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Review

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Polymer-Free Drug-Eluting Stents: An Overview of Coating Strategies and Comparison with Polymer-Coated Drug-Eluting Stents

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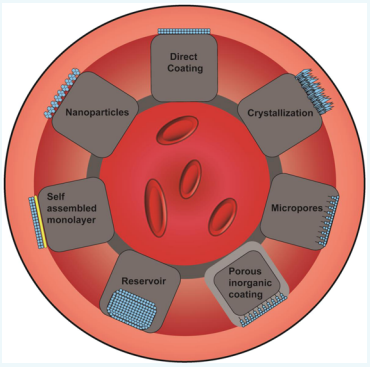
ABSTRACT: Clinical evaluations have proven the efficacy of drug-elution stents (DES) in reduction of in-stent restenosis rates as compared to drug-free bare metal stents (BMS). Typically, DES are metal stents that are covered with a polymer film loaded with anti-inflammatory or antiproliferative drugs that are released in a sustained manner. However, although favorable effects of the released drugs have been observed, the polymer coating as such has been associated with several adverse clinical effects, such as late stent thrombosis. Elimination of the polymeric carrier of DES may therefore potentially lead to safer DES. Several technologies have been developed to design polymer-free DES, such as the use of microporous stents and inorganic coatings that can be drug loaded. Several drugs, including sirolimus, tacrolimus, paclitaxel, and probucol have been used in the design of carrier-free stents. Due to the function of the polymeric coating to control the release kinetics of a drug, polymer-free stents are expected to have a faster drug elution rate, which may affect the therapeutic efficacy. However, several polymer-free stents have shown similar efficacy and safety as the first-generation DES, although the superiority of polymer-free DES has not been established in clinical trials.



INTRODUCTION

Stents are hollow devices that are inserted in an obstructed natural passage (such as the coronary artery) to open and prevent blockage of the passage.[1] The most basic stents are bare metal stents, which can be assembled from a range of metals such as stainless steel (316L), a cobalt chromium alloy, nickel–titanium alloy, and so forth.[2,3] One of the most common problems with bare metal stents in the vascular system is neointimal hyperplasia, which subsequently results in a redevelopment of arterial blockage and obstructed flow, an event also known as in-stent restenosis. Restenosis can be counteracted by systemically administered antiproliferative or immunosuppressant drugs. Local release of these drugs can be achieved by drug eluting stents in which drugs are incorporated in a polymer coating that is deposited on the metal stent.[2,4]

It has been suggested that the polymeric coating of drug-eluting stents provokes a cascade of cellular and biochemical events that cause pathophysiological processes such as release of cytokines which trigger the proliferation of smooth muscle cells, block the endothelization of the nearby tissue, and induce other side effects such as late and very late thrombosis.[5] To combat the risk of thrombosis, at least 1 year of antiplatelet treatment is often prescribed after implantation of vascular stents, since most episodes of stent thrombosis occur within this period.[6] However, up to now, the relation between the polymer carrier of the DES and thrombosis remains controversial. A meta-analysis of randomized clinical trials by Bavry et al. showed that the incidence of early thrombosis within 30 days was 4.4 events per 1000 patients with a polymer-based DES compared with 5.0 events per 1000 patient that received a bare metal stent (P = 0.74). The incidence of late thrombosis more than 30 days after the procedure was 5.0 events per 1000 polymer-based DES patients compared to 2.8 events per 1000 bare metal stent patients (P = 0.22). Thus, no significant differences between polymer-based DES and bare metal stent and early/late thrombosis are present.[7] Giessen et al. tested 5 different biodegradable polymers (polyglycolic acid/polylactic acid [PLGA], polycaprolactone [PCL], polyhydroxybutyrate valerate [PHBV], polyorthoester [POE], and poly(ethylene oxide)/polybutylene terephthalate [PEO/PBTP]) and three nonbiodegradable polymers (polyurethane [PUR], silicone [SIL], and polyethylene terephthalate [PETP]) as stent coatings which were implanted in porcine coronary arteries. After 4 weeks, both biodegradable and nonbiodegradable polymers induced a marked inflammatory reaction within the coronary artery with subsequent neointimal thickening.[8] There are, however, two limitations of this study. First, this 4 week study can just show early thrombosis, while polymer coatings are normally associated with late thrombosis (>30 days after stent implantation). Second, in this study no bare metal stent group was included.

The first-generation polymer coated DES were the Taxus stent which consists of a metal stent coated with the nondegradable copolymer poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) loaded with paclitaxel, and the Cypher stent

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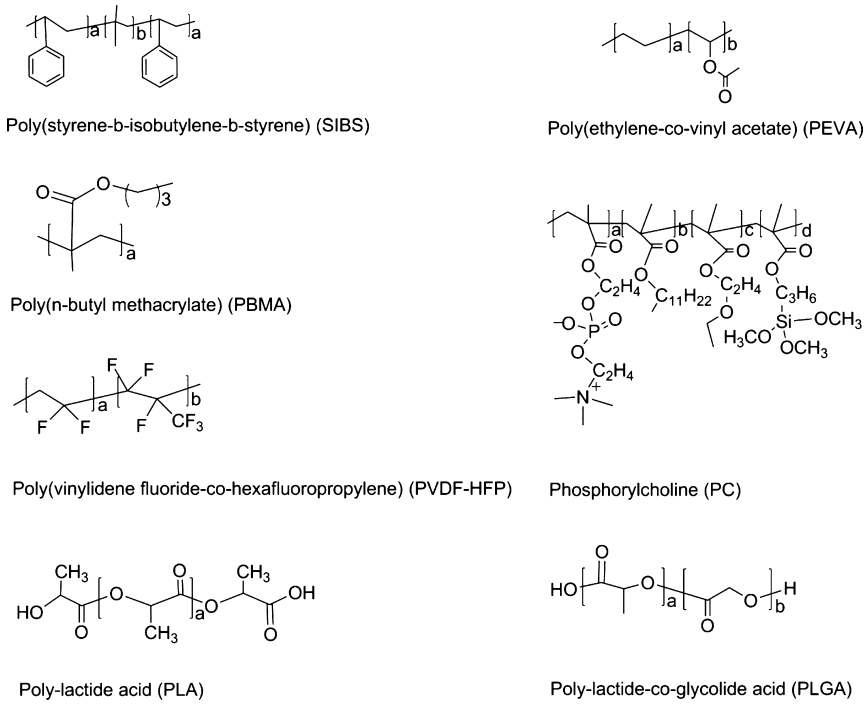

Figure 1. Chemical structures of the polymers used in the DES.

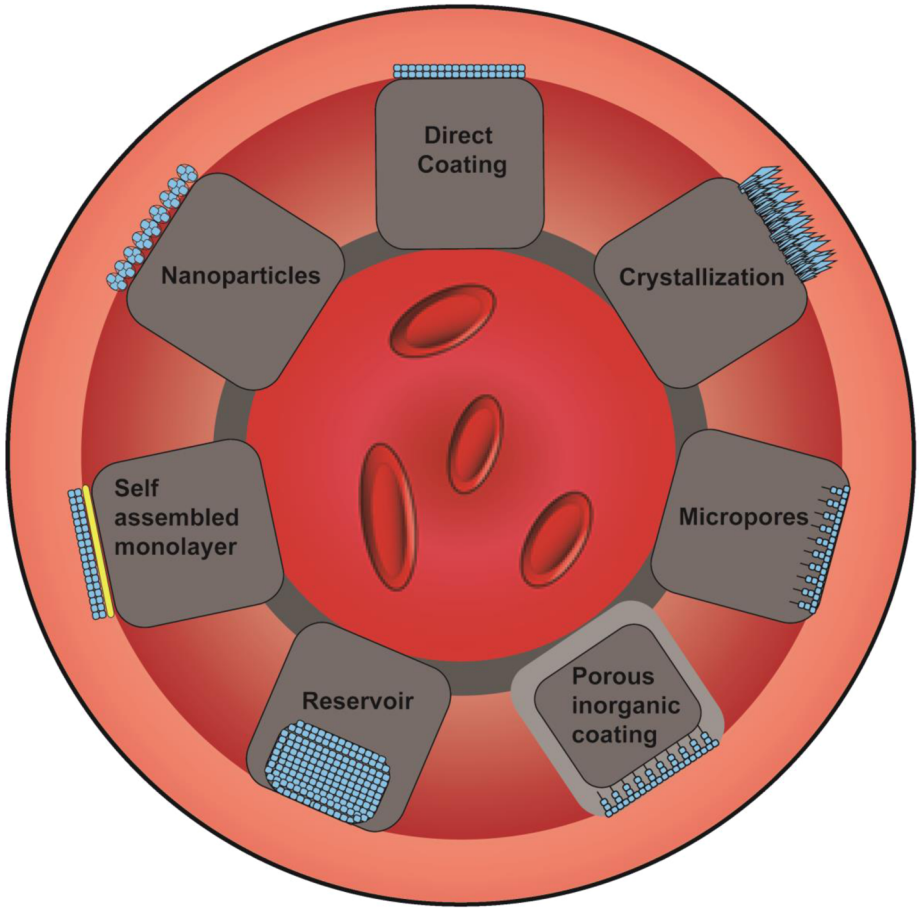

Figure 2. Schematic representation of the techniques used to manufacture polymer-free DES. Blue: incorporated drug. Gray: metal backbone of the stent. Yellow: self-assembled monolayers (SAM) used to chemically attach the drug to the stent. Red: vessel lumen. Pink: vessel wall.

which consists of a metal stent coated with a thin film of a blend of two nondegradable polymers, namely, poly(ethylene-*co*-vinyl acetate) (PEVA) and poly(*n*-butyl methacrylate) (PBMA) loaded with sirolimus.[9] Figure 1 shows the chemical

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structures of the polymers used in DES. Compared to bare metal stents, the first-generation DES were superior in reducing neointimal proliferation and restenosis. Second-generation DES combined promising anti-restenotic efficacy with improved long-term safety.[10,11] They are composed of a cobalt−chromium platform, which exhibits superior radial strength and improved radio-opacity as compared to the 316 stainless steel used in the first-generation stents, allowing for thinner stent struts that act themselves in favor of a lower restenosis rate. These second-generation DES utilized advanced polymers such as phosphorylcholine (PC) and a copolymer poly(vinylidene fluoride-*co*-hexafluoropropylene) (PVDF-HFP), which are nonbiodegradable, similar to the coatings used in first-generation DES. In general, these coatings performed well in facilitating drug release.[9] However, the nondegradable polymers induced local hypersensitivity, inflammatory response, and delayed strut endotheliazation which are the triggers for acute and late stent thrombosis. This prompted the exploration of other stent-coating materials such as biodegradable polymers like poly(lactic acid) (PLA) and poly(lactide-*co*-glycolic acid) (PLGA) that can control drug release and meanwhile avoid adverse pathologic effects.[12] After degradation of these polymeric coatings, a bare metal stent remains in the passages, which however may induce restenosis. Biodegradable polymers like PLA can even be used to design a fully biodegradable drug eluting stent, i.e., without a metal supporting structure. The evident advantage of these biodegradable stents is the decreased long-term side effects, but such stents often display inferior strength and elasticity.[12]

Another option is to completely abandon the use of polymers or other carriers on stents and develop polymer-free DES, based on a bare metal core.[13] The development of polymer-free DES started 14 years ago, and such stents so far have only been developed for vascular applications. This is mainly because in clinical practice the majority of DES is implanted for in obstructed blood vessels. Polymers used in DES have multiple functions including stabilizing the drug, binding the drug to the stent, and slowing down the drug elution rate.[14] Hence the main challenge for the development of polymer-free DES is to preserve these functions and at the same time maintain or even improve the biocompatibility. This review will describe various techniques and drugs that are being used for the design of polymer-free DES that have been marketed or that are still under development. We will discuss their drug-release profiles, as well as preclinical and clinical results reported for polymer free DES.

COATING TECHNOLOGIES

Both physical and chemical methods have been used to develop polymer-free DES, as shown in Figure 2. This figure shows that the stents can be modified by creating pores and reservoirs or by coating the stent with a porous inorganic material. These modifications have their own advantages and disadvantages, and besides improving the duration of drug elution from the stent they may also adversely affect the mechanical integrity of the stent backbone.[15]

1.1. Direct Coating. Dipping the stent in a drug solution followed by evaporation of the solvent is the most basic technique to coat a drug on the metal surface of a stent. The main disadvantages of this technique are the limited drug loading on the stent, rapid drug elution, and drug loss during implantation. However, for the antiproliferative drug paclitaxel this technique has been shown to be a valid approach because paclitaxel has strong adhesion onto the metal surface likely due to the formation of hydrogen bonds with metal oxides on the surface of the stent.[16] In addition, paclitaxel has a very low aqueous solubility which also might contribute to the slow elution kinetics of the drug from the stent. In general, polymer-free DES can only be developed with drugs with an (extremely) low solubility, since without the polymer carrier, hydrophilic drugs will release too rapidly from the stent, resulting in short mode of action. This characteristic of strong adhesion to metal can be exploited to create metal stents coated with high loadings of paclitaxel. Cook Inc. has developed a stent with paclitaxel coating of 300 μg/cm^2, which is 3-fold higher as compared to the commercially available TAXUS stent (100 μg/cm^2).[17] Several of such dip-coated polymer-free stents are now in further development, such as the V-flex Plus stent and the Achieve stent.[18]

1.2. Crystallization of the Drug. The direct coating of the drug from a solvent on the stent will result in an amorphous or partially crystalline drug layer depending on type of drug, type of solvent, and evaporation rate of the solvent. In general, the dissolution rate of a crystalline drug is slower than from its amorphous phase. This feature can be exploited to control the drug release profile. Chemical stability of a crystallized drug is also superior to its amorphous form since a drug in amorphous phase is in a metastable state with a higher energetic level. Therefore, to increase the chemical stability of a drug coated on stents and at the same time prolong the release time, fully crystalline drugs have been coated on stents.[19,20] The two main techniques to develop a fully crystalline drug coating on a stent are the microdrop spray crystallization process and the direct crystallization on the stents using a temperature induced process.[20,21] The microdrop spray crystallization technology is patented by MINVASYS and has so far led to the development of the Nile Pax and the Amazonia Pax stents.[22] Another method to crystallize sirolimus has been developed by Levy et al.[21] On a Co−Cr alloy stent, a thin seeding layer of sirolimus crystals was coated after which large crystals were grown by dipping the seeded stents into a supersaturated sirolimus solution.[20]

1.3. Nano- and Microporous Surfaces. Creating micro- or nanopores in the surface layer of a stent allows a higher drug loading capacity of the stent. Furthermore, the porous structure retards the release of the drug, due to longer diffusion distances.[23,24] Micro- and nanopores as well as other textured rough surfaces can be created by several techniques such as sandblasting and mechanical modification.[24,25] The pores, ranging from 1 nm to 100 μm in size, serve as a reservoir for the drugs and drug loadings up to 500 μg/mm^2 can be achieved.[26] The microporous surface of the stent will also induce its endothelization and can therefore reduce neointima formation.[26,27] Polymer-free stents with microporous surfaces showed equal drug loadings as stents coated with polymers.[28−30]

1.4. Inorganic Porous Coating. Similar to the previously mentioned surface-porous stents (section 1.3), stents with a biocompatible thin porous inorganic coating can be designed with micropores or even nanopores. But instead of etching the metal stent, the pores are created in an inorganic coating. An important advantage of this type of stent is the reduction in release of metal ions, which may induce activation of blood platelets resulting in thrombogenicity of the stent.[31,32]

The degradation products of some biodegradable polymers, like acids, as well as initiators, and catalysts present in these

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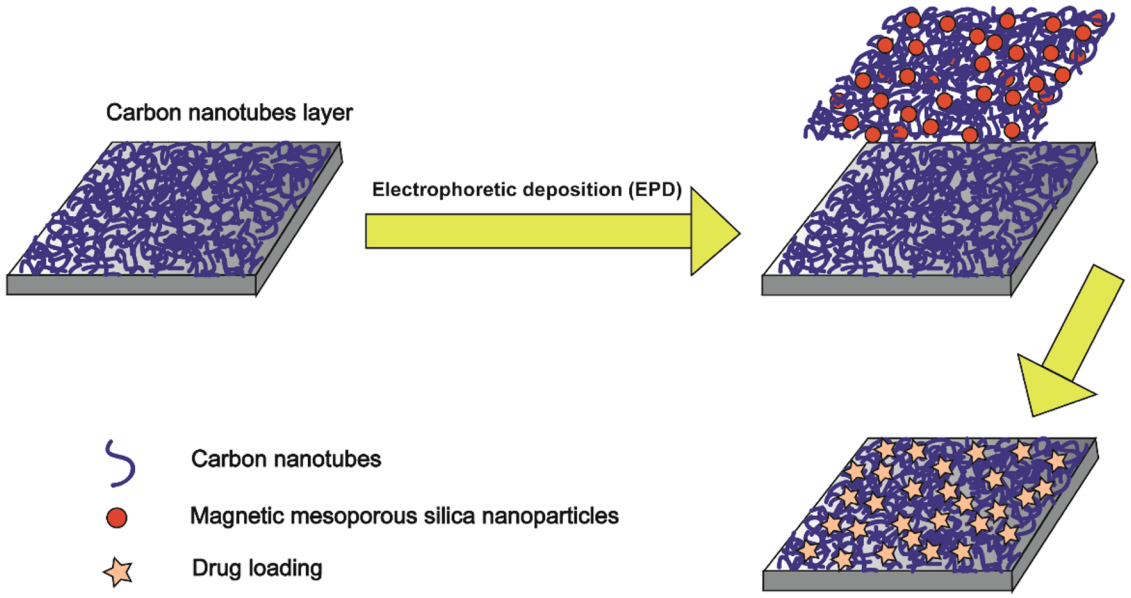

Figure 3. Schematic representation of nanoparticles loaded on the stent strut. Adapted with permission from Wang, Y., Zhang, W., Zhang, J., Sun, W., Zhang, R., and Gu, H. (2013) Fabrication of a novel polymer-free nanostructured drug-eluting coating for cardiovascular stents. *ACS Appl. Mater. Interfaces 5*, 10337−10345. Copyright 2013 American Chemical Society.

polymer coating have been associated with tissue inflammation during the degradation process and may thus cause stent thrombosis.[32] Further, according to a study of Finn et al., the nondegradable coatings of Cypher and Taxus stents provoke eosinophilic/heterophilic infiltration of the arterial wall in rabbits. Detailed analysis of the morphological changes showed a localized immune response, with the presence of CD45-positive lymphocytes and eosinophils.

Techniques such as anodization have been described to form micro- or nanoporous inorganic coatings.[33] A potential drawback of using an inorganic coating (like aluminum oxide) as a drug reservoir is the possible release of aluminum oxide particle after implantation.[34]

1.5. Macroporous Drug Reservoirs. Besides nano- or micropores, macropores can also be used as drug reservoirs. Macropores, more commonly called reservoirs, can be created in a stent in the form of grooves, holes, or channels by mechanical treatment. The use of reservoirs allows both single drug and multiple drug loadings.[15] Although reservoirs retard the elution rate of the drug slightly due to a decreased surface area of the drug, several other techniques can be used to further control the drug release. For instance, the Janus stent and the Optima-Jet stent use a proprietary technique that coagulates the drug, tacrolimus, in an abluminal reservoir.[1,35] Another possible design is connecting the reservoir to the exterior by nanopores which can control drug release time and kinetics.[36]

1.6. Coating of Nanoparticles. Another technique that can be used to design polymer-free DES is coating the stent with a porous composite matrix based nanoparticles.[34,35] Most commonly used are magnetic silicon and carbon nanoparticles.[36,37] As shown in Figure 3, a thin layer of carbon nanotubes was first assembled onto the 316L-BMS stent as the inner layer, and a magnetic mesoporous silica nanoparticles/carbon nanotubes coating was deposited subsequently as the second layer.[38] Sirolimus was loaded onto the stent by immersing the nanoparticles coated stent into a sirolimus−toluene solution, next the stent was removed from the solution and dried. The high surface area and pore volume of magnetic mesoporous silica nanoparticles (M-MSNs) result in a higher adsorption of sirolimus. Carbon nanotubes possess a high aspect ratio and good mechanical properties, which overcome the inherent mechanical shortcomings of inorganic materials, such as poor flexibility.[36] An in vivo study also revealed that this coated stent showed rapid endothelialization in comparison with the commercial polymer-coated DES likely because of its 3D nanostructured topology.

1.7. Self-Assembled Monolayers. Stents can also be chemically modified by coating self-assembled monolayers (SAMs) on their metal surface. SAMs are long hydrocarbon chains with head groups such as alkylthiols, alkylamines, and alkanoic acids that can adhere to metal surfaces. SAMs can assemble on metal surfaces by a two-step deposition method: (a) solution immersion and (b) dip-evaporation cycle.[37] First, the stent was immersed in either dodecylphosphonic acid ($CH_3(CH_2)_{11}PO(OH)_2$) or phosphoundecanoic acid ($COOH-(CH_2)_{10}PO(OH)_2$) in dry THF. Subsequently the samples were transferred to a furnace and heated at 120 °C for 18 h to evaporate the solvent. An in vitro experiment showed that human aortic endothelial cells (HAECs) spread on the SAMs surface with typical polygonal shape indicating that the stent surface is conductive to endothelization.[39] So far, the drugs flufenamic acid, everolimus, paclitaxel, and dipyridamole have been coated on SAM's stents.[40−42] The amount of drug that can be coated by this technique is however low, ranging from 100 ng/cm^2 to 10 μg/cm^2 as compared to 100 μg/cm^2 for polymer coated stent.[41,43]

■ DRUGS

The used drugs in DES are expected to inhibit inflammation and neiointimal formation after stent implantation, which can be achieved by a variety of immunosuppressive, anti-inflammatory, anti-thrombogenic, or antiproliferative drugs. In the absence of a polymeric coating, one would expect that polymer-free drug elution stents will release the drug in a relatively short time period, resulting in a transient tissue and systemic peak concentrations. However, according to pharma-

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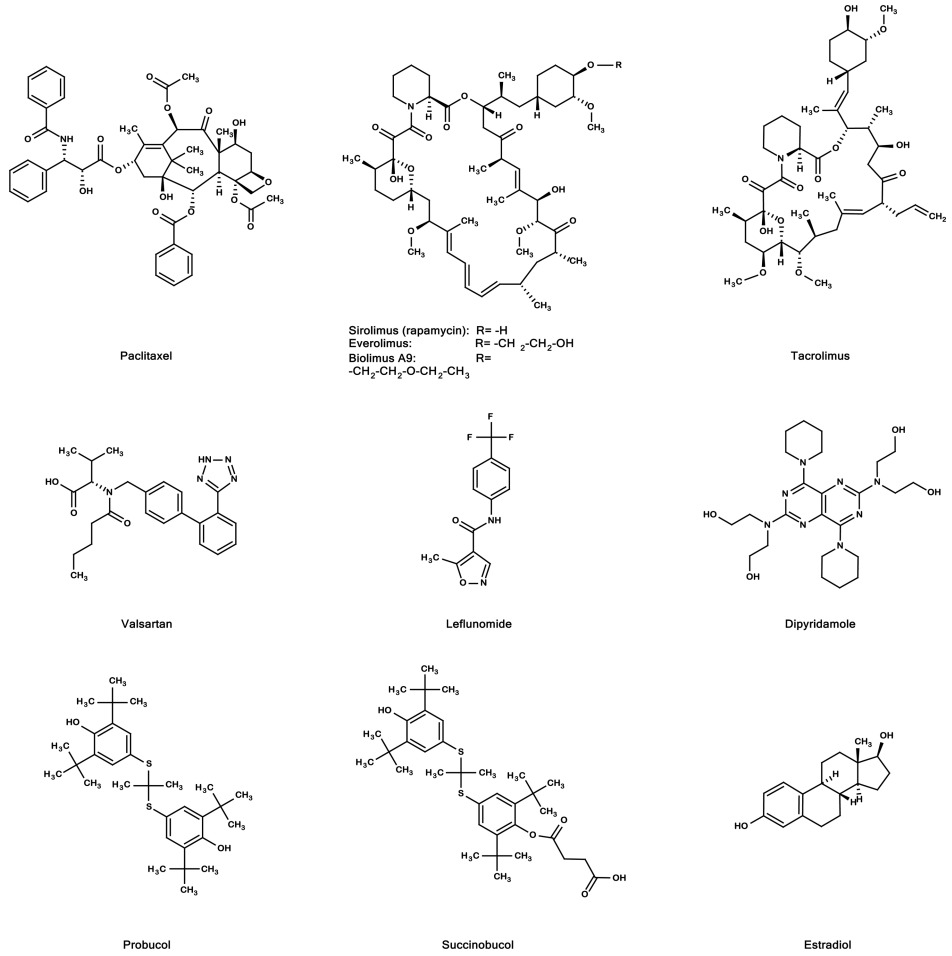

Figure 4. Molecular structures of drugs used in carrier-free DES.

Table 1. Drugs Used in Polymer-Free DES and the Carriers Used

drug	pharmacological action	log P	drug carrier	references
Paclitaxel	Antiproliferative	3.0	Dip coating, crystallization, micropores, nanoparticles, SAM	2,6,22,40,45
Sirolimus	Antiproliferative, Immunosuppressive	4.3	Inorganic coating, micropores, crystallization	4,20
Dipyridamole	Antiplatelet	1.5	SAM	46
Valsartan	Angiontensin II receptor antagonist	5.8	Micropores	29
Leflunomide	Immunosuppressive	2.8	Micropores	47
Succinobucol	Antiplatelet	8.2	Micropores	48
Sirolimus Derivatives				
Biolimus A9	Immunosuppressive	4.2	Textured surface	25,49
Everolimus	Antiproliferative, Immunosuppressive	5.0	SAM	40
Tacrolimus	Immunosuppressive, anti-inflammatory	3.3	Reservoir, inorganic coating	35
Drug Combinations				
Sirolimus and Probucol	Antiproliferative, Immunosuppressive, Antiplatelet	4.3/8.9	Micropores	50
Sirolimus and Succinobucol	Antiproliferative, Immunosuppressive, Antiplatelet	4.3/8.2	Micropores	48
Sirolimus and Estradiol	Antiproliferative, Immunosuppressive	4.3/4.0	Micropores	51

cokinetic analyses discussed below, this was not the case for some of the successful polymer-free DES which showed drug levels in the target tissue for several months. This can be explained by the physiochemical properties of the incorporated drugs and the biological characteristics of the tissues being targeted.[44] Relatively lipophilic drugs can accumulate in lipophilic tissues and cellular compartments after their release from DES. When the metabolism of the drug in the target tissue is relatively slow, the drug can persist in the tissue for a longer period. The drugs (Figure 4) that have been used in the polymer-free DES and their physiochemical properties and pharmacological action are listed in Table 1.

2.1. Paclitaxel. Paclitaxel is a highly lipophilic compound that inhibits cell division by stabilizing the microtubules in the cytoskeleton.[2,6] The lipophilicity of paclitaxel makes it easy to access the vessel wall, while at the same time, the high lipid

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Table 2. Polymer-Free DES and Comparison of Their in Vivo Results to Polymer-Coated DES

stent	application	platform	drug	type of study	outcome[a,b]	references
V-Flex plus	Coronary	Stainless Steel	Direct coating of Paclitaxel	6 months Clinical Trial	−	55
Supra-G	Coronary	Stainless Steel	Direct coating of Paclitaxel	6 months ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial)	+−	56
Achieve	Coronary	Stainless Steel	Direct coating of Paclitaxel	8 months DELIVER Clinical Trial	−	57
Janus	Coronary	316L	Tacrolimus reservoir	1 year Clinical Trial	−	58
Optima	Coronary	316L	Tacrolimus reservoir	N/A	N/A	52
Yukon	Coronary	316L	Micropores filled with Sirolimus	5 years Clinical Trial	+−	30
Yinyi	Coronary	316L	micropores filled with Paclitaxel	1 year Clinical Trial	+−	59
Biofreedom	Coronary	Stainless Steel	Biolimus A9; textured surface	1 year LEADERS FREE Clinical trial	+	60
VESTAsync	Coronary	Co−Cr	Sirolimus; nanoporous hydroxyapatite coating	9 months VestSaync II Clinical Trial	+−	61
Corel-C	Coronary	Co−Cr	Paclitaxel in carbon−carbon coating	N/A	N/A	45
Amazonia Pax	Coronary	Co−Cr	Paclitaxel; crystallization	Pax A and Pax B Clinical Study Design	N/A	22,62
Nile Pax	Bifurcation	Co−Cr	Paclitaxel; crystallization	Bipax Clinical Study Design	N/A	22,62
Zilver PTX	Femoral	Nitinol	Direct coating of Paclitaxel	N/A	N/A	63

[a]− means inferior to the polymer-based DES; + means superior to the polymer-based DES; +− means noninferior to polymer-based DES and N/A means data not available. [b]The comparison between polymer-free DES and polymer-based DES is based on the clinical trial data of angiographic late lumen loss and neointimal hyperplasia volume detected by intravascular ultrasound (IVUS), which are the most appropriate parameters to evaluate the performance of drug-eluting stents.[64]

content of the atherosclerotic human artery may promote its residence in the vessel wall.

2.2. Sirolimus and Derivatives. Sirolimus (or rapamycin) is a lipophilic macrolide type drug with antiproliferative, anti-inflammatory, and immunosuppressive effects. Besides sirolimus, several sirolimus structural analogues have also been used in polymer-free DES. Biolimus A9 is a derivative of sirolimus and its lipophilicity is higher than that of sirolimus due to the replacement of hydrogen by alkoxy-alkyl group at the 40-O position (as shown in Figure 4).[6,25] The higher lipophilicity of Biolimus A9 favors slow release from the stents into the target tissue.[25] Everolimus, another sirolimus derivative, has a higher logP value than sirolimus, which also will delay the drug release rate. Everolimus-eluting stents have been shown to lead to less revascularization, major adverse cardiac events (MACE), and thrombosis than sirolimus-eluting coronary stents.[10] The anti-inflammatory macrolide tacrolimus is another structural analog of sirolimus. This macrolide is less potent than sirolimus in inhibiting proliferation of vascular smooth muscle cells and endothelial cells. But with its potent anti-inflammatory effects, tacrolimus is an attractive and frequently used drug in DES.[52]

2.3. Other Drugs. Positive results have been found for the use of probucol in combination with sirolimus in a polymer-free design. Probucol, a lipophilic antioxidant, inhibits neointimal hyperplasia, prevents constrictive remodeling, and improves re-endothelization of the stent.[53] Succinobucol, a derivative of probucol, has also been loaded on polymer-free stents.[48] The addition of the hormone estradiol to a sirolimus-eluting polymer-free stent did not have additional benefits.[51] This might be explained by the powerful inhibitory actions of sirolimus on vascular smooth muscle cells, and consequently there may be no further inhibition of smooth cell proliferation by locally delivered estradiol.[54]

Another drug that has been used in a polymer-free stent is the prodrug leflunomide, which has a long half-life of several days. The active metabolite teriflunomide inhibits de novo pyrimidine biosynthesis[47] which is a critical process in rapidly dividing cells such as T-leukocytes, while other anti-inflammaotry and antiproliferative effects have also been ascribed to this inhibitor. Promising in vivo results have been reported for leflunomide-eluting DES such as a significant reduction in neointimal area and stent thickness ratios.[47]

IN VIVO APPLICATION OF POLYMER-FREE DES

Polymer-free DES have so far been developed for vascular applications, mainly for use in coronary arteries. The preclinical and clinical experiences of the developed polymer-free DES as listed in Table 2 will be discussed in the following chapter.

3.1. V-Flex Plus: (Supra-G and Achieve). The V-Flex plus stent was developed by Cook Inc. in 1999. It is a polished polymer-free metal stent with paclitaxel (2.7 $\mu g/mm^2$) coated on the adluminal exterior.[18,65] The V-Flex plus stent showed initial clinical success in a pilot trial. However, late studies showed it to be inferior to polymer-based stents in preventing restenosis and cardiac events, which may be due to significant drug loss during the stent delivery and rapid release of the remaining drug, thus leading to attenuated effectiveness of the stent in suppression of neointimal formation.[18,55,65] The Supra-G and Achieve stents are similar to the V-Flex design and were also developed by Cook Inc. The Supra-G stent was shown to be safe and effective in a clinical trial addressing de novo coronary lesions, but the Achieve stent did not sufficiently decrease restenosis and revascularization compared to a bare metal stent.[56,57]

3.2. Janus Stent and Optima-Jet Stent. The Janus stent is a reservoir stent with a polymer-free tacrolimus depot on the adluminal side of the stent covered with a carbofilm.[35]

Preclinical and clinical trials with this stent for the treatment of native coronary artery both showed a decrease in neointimal proliferation, a decrease in inflammation and a reduction in MACE as compared to a bare metal stent.[35,66] As an improved product, the Optima-Jet stent showed a better safety profile and efficacy than Janus stent in a 12 month clinical follow-up study.[52] Both stents were proven to be safe and allowed reducing the dual antiplatelet therapy from 6 to 2 months.[52,67]

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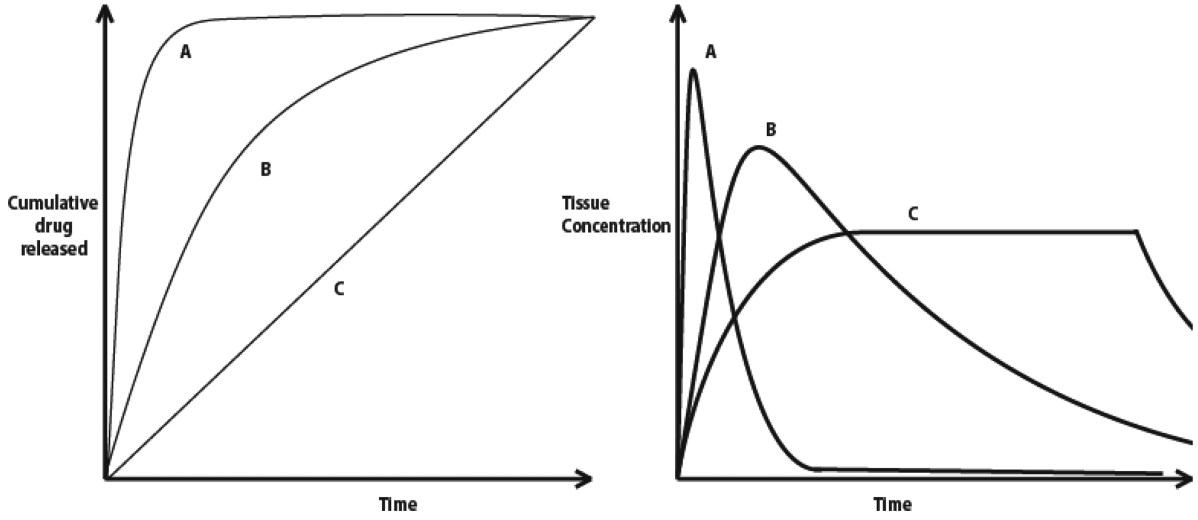

Figure 5. Kinetic profiles of polymer-free DES, showing the cumulative drug released over time (left) and the tissue concentration (right): A, burst release; B and C, sustained release.

3.3. Yukon Choice Stent. Another polymer-free DES is the Yukon Choice stent (a stainless steel stent with a microporous surface filled with different drugs).[24,26] So far, sirolimus and paclitaxel coated Yukon Choice stents have been approved for clinical practice and have received the CE mark.[28] The Yukon stent was compared with the Taxus stent in a randomized clinical trial and showed noninferiority in safety and efficacy, both on short-term and 5 year clinical follow-up.[30,68] The Yukon stent was also used as a dual-DES and different drugs combined with sirolimus gave varying results. The dual sirolimus- and probucol-eluting dual-DES demonstrated an anti-restenotic efficacy comparable with polymer-based sirolimus-eluting stents, while estradiol showed no beneficial effects.[50] The success of the combination of sirolimus and probucol coated on the Yukon stent was demonstrated in several clinical trials and this stent was shown to be noninferior to the second-generation DES.[50,53,69]

3.4. Yinyi Stent. The Yinyi stent is a 316L stainless steel stent with a microporous surface. The stent was loaded with paclitaxel by guidance of ultrasound.[70] In a 1-year multicenter prospective study with 1045 patients, low thrombosis rates and MACE rates were found.[70] In a randomized clinical study the Yinyi stent was compared with the polymer-based sirolimus-eluting stent.[59] Comparable rates of target lesion failure (10.9% vs 12.0%) and stent thrombosis (1.8% vs 2.0%) were found after a 1 year follow-up. Also, in-stent stenosis and restenosis rates were not significantly different between the two stents after 6 months follow up.[59] The study suggests that the safety and efficacy of Yinyi stents are comparable to polymer-based sirolimus-eluting stents.

3.5. Biofreedom Stent. Another polymer-free stent that uses a textured stent surface is the Biolimus A9-eluting Biofreedom DES. In a porcine overstretch coronary model, the Biofreedom stent was noninferior to the sirolimus-eluting Cypher stent after 28 days (short-term study), and significantly superior to the Cypher stent and the bare metal stent in reduction of neointimal hyperplasia formation after 180 days (long-term study). A reduction in inflammation was also observed for the Biofreedom stent compared to the Cypher stent.[60]

Further, in a randomized single-blind clinical trial the Biofreedom stent was compared with the Taxus stent. A noninferiority was found for the Biofreedom stent in median late lumen loss (0.17 mm vs 0.35 mm), and the Biofreedom was also shown to have significantly lower MACE rates (6.8% vs 10.0%) and target lesion revascularization (3.4% vs 6.7%) after 2 years.[60] These findings provide positive evidence of long-term advantages for the use of a polymer-free DES over a traditional polymeric DES.

3.6. VESTAsync Stent. The VESTAsync stent is a stainless steel stent with a thin microporous hydoxyapatite coating and loaded with sirolimus.[71−73] In a randomized double-blind clinical trial the sirolimus-filled VESTAsync stent was compared with the same stent platform, Gen X, without drug loading. Significant decreases in neointimal hyperplasia (9.3% vs 17.6%) and in-stent restenosis (0.39% vs 0.71%) were found.[61] Similar results were found in earlier clinical trials in which the safety of the VESTAsync stent was confirmed.[71−73]

3.7. Corel-C Stent. On the Corel-C stent, a porous composite matrix synthesized from amorphous carbon nanoparticles embedded in glassy polymeric carbon was coated on the Co−Cr backbone.[45] For use in a porcine artery model, 0.4 μg/mm^2 paclitaxel was coated on the carbon−carbon coating. Compared with historical data of Cypher stent, positive results for both efficacy and safety were found in a preclinical trial. However, no clinical data were published so far.

■ DRUG RELEASE KINETICS FROM STENTS

The elution rate (or release) of drugs from stents depends not only on the design of the stent, but also on the physiochemical properties of the drug itself.[74] For instance, the hydrophobicity of drugs plays an important role in local drug concentrations. Hydrophilic drugs were found to wash away more quickly, while hydrophobic drugs can attain higher concentration in the artery wall due to their preferential binding to artery wall structural proteins.[75,76] The physical state of the drug can also influence the drug elution rate, and as mentioned earlier the dissolution rate of crystalline drugs is slower compared to amorphous phases. The amorphous phase is a metastable state with higher energetic level than the crystalline phase resulting in higher drug solubility and faster release rate. Different drug release profiles as shown in Figure 5: profile A is typical burst release, and profiles B and C are sustained release. In most cases, sustained release without initial burst release (profile C)

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is preferred as it ensures long-term local activity of the drug. Researchers seek to avoid initial burst release, because the initial high release rate may lead to drug concentrations near or above the toxic level in vivo; also the drug released during the burst stage may also be metabolized or excreted without being effectively utilized.[77]

The biological effects of drugs delivered locally are also influenced by local transport forces, which are related to the properties of the target tissue. The highly heterogeneous composition of the arterial wall and its asymmetric geometrical organization (as shown in Figure 6) represents a challenge for most drugs applied in DES technologies.[78] The ideal compound for intramural delivery should contain hydrophobic elements to ensure high local concentrations as well as hydrophilic properties to allow homogeneous drug diffusion.

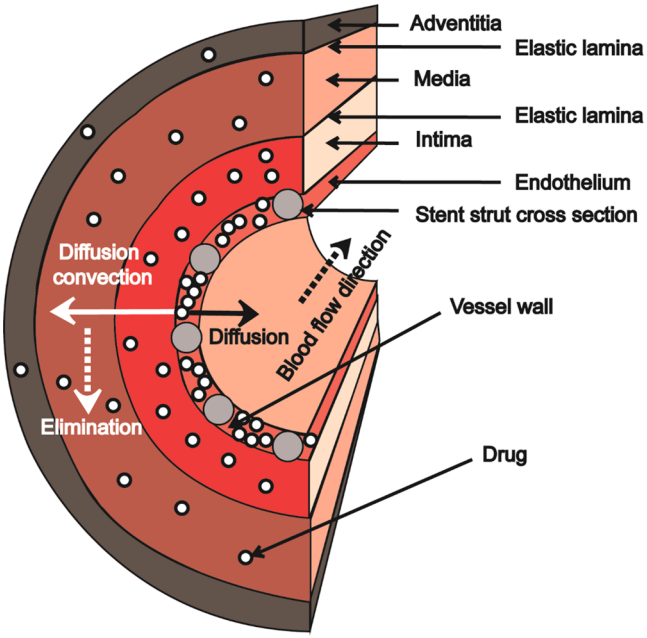

Figure 6. Cross-section of a stent implanted blood vessel. The drug (white spheres), once released from a drug eluting stent, can diffuse into the vessel wall or it can be released into the bloodstream. Adapted with permission from Grassi, M., Lamberti, G., Cascone, S., and Grassi, G. (2011) Mathematical modeling of simultaneous drug release and in vivo absorption. *Int. J. Pharm. 418*, 130−141. Copyright 2011 Elsevier.

4.1. Burst Release. In controlled release formulations, an initial large bolus of drug is released before the release rate reaches a stable profile is typically referred to as "burst release".[77] For DES, drug release over 90% of the total loaded amount in around 2 days is considered as burst release. The burst release should provide just enough drug immediately after stent implantation to prevent neointimal hyperplasia, whereas too much drug release in the first few days may cause serious side effects.[14] However, this is not always the case for polymer-free DES. The in vitro drug elution rates of polymer-coated and polymer-free stents and the kinetic profile of the drugs are listed in Table 3. For instance, the Zilver PTX stent releases 95% of its paclitaxel loading within 24 h; nevertheless, there were sustained paclitaxel levels in the artery wall for 56 days.[80] This can be explained as paclitaxel is highly hydrophobic. It can bind nonspecifically to serum proteins, hydrophobic components of the tissue microenvironment, and specifically to polymerized microtubules with high affinity. As a result, it can be efficiently absorbed by surrounding tissue, gain cellular entry, and bind tightly to proteins within cells and the interstitium. Similarly, the polymer-free textured Biofreedom stent releases >90% of the coated Biolimus A9 in 50 h in vitro.[81] However, this did not lead to local toxicity in vivo and the drug concentration in the blood did not show an early peak. Surprisingly, Biolimus A9 can still be measured in the local tissue 180 days after implanting the stent and the concentration was high enough to exert a pharmacological effect.[25] According to Tada et al., the positive results found in vivo are due to a combination of Biolimus A9's high hydrophobic characteristics, which lead to a fast absorption in cell membranes, and long half-life of Bioliminus A9 in the surrounding tissue.[25] More research should be done to study whether the use of other drugs will lead to similar results.

4.2. Sustained Release. Although many polymer-free DES have an initial burst release, for most polymer-free DES a sustained release phase follows. For example, the Nile Pax and Amazonia Pax stents released 60% of the coated paclitaxel within 2 days, followed by a sustained release of the remaining loading during the next 30 days.[22]

A similar release rate was found for the Yukon stent, which showed a sustained release of over 21 days in vitro. However,

Table 3. In Vitro Drug Elution Rates of Polymer-Coated and Polymer-Free Stents and the Kinetic Profile of the Drugs

polymer-coated DES	drug	amount of drug loaded	release time	kinetic profile	reference
Cypher	Sirolimus	1.4 $\mu g/mm^2$	66% in 7 days 100% after 30 days	B	14
Taxus	Paclitaxel	1 $\mu g/mm^2$	50% in 2 days 100% after 14 days	B	79
Polymer-Free DES					
Zilver PTX	Paclitaxel	3.0 $\mu g/mm^2$	95% in 24 h	A	80
Biofreedom	Biolimus A9	15.6 $\mu g/mm$	90% in 50 h	A	81
Nile Pax and Amazonia Pax	Paclitaxel	2.5 $\mu g/mm^2$	60% within 2 days 100% after 45 days	B	22
V-Flex plus and Achieve	Paclitaxel	2.7 $\mu g/mm^2$ 3.0 $\mu g/mm^2$	28% within 4 h; 69% after 14 days	B	18
Yukon	Sirolimus	479 $\mu g/mm^2$ varying	66% in 6 days 100% after 21 days	B	24
Yinyi	Paclitaxel	1.0 $\mu g/mm^2$	42% in 24 h 83% in 15 days	B	70
VESTAsync	Sirolimus	55 μg	100% in 3−4 weeks	B	61,73
Janus and Optima	Tacrolimus	2.3 $\mu g/mm^2$	Peak in few days 50% in 30 days	B	35
Corel-C stent	Paclitaxel	100 ng/cm^2 to 10 $\mu g/cm^2$	100% in 14 days	B	41,82
Co-Cr stent	Sirolimus	~100 μg	50% in 90 days	C	20

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over two-thirds of the sirolimus loading was eluted within 6 days.[24] Many drugs have been incorporated in the Yukon stent and they all have similar elution rates. In a test comparing a Yukon stent loaded with either sirolimus or leflunomide, interchangeable elution rates were found in vitro.[47]

According to the in vitro release experiment of Mani et al., flufenamic acid was released from the SAMs in a sustained pattern for 2 weeks up to 1 month.[40,82] Approximately 80% of the flufenamic acid was released after 4 weeks, and the release behavior was governed, as assumed by the authors, by the hydrolysis of the ester bond between flufenamic acid and SAM.[40] In another study, solutions of two different concentration of paclitaxel (25 and 100 μg/mL) were deposited on SAM coated Co−Cr surfaces, and the in vitro release of paclitaxel from SAM coated Co−Cr surfaces was compared with that of paclitaxel directly coated on Co−Cr surfaces. It turned out that paclitaxel was released from the SAM coated Co−Cr surfaces in a biphasic manner (an initial fast release in the first 7 days followed by a slow release for up to 35 days), while the paclitaxel was released from Co−Cr surfaces within 1−3 days.[41] The mechanism proposed for the paclitaxel delivery from SAMs explained by the authors are (a) cleavage of hydrogen bonds between paclitaxel molecules and SAMs by ions in the PBS/Tween 20 solution; (b) cleavage of ester bonds between paclitaxel and SAMs by hydrolysis; and (c) cleavage of hydrogen bonds between paclitaxel molecules by the ions in the PBS/Tween 20 solution.[41] However, again there is no evidence that a hydroxyl group of paclitaxel has reacted with COOH groups of the SAM during the coating procedure.

Stents coated with sirolimus via a temperature-induced crystallization process showed a sustained release of the drug both in vitro and in vivo. An in vitro study showed that 50% of the drug was slowly released in PBS within 90 days without burst release. The stent showed a very similar release pattern as the Cypher stent.[20] In another in vitro study various media were used.[83] In all media, including saline−isopropyl alcohol (NS-IP, 10%) mixture, phosphate buffer (PB, pH 7.4), phosphate buffered saline (PBS, pH 7.4), a sustained release of sirolimus was achieved for 80 days.[22] Simultaneously, sirolimus released at the site of implantation and biocompatibility of developed stents was determined after subcutaneous implantation in the SD rats.[84]

The in vitro drug release from DES is mostly performed in PBS buffer (with or with low concentration of surfactant, such as 0.05% of Tween-20); however, in most studies it was not checked whether sink conditions were maintained. For in vivo drug release studies, it should be mentioned that it is technically difficult to separate the surrounding tissue from the stent, which makes it difficult to get accurate tissue drug data. In addition, the variation of the methods used in different studies also makes it difficult to compare the release behavior from different DES systems. It is therefore recommended that standardized methods for evaluating the in vitro and in vivo drug release from DES have to be developed and validated for future preclinical and clinical studies.

CONCLUSION

The design of polymer-free drug elution stents was initiated because of the assumed increased risk of thrombosis and inflammation ascribed to polymer-coated drug eluting stents. The (pre)clinical evidence that these polymer coatings indeed cause these adverse effects is however weak. Advanced design of porous surfaces and reservoirs allows the polymer-free stent to be coated with substantial amounts of anti-inflammatory or immunosuppressive drugs. The drug's physicochemical properties and water solubility should be taken into account to obtain the desired sustained release profile, which has been achieved for several hydrophobic drugs. Although polymer-free DES have performed well in both preclinical and clinical trials, it is important to notice that polymer-free DES almost without exception do not show better performance in clinical trials than the second-generation drug-elution stent. We therefore conclude that polymer-free DES may be efficacious, although it has not been demonstrated convincingly that polymeric coatings in DES are a serious problem.

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Notes

The authors declare no competing financial interest.

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