrug

poly(lactic acid), and poly(-caprolactone), are not water-soluble and yet degrade slowly by hydrolysis for weeks and months. Since drug delivery from stents requires delivery for weeks and months, the biodegradable polymers can be used effectively in development of DESs.

2.3. Ion exchange-based drug release

Ion exchange can be used very effectively for controlled release of ionized drugs which binds to the matrix through electrostatic interactions. The ions having the same charge as the drug replace the drug molecules for release. This approach is quite useful for delivery of ionized drugs including DNAs. The ion exchange approach has become more important and useful, since recent advances in layer-by-layer (LBL) assembly approach [17] allow loading of charged drugs in multilayers, leading to higher amounts of drugs on the surface.

2.4. Other controlled release technologies

In osmosis-based controlled release devices, the drug is released at zero order because the osmotic pressure inside the devices builds up at a constant rate defined by the system. Since the drug molecules are pushed into the environment through a very small orifice, the drug molecules are pumped out into the environment with convection, not just by diffusion. This type of drug release may be a good option where drug delivery by convection is important [18,19]. Prodrug approach is based on chemical (e.g., hydrolysis) or enzymatic degradation in the body, the drug release kinetics is likely to be affected by the parameters, such as pH and the enzyme concentration, which cannot be controlled by the system itself. Various controlled release dosage forms can be made based on one or combination of a few mechanisms listed in Table 1. Selection of the drug delivery mechanism(s) is largely dependent on the nature of the drug to be delivered.

3. Drugs used in controlling restenosis

The drugs that are released from DESs are expected to inhibit inflammation and neiointimal formation after stent implantation. Since the inflammatory and proliferative responses are results of the complex cascade of events, various cells and tissue components involved in the vascular reparative process are all potential targets of therapeutic approaches [20]. For this reason, various drugs with widely different properties can be used for the same purpose of reducing neointimal proliferation [21]. Detailed understanding of the biological events following the stent implantation allows proper selection of drugs for DESs based on physicochemical properties, such as molecular weight, water solubility, and partitioning coefficient. It is the physicochemical properties of a drug that largely determines the drug delivery technology. The physicochemical properties of a drug are also important in drug absorption into the surrounding tissues [18]. The drug, polymer, and interactions between the two significantly affect the clinical outcome [22].

Various drugs used in coating drug-eluting stents fall under immuno-suppressive agents (e.g., sirolimus, tacrolimus, and everolimus), cellular proliferation inhibitors (e.g., paclitaxel and actinomycin D), anti-inflammatory agents (e.g., dexamethasone), or prohealing agents. Sirolimus (rapamycin), which inhibits smooth muscle cell proliferation and migration to reduce neointima formation, has been used in the DES developed by Cordis Corp. (Miami, FL). Tacrolimus, which is structurally and functionally related to sirolimus, is used in the DES developed by Jomed (Helsingborg, Sweden). Paclitaxel, which is a microtubule-stabilizing agent with potent antiproliferative activity, has been used in the DES manufactured by Boston Scientific (Natick, MA). Actinomycin D was used in the Guidant's (Indianapolis, IN) DES program ACTION, which was prematurely stopped due to an unacceptably high target vessel revascularization rate in the actinomycin group [23]. Dexamethasone, a proven antiinflammatory agent, has been used in the study of antirestenosis of the BiodivYsio DES manufactured by Biocompatibles UK, Ltd. (United Kingdom) [24]. More than a dozen of DESs have been tested for their clinical efficacy, and many of them have been shown to be ineffective in preventing restenosis. The lack of beneficial clinical effects is, in large part, due to the inadequate delivery of the drug, such as delivery of subtherapeutic level of the drug or delivery for insufficient

duration. Thus, selection of the right drug delivery technology for the drug to be delivered is critically important.

4. Coating strategies for prevention of restenosis

Many different approaches have been used for drug delivery from stents, and the duration of drug delivery has been varied. It has been suggested that vascular smooth muscle cells start proliferation only a day after the injury resulting from balloon angioplasty/stent deployment for about 2 weeks [25]. Thus, it is believed that antirestenotic drugs need to be delivered for at least 3 weeks after stent deployment to prevent smooth muscle cell migration and proliferation [26,27]. It is important to have the precise control of the drug release kinetics, since the release kinetics should be tailored to the pathophysiologic phases of restenosis depending on the specific mechanism of drug action [28,29]. Drug delivery for weeks and months from the stents requires a rate-controlling system, which is usually made of polymers [23]. The rate-controlling system ensures drug retention during stent deployment and modulates drug-elution kinetics. The controlled drug delivery technology also makes it possible to target distinct phases of the restenotic process by altering the release kinetics of the same drugs or different drugs.

Many different materials can be used to cover a stent surface using an array of techniques, such as dip coating, spray coating, plating, sputtering, and surface induced mineralization. The dip coating method involves dipping of a stent in a polymer or a polymer–drug solution followed by drying to obtain a thin, uniform and continuous coating (or a layer). This method is the simplest of all the methods. The spray coating involves spraying of microdroplets of a polymer or a polymer–drug solution directly onto the stent surface using various spraying devices. Very thin polymer coatings can be made by the spray coating approach. Even thinner polymer coatings in the nanometer scale can be obtained by using recently developed layer-by-layer (LBL) assembly technologies, in which oppositely charged polymers and drugs can be sequentially adsorbed to achieve coatings in the micrometer scale [17,30]. Instead of coating the drug–polymer layers throughout the entire strut surfaces, some approaches utilized filling the reservoir spaces in the form of grooves and holes available on the struts using microdispensers. The grooves and holes vary in size and shape. For these approaches to be useful, the strut should have dimension large enough to have the reservoir spaces. Studies using polymer sleeves wrapping around the metal stents have also been used in animal studies, but they may not be practical for clinical applications.

4.1. Coatings for diffusion-controlled drug release

Diffusion-controlled drug delivery utilizes water-insoluble polymers. As discussed below in Section 5, Coating Strategies for Improving Biocompatibility, the surface-induced thrombosis is still one of the major problems in the DES area. Thus, in the selection of polymeric materials, their biocompatibility has to be considered in addition to other properties, such as

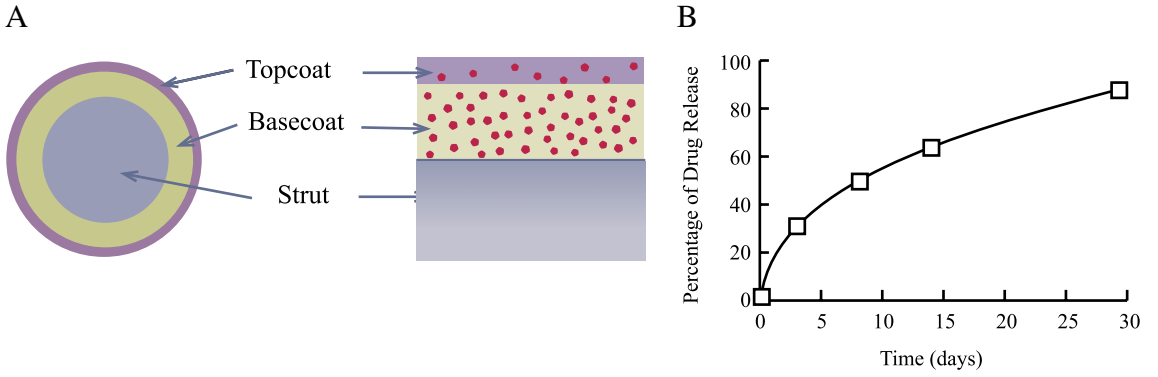

Fig. 1. Schematic description of the cross-sectional (left) and side (right) views of a strut of the Cypher stent (A), and the in vitro sirolimus release profile from the Cypher stent (B). From Reference [31].

elasticity (required for stent expansion) and drug release properties.

4.1.1. Cypher™ stent

The Cypher stent of Cordis Corp. uses poly(ethylene-co-vinyl acetate) (PEVA) and poly(n-butyl methacrylate) (PBMA). The combination of PEVA and PBMA is mixed with sirolimus at the ratio of 67% polymer and 33% drug. This is applied to the stent surface as the base coat (meaning the drug reservoir layer). This base coat is then covered with another thin layer of PBMA. The presence of the topcoat makes the Cypher stent a diffusion-controlled reservoir device. Fig. 1A show the cross-sectional and the side views of the strut coated with the base coat and top coat, and Fig. 1B shows the in vitro release profile of sirolimus for the first 30 days.

Drug release from the diffusion-controlled systems can be described by the following equation:

$$M = SDK\frac{\Delta C}{h}\left(t + \frac{h^2}{3D}\right) \quad (1)$$

where M is the total amount of drug released, S is the surface area available for drug delivery, D is the diffusion coefficient of drug through the rate-controlling membrane, K is the partition coefficient of drug to the rate-controlling membrane, ΔC is the concentration gradient, which is the same as the saturated drug concentration in the drug reservoir, h is the thickness of the rate-controlling membrane, and t is the time for drug release. The term $h^2/3D$ in Eq. (1) accounts for the initial burst release before reaching the steady state release.

The sirolimus release profile for the first 30 days in Fig. 1B can be explained by Eq. (1). The topcoat in the Cypher stent is the rate-controlling membrane that controls the drug release kinetics. Even though the top coat is applied without any drug, the drug migrates to the topcoat during storage after preparation, resulting in the initial burst release during the first few days. Applying the drug-free topcoat is important for minimizing the extent of the initial burst release. The initial burst release should provide just enough sirolimus immediately after stent implantation to prevent neointimal hyperplasia. Too much release of sirolimus in the first few days may cause serious side effects. After reaching the steady state, the drug release rate remains constant for a while. As most of the drug is released in about 3 weeks, the concentration in the base coat decreases (i.e., the value of ΔC decreases), resulting in decreased release rates.

4.1.2. Taxus™ stent

The TAXUS stent by Boston Scientific employs Translute™ polymer, which is poly(styrene-*b*-isobutylene-*b*-styrene) triblock copolymer, for sustained delivery of paclitaxel. Paclitaxel is released from the Translute polymer matrix directly into the environment without going through the rate-controlling membrane, and thus the Taxus stent is a diffusion-controlled matrix system. Fig. 2A shows the cross-sectional and the side views of the strut of the Taxus

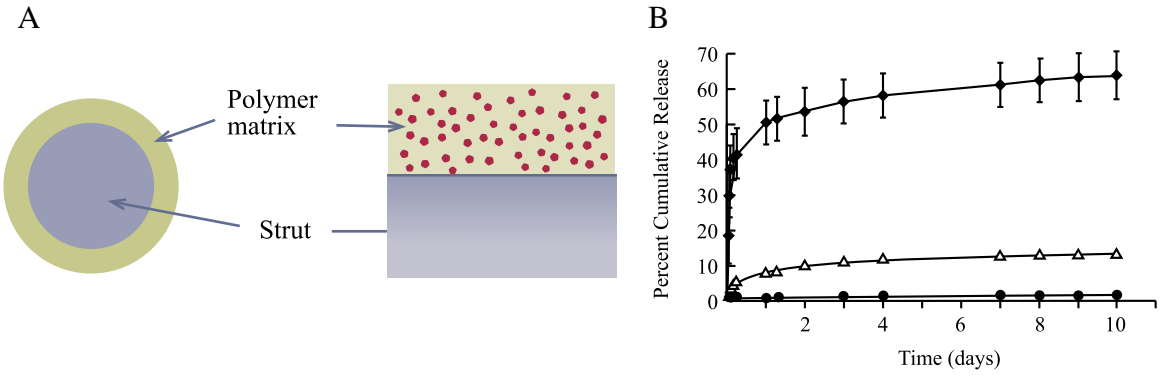

Fig. 2. Schematic description of the cross-sectional (left) and side (right) views of a strut of the Taxus stent (A), and three different in vitro paclitaxel release profiles from the Taxus stent (B). Symbols ♦, Δ, and ● represents paclitaxel release at fast, moderate, and slow release profiles. From Reference [32].

stent, and Fig. 2B shows the paclitaxel release profiles from the stent.

The drug release profile of matrix devices containing excess drugs over the dissolved drug is described by the following equation:

$$M = S[D\ C_s(2A - C_s)t]^{1/2} \quad (2)$$

where M, S, D, and t have the same meanings as described in Eq. (1). C_s and A are the solubility of the drug in the polymer matrix and the total drug concentration (*i.e.*, dissolved drug+dispersed drug), respectively. If the total drug concentration (A) is substantially larger than the solubility of the drug in the polymer matrix (C_s), then Eq. (2) becomes:

$$M = S[2\ D\ C_s\ A\ t]^{1/2}. \quad (3)$$

Eqs. (2) and (3) show that the total amount of the released drug decreases slowly as time passes. This, however, will not affect the efficacy of the device as long as the concentration of the released drug in the target site is higher than the minimum effective concentration (C_{min}). Fig. 2B shows three different paclitaxel release profiles from the Taxus stents. Three formulations having the same dose of 1 μg/mm^2 resulted in three different release profiles. Assuming the surface area of the stent remains the same for three formulations, the different release profiles result from the different D values, which can be varied simply by adjusting the polymer concentration in the matrix. The paclitaxel:polymer ratios in the Taxus stent for fast, moderate, and slow release profiles are 35:65, 25:75, and 8.8:91.2, respectively. As the drug–polymer ratio decreases, the mass of the polymer, and thus the thickness of the polymer matrix, increases. This is a simple approach of controlling the release kinetics using the same drug–polymer system. For the fast release formulation, the burst release of paclitaxel in the first day is followed by a slow release over the next 10 days. In clinical applications, only the moderate and slow release formulations are used. The initial burst release from the moderate release profile provides an immediate dose necessary for arresting the cell division, and thus preventing restenosis.

4.1.3. Stents with a polymer sheath

Instead of coating the stent struts with drug-containing polymer layers, the unexpanded stent can be wrapped around with a polymer sheath containing a drug [33,34]. The idea is that the polymer sheath is trapped between the expanded stent and the vessel wall [33]. While this approach appears simple for delivery of various drugs in animal experiments, it may not be suitable for clinical applications.

4.2. Coatings for dissolution/degradation-controlled drug release

Drug delivery from stents based on the dissolution or degradation mechanism relies on slow dissolution of water-soluble polymers or slow degradation of hydrophobic polymers by hydrolysis. Sometimes, the drug can be attached to the stent surface in the absence of polymers. This approach can also provide sustained drug release if the drug is hydrophobic, and thus the drug release depends primarily on the dissolution in aqueous environment.

4.2.1. Achieve™ stent

The Achieve Stent is a metallic stent from Cook, Inc. which can be directly impregnated with a drug without a polymer layer. The stent was simply dipped into a paclitaxel ethanol solution before drying to deposit a fine residue of paclitaxel on the surface [35]. The reason for direct attachment of paclitaxel to the metal surface was to eliminate undesirable complications (inflammation and thrombosis) associated with certain polymers. Since there is no protective layer for the attached paclitaxel particles, it is likely that most of paclitaxel is lost rather quickly. Tests with dip-coated stents showed that most of the drug loss occurred before stent expansion and deployment, arguing for modification of the coating procedure. Clinical evaluation showed that the paclitaxel-coated Achieve Stent did not meet the predetermined primary end point of target vessel failure and the secondary end point of binary restenosis [36] (Fig. 3).

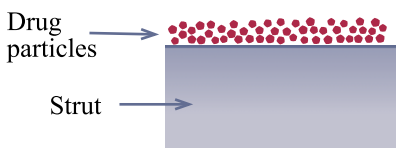

Fig. 3. Schematic description of the side view of a strut of the Achieve stent. Paclitaxel particles are directly deposited to the stent surface without any polymer matrix.

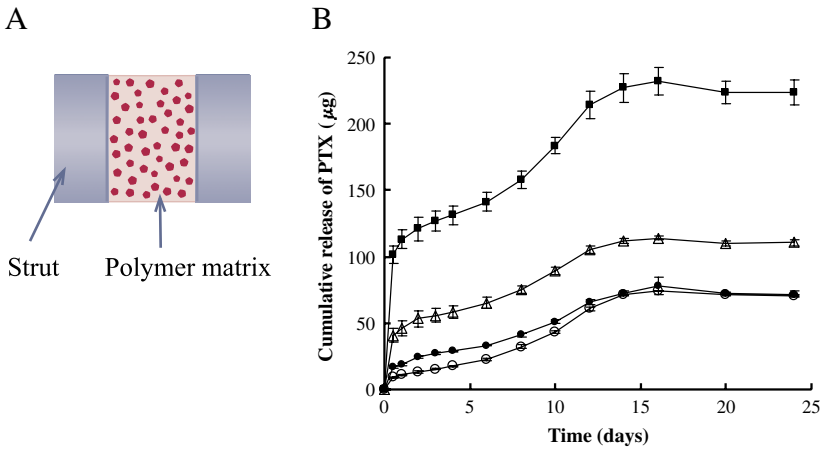

Fig. 4. Schematic description of the side view of a strut of the Conor stent (A), and four different in vitro paclitaxel release profiles from the Conor stent (B). From Reference [38].

4.2.2. Stents coated with natural polymer films

To preserve the paclitaxel residues that are physically adsorbed on the stent, the stent was further coated with natural polymers. Paclitaxel was deposited on ACS Multi-Link™ stents (Guidant Corp.) by the same method used in the Achieve Stent, i.e., evaporation of a volatile solvent leaving paclitaxel residues. The paclitaxel-deposited stents were first dipped into a molten gelatin solution and then into a chondroitin sulfate solution containing glutaraldehyde [37]. The formation of a polymer film is based on the coacervation of two oppositely charged polymers, gelatin and chondroitin sulfate. The coacervate film was further cross-linked by glutaraldehyde. While the presence of a polymer film certainly protects the underlying paclitaxel, the animal study showed that all paclitaxel was released within 2 weeks [37]. For release of paclitaxel for more than 2 weeks, the polymer concentrations and the cross-linking density can be increased.

4.2.3. Conor Medstent™

The Conor stent made by Conor Medsystems has numerous holes on its struts. Each hole is filled with a solution of drug and biodegradable polymer (e.g., paclitaxel and poly(lactide-co-glycolide) (PLGA)) using a piezoelectric microdispenser [38]. The solvent evaporates to leave a thin layer of paclitaxel/PLGA inside the holes, and the loading process is repeated many times to build up the drug–polymer matrix. The loaded paclitaxel is released slowly due to degradation of PLGA inside the holes. The paclitaxel release profile can be controlled easily by controlling the degradation kinetics of PLGA through changing the ratio of lactic acid and glycolic acid and the polymer

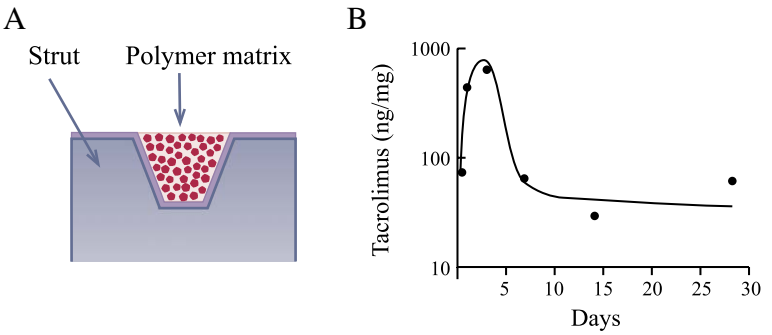

Fig. 5. Schematic description of the side view of the strut of the Janus CarboStent (A), and in vivo tacrolimus release profile from the CarboStent as measured by the concentration in the vascular tissue (B). From Reference [39].

molecular weight. Fig. 4A shows the side view of a strut of the Conor stent, and Fig. 4B shows the paclitaxel release profiles from the stent. The initial burst release is sometimes very large, especially when the paclitaxel amount is high (the top release profile in Fig. 4B). Simply lowering the paclitaxel amount can lower the initial burst release, but it comes with lower amounts of the delivered drug (the bottom three release profiles in Fig. 4B). The initial burst release can be further reduced by placing plain polymer layers on top of the drug–polymer matrix. The sudden increase in the release rate (i.e., the slope) after about 10 days resulted from autoaccelerated degradation of PLGA.

4.2.4. Janus Carbostent™

Janus CarboStent™ is a unique stent characterized by deep grooves, or sculptures, on the outer stent surface that can be used to hold a drug, tacrolimus [39]. The stent surface is first treated with an integral carbofilm coating, which is known to render the stent surface non thrombogenic when in contact with blood. The deep sculptures on the surface increase the drug loading capability up to five times in comparison to the other available drug-eluting stents in the similar size. The grooves can be filled with a drug only or with a polymer matrix containing the drug (Fig. 5A). Fig. 5B shows the in vivo tacrolimus release profile after implantation of the Janus CarboStent loaded with tacrolimus in the rabbit iliac artery. The tacrolimus concentration in the rabbit iliac artery reached the maximum in the first few days. It is interesting to notice that the maximum concentration was an order of magnitude higher than the steady state values in the following weeks. About 50% of the loaded drug was released during the first month of implantation.

4.2.5. Stent covered with a PLGA film

A uniform film of PLGA containing green fluorescent protein plasmid DNA was formed over the outer surface of a stent [40]. A solution of plasmid DNA was added to a PLGA solution in chloroform, and the emulsion was coated in multiple thin layers onto stents or unfenestrated steel rods. The approach resulted in formation of uniform film covering the whole stents, i.e., with a thin polymeric web between the struts, which remained intact during stent expansion and deployment.

In vitro release of plasmid DNA from the polymer film is shown in Fig. 6. More than 50% of the loaded DNA was eluted during the first hour of incubation, and this is followed by slower release for a week. In this particular case, delivery of more than 50% of the loaded DNA within an hour may be necessary, since the DNA transfection efficiency is usually very low, and thus large initial burst release may be beneficial. The assay demonstrated that the released DNA was structurally intact for successful transfection of arterial vascular smooth muscle cells in the presence of a transfection enhancing agent.

4.3. Coatings for ion exchange-controlled drug release

Ion exchange is used frequently in our daily lives. For example, soft water is produced by removing calcium ions from water by exchanging with sodium ions that were complexed to ion exchange resins. Since there are abundant amounts of ions in the body, ion exchange is a very viable approach in controlled delivery of charged drugs including DNAs and RNAs.

4.3.1. BiodivYsio stent

The BiodivYsio stent, a stainless steel metal stent, is coated with a synthetic polymer containing a phosphorylcholine head group to make the surface more biocompatible [41]. The phosphorylcholine coating consists of a copolymer of methacryloylphosphorylcholine and lauryl methacrylate. The stents are

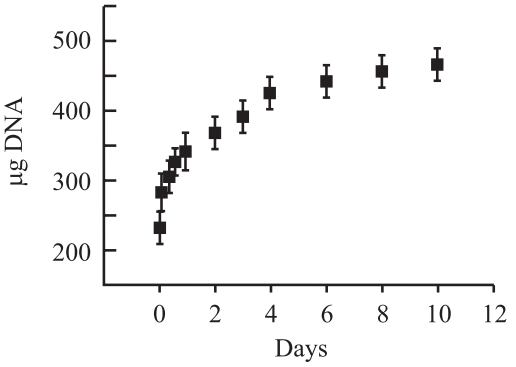

Fig. 6. In vitro DNA release profile from a PLGA film wrapping around the stent. From Reference [40].

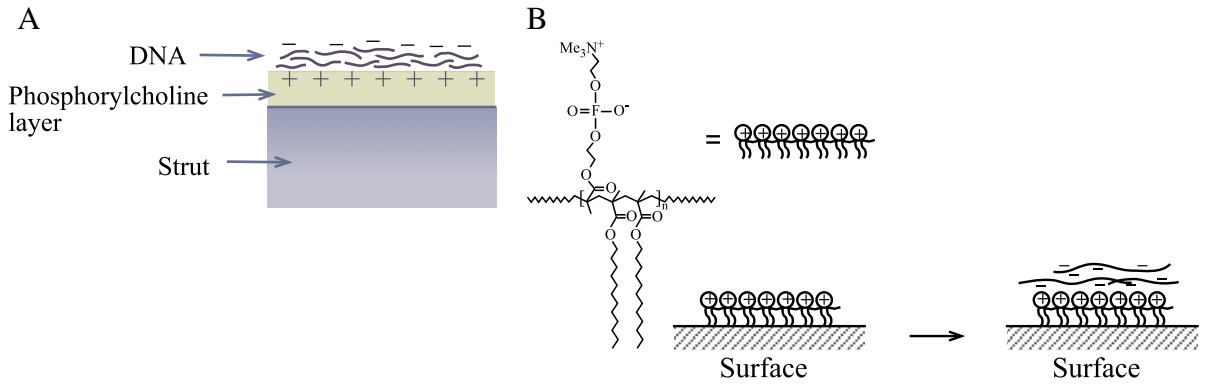

Fig. 7. Schematic description of the cross-sectional view of a strut of the BiodivYsio stent coated with a phosphorylcholine layer (A), and the chemical structure of a copolymer of methacryloylphosphorylcholine and lauryl methacrylate interacting with DNA by electrostatic interactions (B). From Reference [41].

dip coated from a solution of the polymer in ethanol to give a coating that is approximately 50 nm thick. The positively charged phosphorylcholine interacts with negatively charged molecules, such as DNA, by electrostatic interactions. The bound DNA can be slowly replaced by negatively charged ions present in the body, such as chloride ions. Because of the multiple interactions of polymeric DNA molecules to the surface, replacement of DNA from the surface is slow, and this may be useful in the development of sustained gene eluting stents.

The BiodivYsio stent was coated with naked plasmid DNA (5283-bp) encoding for human vascular endothelial growth factor (phVEGF-2) through electrostatic interactions, as shown in Fig. 7 [42]. The amount of phVEGF-2 plasmid coated on the stent ranged from 100 to 200 μg. The study showed that therapeutic local gene transfer was possible as shown by effective prevention of restenosis. The experimental data showed that transcript and protein were detected for up to 10 days after stent implantation, and neointimal proliferation was reduced at 3 months of follow-up.

5. Coating strategies for improving biocompatibility

In addition to prevention of restenosis, another important requirement of DESs is absence of inflammation and thrombogenicity [20,21]. Selection of noninflammatory, nonthrombogenic coating materials has been a major obstacle in the development of DESs. This problem has been compounded by the possibility that delivery of unnecessarily high drug dose may result in delayed wound healing and endothelialization, which would increase thrombogenicity. The Cypher stent and the Taxus stent, the two most successful DESs, employ a mixture of poly(ethylene-co-vinylacetate) and poly(*n*-butyl methacrylate) and Translute™ poly(styrene-*b*-isobutylene-*b*-styrene) triblock copolymers, respectively. Despite their clinical successes, the stent thrombosis is still one of the major concerns in the DES area. In a prospective follow-up study of Cypher implantations performed outside of controlled clinical trials, 1.1% of the patients experienced stent thrombosis at a mean time of 7 days (range 2 to 13) [43]. This stent thrombosis rate is similar to historical reports in bare metal stents. Thus, all materials currently in clinical applications need to improve their biocompatibility further.

One of the suggested approaches of surmounting the stent thrombosis has been using biodegradable polymers [44]. It does not appear, however, that this approach will solve the problem, since the stent thrombosis occurs in the first few weeks while it takes months for biodegradable polymers to degrade. Many approaches have been tried to make the stent surface more biocompatible, and the common approaches have been to graft surfaces with water-soluble polymers, such as heparin [45], phosphorylcholine-containing polymers [41], fibrin [46], albumin [47], and poly(ethylene oxide) [47,48], and to deliver anti-thrombogenic agents, such as antibody against platelets, from the surface [49].

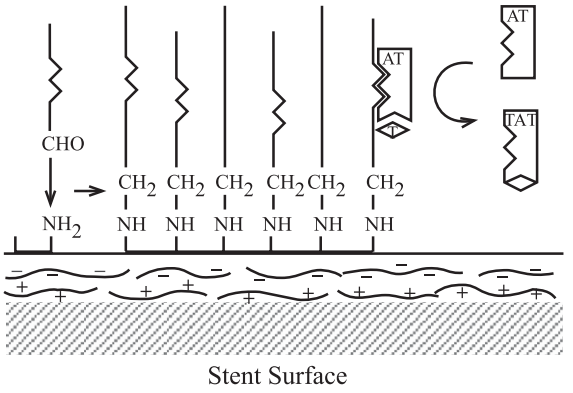

Fig. 8. Schematic description of heparin coating on the stent surface. The surface is primed with functional amino groups that can bind covalently with the aldehyde group of fragmented heparin molecules (A). The end grafted heparin can interact with antithrombin III (AT) which inhibits thrombin (T) (B). The inactive antithrombin/thrombin complex (TAT) is then released into the bloodstream (C). From Reference [45].

5.1. Heparin–coated PalmazSchatz stent

Heparin has been bonded onto solid surfaces by end-point attachment, and this allows heparin to interact freely with circulating antithrombin III [45]. The stent surface is sequentially coated with polyethyleneimine, dextran sulfate, and another polyethyleneimine layers (Fig. 8A). The functional amino groups of the third layer of polyethyleneimine are then covalently coupled to the aldehyde groups of partially degraded heparin molecules (Fig. 8B). Approximately 15% of the end point-attached heparin molecules carry the high-affinity antithrombin III-binding site, which is responsible for the anticoagulant action of the compound (Fig. 8C). The in vitro studies have shown that mounting and expansion of the stent did not affect the integrity of the coating. Sterilization with heat or ethylene oxide reduced the antithrombin III-binding activity considerably. In vivo study showed that the thickness of the neiointimal layer was not reduced by the heparin coating.

5.2. Phosphorylcholine-coated stent

The phosphorylcholine coating applied to the divYsio stent consists of a copolymer of methacryloylphosphorylcholine and lauryl methacrylate, as described in Fig. 7. Previous work has shown its success in improving biocompatibility of surgical equipment and guide wires in reducing neointimal hyperplasia in synthetic vascular grafts in a canine model [41]. The phosphorylcholine coating remained intact for the duration of the study, up to 6 months, without inducing stent thrombosis [50]. The phosphorylcholine layer coated on the stent did not interfere with endothelialization, as measured at 5 days after implantation. During the subsequent process of wound healing, the coated and non-coated stents elicit a tissue response that is similar in nature.

5.3. Antibody-eluting stents

As an alternative way of making the stent surface more biocompatible, the stent surface was coated with a polymer layer that elutes antibody (AZI) against platelet glycoprotein IIb/IIIa, which is known to interact with fibrinogen for formation of thrombi on the surface [49]. This is an active approach toward neutralizing the source of the problem, platelets. Stainless steel stents (Cook, Inc.) coated with a 30 μm thick cellulose layer were immersed in a solution of radio-labeled (^{125}I) AZ1 antibody solution. The amount of antibody adsorbed depends on the antibody concentration and immersion time. At the concentrations used (1.0 mg/ml or less), the saturation adsorption occurred within 24 h of adsorption. The maximum amount of antibody adsorbed was

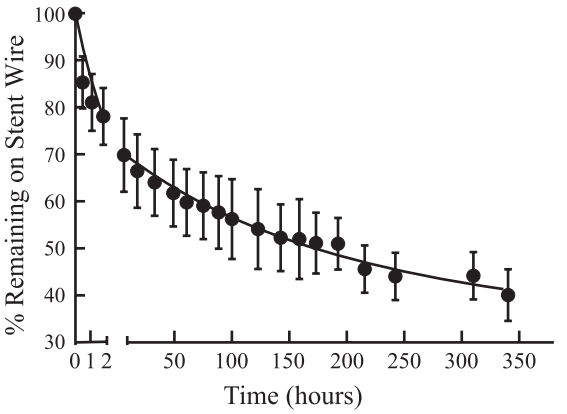

Fig. 9. Percentage of AZ1 antibody remaining bound to stent wires over 14 days of continuous perfusion. The initial rapid wash-off (equivalent to burst release) is followed by much slower release. From Reference [49].

10 ng/mm wire. The antibody-adsorbed wires were placed in a device with a continuous flow of a buffer solution.

Fig. 9 shows the release profile of the surface adsorbed antibody for more than a 2-week period. Even after 14 days of perfusion, almost 40% of the originally adsorbed antibody remained bound to the wire surface. This is typical of release of proteins adsorbed to the solid surfaces. It is very difficult to remove the tightly bound portion of the adsorbed proteins even using surfactants. Animal experiments showed that the platelet deposition onto the antibody-eluting stent was only half of that on the control stents. The limitation of this type of approaches is that the device loses its ability to reduce the platelet deposition when all adsorbed antibodies are released. Since the platelet deposition and thrombus formation is not limited to the short-term exposure, more fundamental approaches of improving biocompatibility is preferred.

6. Some issues in the development of drug-eluting stents

Drug delivery from stents has become a very important research area that has shown immediate, huge benefits in clinical applications. The fact that there are a few DESs in clinical applications should not mask the importance and need of continued research on drug delivery from stents. There are still a few issues to be resolved in the development of DESs.

6.1. Importance of controlling the drug release kinetic

While there is no doubt on the benefits of the DES, one has to understand that the inhibition of neointima proliferation is not restricted to vascular smooth muscle cells but also affects the process of re-endothelialization, that may lead to late stent thrombosis [51]. Large randomized clinical studies also revealed potential risks of the revolutionary DES unless the dosage of the drug and the release kinetics are optimized [51]. The optimized drug dose and release kinetics would be those that prevent proliferation of vascular smooth muscle cells without affecting the re-endothelialization process. Such optimized conditions have yet to be identified. In such efforts, the ability to control the dose and release kinetics of the test drug is essential.

6.2. Variable drug release profiles from the same stent

It is often assumed that eluting the drug only from the external surface of the stent which is in direct contact with the vessel wall is most desirable, since it avoids loss of a significant portion of the drug into the blood stream. This has been the premise of developing unique stent designs, such as Conor stents and Janus CarboStents. The idea of unidirectional drug release appears to make sense at first glance, but careful examination on the tissue distribution of the drug released from the stent [18] indicates that the unidirectional release may not be the most desirable mode of drug delivery. The inhomogeneity in the circumferential and longitudinal distribution of stent struts results in inhomogeneous drug distribution in the tissue surrounding the stent [18]. There are substantial differences between the local and mean concentrations in the tissue. This problem will be amplified with the unidirectional release of the drug. For example, in Fig. 5B, the peak tissue concentration in the first few days is an order of magnitude higher than the concentration at the steady state. Considering the fact that the local and mean concentrations in the tissue are very different, one can easily assume that the concentration of the drug adjacent to the stent struts would be even higher. The striking fluctuations in concentrations may result in the toxic level near struts, especially adjoining struts, and subtherapeutic level away from the struts [18]. Since biological effect is governed by the local concentrations, rather than the mean tissue concentration, it may be necessary to design the drug release in such a way that the local drug concentrations do not fluctuate too much.

One way of maintaining the homogeneous local drug concentrations in the tissue is to release different amounts of a drug depending on the density of the struts is highly important [19]. The different drug release profiles can be obtained, at least in theory, by loading different amount of a drug at different sites on the stent or by using different polymer systems for varying the drug diffusion and release. This heterogeneous coating may be difficult for the currently used coating methods, such as dip coating or spray coating, since these approaches cannot differentiate

different segments of a stent. In the age of nanotechnology, however, heterogeneous coating of a drug or a polymer at different concentrations is feasible. For example, ink-jet type microdispensers can be used to coat different amounts of a drug on different places of a stent.

6.3. Layer-by-layer assembly for drug loading

One of nanotechnologies that can be useful for developing DESs is layer-by-layer (LBL) assembly technology. The LBL assembly of polyelectrolytes has emerged as a powerful and versatile, yet simple strategy to engineer surfaces with specific properties [52,53]. The LBL approach can find immediate applications in drug delivery from stents [30,54] and making the surface more biocompatible [55,56]. As described in above, the BiodivYsio stent, which has positive charge on the surface, was coated with negatively charged DNA. The DNA-coated stent can be further coated with additional layers of DNA using the LBL approach. A polycation can be adsorbed to the first DNA layer to introduce a fresh positively charged layer, and this new layer will allow electrostatic adsorption of a new DNA layer, and this process can be repeated many times to increase the total amount of DNA on the stent surface. The heparin-coated stent can also be used for drug loading by the LBL approach because of the presence of the negative charge of heparin on the surface. On top of the heparin layer can be adsorbed a polycation, e.g., polyethyleneimine, followed by DNA or any other protein drugs with net negative charges. In this way, the amount of DNA loaded on the stent surface will be increased substantially. The LBL assembly approach is not limited to the delivery of ionized drugs. The same approach can be used to deposit various drugs onto the stent surface by preparing charged LBL building blocks that may contain various types of drugs.

7. Summary

Despite the phenomenal advances in stent design, incidence of restenosis of bare metal stents remains unacceptably high. The interventional cardiology has been rapidly evolving and DESs have emerged as a breakthrough technology. The localized delivery of a drug directly to the target site resulted in prevention of restenosis without side effects associated with systemic delivery of the same drug at much higher concentrations. A number of different controlled drug delivery technologies can be used for designing DESs. Diffusion-controlled drug delivery systems are most commonly used due to their easiness of preparation as well as the excellent ability to control the release kinetics. Since it is likely that many different drugs with different physicochemical properties will be found useful in prevention of restenosis, further development of drug coating technologies is essential. New drug coating technologies are also required for controlling the drug release profiles on different sites of the same stent. Further advances in the stent coating technology will undoubtedly elevate the DES technology to a pre-eminent position in the management of coronary artery disease.

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