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Review

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Controlled Slow-Release Drug-Eluting Stents for the Prevention of Coronary Restenosis: Recent Progress and Future Prospects

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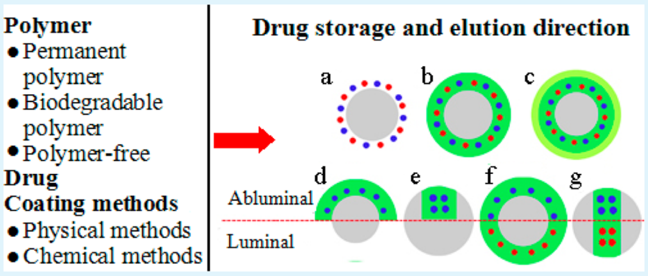
ABSTRACT: Drug-eluting stents (DES) have become more widely used by cardiologists than bare metal stents (BMS) because of their better ability to control restenosis. However, recognized negative events, particularly including delayed or incomplete endothelialization and late stent thrombosis, have caused concerns over the long-term safety of DES. Although stent-based drug delivery can facilitate a drug's release directly to the restenosis site, a burst of drug release can seriously affect the pharmacological action and is a major factor accounting for adverse effects. Therefore, the drug release rate has become an important criterion in evaluating DES. The factors affecting the drug release rate include the drug carrier, drug, coating methods, drug storage, elution direction, coating thickness, pore size in the coating, release conditions (release medium, pH value, temperature), and hemodynamics after the stent implantation. A better understanding of how these factors influence drug release is particularly important for the reasonable use of efficient control strategies for drug release. This review summarizes the factors influencing the drug release from DES and presents strategies for enhancing the control of the drug's release, including the stent design, the application of absorbable stents, the development of new polymers, and the application of nanocarriers and improvements in the coating technology. Therefore, this paper provides a reference for the preparation of novel controlled slow-release DES.



KEYWORDS: *control strategies, drug-eluting stents, drug release, influencing factors, controlled slow-release*

1. INTRODUCTION

In the light of the World Health Organization, coronary artery disease (CAD) will be one of the four primary causes of death in the world in 2030. The cardiovascular deaths are estimated to add up to 23.4 million.[1,2] The percutaneous transluminal coronary angioplasty (PTCA) was used for the management of CAD symptoms,[3] but has proved to be inadequate when used alone and carries major risks, such as an early abrupt closure and late restenosis.[4] Stent implantation is used to mechanically recover the vessel dimensions to ensure a smooth blood flow.[5] The implantation of bare-metal stents (BMS) has an in-stent restenosis (ISR) rate of 20−30%.[6] The development of drug-eluting stents (DES) has significantly decreased the restenosis rate to 3−20%.[7] The phenomenon of stent thrombosis is associated with the application of coronary stents two decades ago. For example, about 70−80% of patients with stent thrombosis also experience myocardial infarction, and no less than one-third of patients with stent thrombosis will die.[8] These syndromes are caused by many factors. One possible reason for their occurrence is that the cytostatic drugs currently being used may not be the best option for the treatment of this disorder, as they do not promote endothelial growth. Another important reason is that the premature release of a drug from a DES may reduce its pharmacological effects. It should also be noted that the current level of drug release is an overdose of the drug, and the loss of control over the drug release may postpone the regeneration of endothelium and raise the risk of adverse events.[9]

After a percutaneous coronary intervention (PCI), the pathological changes of the implantation site is time-programmed in response to the presence of a BMS, which can be distributed into three phases. In the first phase, there are the dangers of acute and subacute stent thrombosis. These complications can occur within a few minutes to a few hours and within a few days to a month, respectively, and are caused by the mechanical injury during the BMS implantation. In the second stage, the stent surface begins to be covered by the surrounding tissue. But a delayed or imperfect endothelialization may lead to the occurrence of thrombosis and ISR. These adverse events can appear from 1 to 3 months. In the third phase, the stent is usually imbedded in the vascular tissue, but the dangers of late thrombosis and restenosis may be induced

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by adverse material-tissue interactions, which can occur after 3 months.[10] Therefore, for DES, it is essential to control the dose and the release behavior of the drug. Optimal drug kinetics is as important in inhibiting neointimal hyperplasia as the absolute drug dose.[11] It is very significant to pay attention to this time-programmed pathological change and to put to use a stage-adjusted remedy. The ideal DES should have a slow and controlled drug release, with release kinetics in which the antivascular smooth muscle cells (VSMCs) proliferation drug can be quickly released initially in the first week, but the total release time should be maintained for at least a month after the DES implantation. In the first week after the DES implantation, appropriate burst release behavior is beneficial to the developmental needs of the pathology. Similarly, the total release time of the antithrombotic and endothelialization-promoting drug should be 1−3 months or longer.[10]

Drug release behavior straightly influences drug persistence in the arterial wall, which can impact the healing of blood vessel and the curative effects. A balance between the rate of the drug release and the arterial drug absorption presented to the artery, i.e., neither releasing so rapidly that the rate of tissue uptake is exceeded nor too slowly that the dosage of the drug is limited.[9] Large randomized clinical studies have revealed that the optimal release kinetics would prevent the proliferation of VSMCs without affecting the re-endothelialization process.[12] However, many studies have shown that the side effects of DES still remain, e.g., inflammation, late thrombosis, and late restenosis. These side effects are caused by the DES's lack of capacity for adjusting the drug dose, drug effectiveness, and release behavior according to the disease condition of the treated blood vessel. In other words, the drug release time is before the healing time needed by the endothelial denudation area.[13] The drug burst release phenomenon is still one of the major factors leading to undesirable symptoms. In addition, the drug release and polymer erosion should be simultaneous; hence, there are not drug remnants in the tissue after hydrolytic degradation of the polymer. In the complex fluid environment, the hydrophobic drugs, such as paclitaxel (PAT) and sirolimus, which hydrophobicity affects the vascular absorption of drugs. Therefore, the corrosion-resistant and degradation behavior of polymer and the hydrophobic behavior of the drugs are also major factors causing these pathologies.[14] The drug release rate has become one of the important criteria for the evaluation of drug-eluting stents.

In our previous work, our laboratory focused on the development of DES by selecting ideal stent materials for maintaining the balance between the mechanical integrity and degradation process. An individualized choice of stents that takes into account the individual patient and the lesion's characteristics are the prerequisites for determining the actual clinical practice and the outcome.[7] Our research group has made some progress in the strategies for controlling drug-release, e.g., by the design of core−shell nanoparticles (NPs) and the preparation of a multilayer shielding layer, etc., to achieve a controlled slow-drug release (unpublished). The selection of the drugs and the carriers as well as the drug-coating preparation process can reduce or negate the potential disadvantages of DES. This review outlines the influencing factors and the strategies for controlling DES drug release. We hope that this paper will provide a reference for the preparation of novel controlled slow-release DES.

2. MECHANISM OF DRUG RELEASE FROM DESS

DESs have the advantage of keeping a steady drug release to a specific action site. This not only helps to avoid the problem of blood concentrations fluctuating greatly and inducing adverse reactions but also reduces the amount of drugs administered, thus increasing the patients' medication compliance. Overall, the mechanism of drug release from DES may be categorized into physical and chemical mechanisms. The former contain the drug's diffusion by a polymer layer, the dissolution or degradation of the polymer, the permeation pressure, and the ion exchange. The latter are due to the breakage of the covalent bonds by either chemical degradation or enzymatic degradation, such as prodrugs.[9]

According to the physical or chemical properties of the polymer matrix, the drug release mechanisms can be classified into three primary controlled systems. The first is a diffusion-controlled system in which the drug diffuses from the nondegraded polymer. The second is a swelling-controlled system that enhances the drug's diffusion because of polymer swelling. The third is an erosion-controlled system in which the drug's release is due to the polymer's degradation and erosion.[15] All three of the controlled systems involve diffusion.[16] For a permanent polymer, drug release is due to the concentration gradient by either a swelling-controlled system or a diffusion-controlled system. For a biodegradable polymer, the hydrolytic cleavage of the polymer chains leads to the degradation or erosion of the matrix, which usually controls the release of drug.[16]

3. FACTORS INFLUENCING DRUG RELEASE

There are many factors that influence the drug release from DES, such as the polymer, drug, coating methods, drug storage, elution direction, coating thickness, pore size in the coating, and release conditions as well as the influence of the hemodynamics after the implantation.

3.1. Polymer.

The polymer that makes up the DES functions as the drug carrier and controls the drug's release. Polymers can be generally grouped into two categories: nonbiodegradable (or permanent) polymers and biodegradable polymers. In recent years, the polymer-free DES has been developed.

3.1.1. Permanent Polymer. Nonbiodegradable polymers were used in the first generation drug-eluting stents, which includes parylene C (PC), poly(*n*-butyl methacrylate) (PBMA), poly(ethylene-*co*-vinyl acetate) (PEVA), poly(styrene-*b*-isobutylene-*b*-styrene), polyvinylidene fluoride (PVDF), and hexafluoropropylene (HFP) etc. (Table 1).

Both the PROMUS Element everolimus-eluting stent (PtCr-EES) and the Xience-V/PROMUS everolimus-eluting stent (CoCr-EES) contain the antiproliferative agent everolimus and the same polymer layers. The identical polymer coatings consist of a primer layer (PBMA) and a drug matrix layer (PVDF-HFP) blended with the identical drug dose. (100 $\mu g/cm^2$), which provides a similar drug elution kinetics (Table 1).[17,18] The results of the clinical analysis are consistent with prior studies, which demonstrated no obvious differences in the death rate, myocardial infarction, revascularization, or stent thrombosis between CoCr-EES and PtCr-EES.[19] The principal difference between the Endeavor zotarolimus-eluting stent (E-ZES) and the Endeavor Resolute zotarolimus-eluting stent (R-ZES) is the durable polymer coating of the former. The polymer coating (BioLinx) of the R-ZES is a combination of

Table 1. Primary Permanent Polymer Drug-Eluting Stents[a]

stent name	drug (concentration)	polymer	coating method	coating thickness	manner or mechanism of controlled release	drug release rate (days)	refs
Cypher stent (Cordis Corporation, Bridgewater, NJ, USA)	sirolimus (140 $\mu g/cm^2$)	PC PEVA PBMA	base coat: PC; drug coat: (PBMA+PEVA)+sirolimus (67%/33%); Topcoat: PBMA	12.6 μm	diffusion	40% (5); 52% (10); 64% (15); 85% (30)	6
Xience-V/Promus (Abbott Vascular, Santa Clara, California, USA)	everolimus (100 $\mu g/cm^2$)	PBMA PVDF-HFP	base coat: PBMA; drug coat: Everolimus+ PVDF-HFP/ spraying	7.8 μm	diffusion	80% (28); 100% (120)	18
Promus Element (Boston Scientific, Natick, Massachusetts, USA)	everolimus (100 $\mu g/cm^2$)	PBMA PVDF-HFP	base coat: PBMA; drug coat: PVDF-HFP+everolimus (83%/17%) /spraying	6 μm	diffusion	80% (28); 87% (90)	19
Endeavor (Medtronic Cardio Vascular Inc., Santa Rosa, CA, USA)	zotarolimus (100 $\mu g/cm^2$)	PC	base coat: PC; top coat: zotarolimus	>5 μm	dissolution/degradation	75% (2); 95% (15); 100% (28)	21
Endeavor Resolute (Medtronic Cardio Vascular Inc., Santa Rosa, CA, USA)	zotarolimus (100 $\mu g/cm^2$)	BioLinx	drug coat: zotarolimus + biolinx polymer	5.6 μm	dissolution/degradation	50% (7); 70% (28); 85% (60); 100% (31)	18, 21
Taxus (Boston Scientific, Natick, MA, USA)	paclitaxel (100 $\mu g/cm^2$)	SIBS	paclitaxel+SIBS, without a top coat layer (primer)	16 μm	diffusion	<10% (28)	22

[a] SIBS, styrene-*b*-isobutylene-*b*-styrene; PEVA, polyethylene-*co*-vinyl acetate; PMBA, poly(*n*-butyl methacrylate); PC, phosphorylcholine; PVDF, polyvinylidene fluoride; HFP, hexafluoropropylene.

C10, C19, and polyvinylpyrrolidone (PVP). C10 polymer is a copolymer of *n*-butyl methacrylate and vinyl acetate with 2,2-azobis(isobutyronitrile); and C19 is a copolymer of vinyl acetate, N-vinyl pyrrolidinone, and *n*-hexyl methacrylate.[20] This system contains a hydrophilic surface elements and a hydrophobic core, which provides a enhanced drug-release profile and potentially improved biocompatibility. Compared with the E-ZES, the R-ZES has a more delayed drug release after stent implantation. The release rates of the R-ZES were 50 and 85% at 7 and 60 days, respectively, whereas the drug release rates of the E-ZES stent was 75% at 2 days drug.[21]

3.1.2. Biodegradable Polymer.

The polymer element was not doing anything at all once the drug elution was complete. Some of the permanent polymers have been involved as potential triggers of late and very-late stent thrombosis by an immunological response.[8] Thus, biodegradable polymers may act as a "second generation" of polymers for DES (Table 2). Biodegradable polymers should satisfy the following conditions: (1) The polymers possess proper mechanical characters for their intended application. (2) They contain proper processability and permeability for the designated application. (3) They do not induce a constant inflammatory response. (4) Their degradation times are in line with their function. (5) Their degradation products are nontoxic and can be easily resorbed or excreted.[23]

The use of biodegradable polymers as a stent element is largely experimental. Biodegradable polymers are often composed of polylactides such as polylactic acid or polycarbonate, which are completely metabolized in approximately 12 to 18 months.[24] Different polymers have different degradation mechanisms. Poly(lactide-*co*-glycolide) (PLGA) displays a two-stage release profile of degradation and diffusion, while poly(lactide-*co*-caprolactone) (PCL) displays a common single stage of pattern-diffusion.[25] The paclitaxel was loaded with three different matrix formulations, including PLGA−PAT, PCL−PAT and PLGA−PEG-PAT. An in vitro release investigation revealed that the PLGA−PAT film showed an exceedingly slow release rate that continued over 80 days. The PCL−PAT exhibited the fastest release rate that was sustained for only approximately 30 days, whereas the PLGA−PEG-PAT showed a moderate release rate that continued for about 45 days.[26] Therefore, by modifying the polymer matrix composition, the PAT release rate can be effectively controlled.

3.1.3. Polymer-Free.

Clinical studies have shown that the toxic ions from the degradation of implanted polymers and metals or alloys lead to a whole train of inflammatory reactions, such as calcification and restenosis.[46] The problems with using polymers for DES include the following. First, the polymers containing the drugs are usually coated on the stent surface. When the stent is expanded in patients, the stress of the expansion may cause mechanical damage to some polymer coatings. A series of irregularities, such as cracks, waviness, wrinkles, depressions, and peeling, have been observed, which may leads to a variety of adverse reactions. Second, some polymer coatings can cause chronic inflammatory and hypersensitivity reactions. Third, polymers may inhibit or delay the growth of the vascular endothelial cells (VECs).[47]

The DESs made without using a polymer may avoid the occurrence of late in-stent thrombosis caused by the unabsorbable polymer.[48] Nevertheless, the polymer-free stents still have encouraging drug release curves and play a role in the treatment of restenosis.[49] The primary polymer-free stents are listed in Table 3. In contrast to the polymer-based DESs, the

Table 2. Primary Bioresorbable Polymer Drug-Eluting Stents[a]

stent name	drug dosage	polymer/biodegradation time (months)	coating method	manner or mechanism of controlled release	drug release rate (days)	coating thickness	refs
BioMime (Meril Life Science Pvt. Ltd., Gujarat, India)	sirolimus (1.25 μg/mm^2)	PLLA+PLGA/3	N/P	hydrolysis/degradation	100% (30)	2 μm	27
BioMatrix-Flex (Biosensors Inc., Newport Beach, CA, USA)	Biolimus A9 (15.6 μg/mm)	PLA/6–9	abluminal: Biolimus A9+PLA	diffusion/dissolution/degradation	45% (28); 70% (90)	10 μm	28
Nobori (Terumo Corporation, Tokyo, Japan)	Biolimus A9 (15.6 μg/mm)	PLA/6–9	abluminal: Biolimus A9+PLA (50%/50%)	hydrolysis/degradation	45% (30)	10 μm	29
Supralimus (Sahajanand Medical Technologies, Pt. Ltd., India)	sirolimus (1.4 μg/mm^2)	PLLA, PLGA, PLC, PVP/7	the layer: sirolimus +PLLA, PLGA, PLC (35%/65%); the outer: PVP	two-layer prebent premature drug release.	in vitro: 50% (9–11); 80% (28); 100% (48)	4–5 μm	30
Excel (JW Medical System, Shandong Province, Weihai, China)	sirolimus (13–14 ug/mm)	PLA/6–9	abluminal: sirolimus +PLA	diffusion/dissolution/degradation	N/A	10–15 μm	31
Axxess (Biosensors Europe SA, Morges, Switzerland)	Biolimus A9 (22 μg/mm)	PLA/6–9	abluminal: Biolimus A9+PLA	diffusion/dissolution/degradation	45% (30)	15 μm	32
Orsiro (Biotronik AG, Blach, Switzerland)	sirolimus (1.4 μg/mm^2)	abluminal side: PLLA; luminal side: silicon carbide layer/24	abluminal: the Biolute polymer: PLLA and sirolimus; luminal: amorphous hydrogen rich silicon carbide (aSiC:H) (plasma-enhanced chemical vapor deposition technique)	diffusion/degradation	42% (20); 50% (30); 80% (90)	abluminal side: 7.5 μm; luminal side: 3.5 μm	33
MAHOROBA (Kaneka, Osaka, Japan)	tacrolimus (0.94 μg/mm^2)	PLGA/6	rollcoat abluminal: tacrolimus +PLGA (20%/80%)	diffusion/dissolution/degradation	in vivo: 26% (28); 45% (84)	N/A	34
Synergy (Boston Scientific Corp, Natick, MA, USA)	everolimus (38–179 μg/stent)	PLGA/3	abluminal: everolimus+PLGA	diffusion/degradation	50% (60); 100% (90)	4 μm	35
NOYA (Medfavor Medical, Beijing, China)	sirolimus (8.8 μg/mm)	PDLLA/>4	sirolimus+PDLLA	diffusion/degradation	in vivo: 75% (7); 81% (14); 83% (21); 85% (28); 87% (30)	6 μm	36
Combostent (Orbus Neich Medical, Hongkong, China)	sirolimus (5 μg/mm); CD34 antibody	SynBiosys: the degradation of the polymer/3–6	abliminal surface: sirolimus+SynBiosys; Luminal: CD34 antibody layer	hydrolysis/degradation	58% (7); 82% (14); 100% (30)	N/A	37
Inspiron (Scitech Medical, São Paulo, Brazil)	sirolimus (56 μg/mm)	PLLA+PDLLGA/6–9	abluminal: sirolimus+PLLA +PDLLGA	hydrolysis and enzymatic action	in vivo: 45% (5); 55% (10); 74% (30); 80% (30)	5 μm	38
TIVOLI stent (Essen Tech-	sirolimus (8 μg/mm)	PLGA/6	sirolimus+PLGA	diffusion/degradation	80% (30)	6 μm	39

Table 2. continued

stent name	drug dosage	polymer/biodegradation time (months)	coating method	manner or mechanism of controlled release	drug release rate (days)	coating thickness	refs
nology Beijing Co. Ltd. China)							
BuMA (SinoMed, Beijing, China)	sirolimus (6–8 μg/mm)	PLGA/2.5	abluminal: base layer: electro-grafting (eG) (poly [*n*-butyl methacrylate] coating); drug layer: sirolimus+PLGA (spray method)	diffusion/dissolution/degradation	in vivo: 100% (30)	base layer: 100–200 nm; drug: 3.8–10 μm	40
Infinnium (Sahajanand Medical, Ltd., India)	Paclitaxel (1.4 μg/mm^2)	PLLA, PLGA, PLC, PVP/7	the drug is coated in 3 different layers of combination of drug and polymer, and each layer has a different release profile	the stents have slotted tubes. Design/diffusion/dissolution/degradation	50% (9–11)	4–5 μm	41
Firehawk stent (MicroPort Medical, Shanghai, China)	sirolimus (3 μg/mm)	PDLLA/9	an abluminal groove: sirolimus +PDLLA; luminal: PDLLA	grooves/degradation	ex vivo: 75% (30); 90% (90)	N/A	42
Conor (Conor Medsystems, Menlo Park, CA, USA)	paclitaxel (10 μg/stent)	PLGA/6	reservoirs: PLGA and paclitaxel. (An automated microjet system is used to evenly load the polymer/drug combination by depositing individual drops within each hole)	reservoirs/diffusion/erosion of the polymer	20% (2); 50% (10); 60% (14); 85% (21); 100% (30)	N/A	10, 43
Jactax (Boston Scientific, Natick, MA, USA)	paclitaxel (9.2 μg/stent)	PLA/4	abluminal (have 2750 discrete microdot): paclitaxel+PLA (50/50) (juxtaposed ultrathin abluminal coating process.)	reservoirs/hydrolysis/degradation	100% (60)	<1 μm	44
NEVO (Cordis Corporation, Bridgewater, NJ, USA)	sirolimus (166 μg/stent)	PLGA/3	it is the first DES applying the Cordis RES Technology reservoir: sirolimus +PLGA	reservoirs/hydrolysis/degradation	80% (30)	N/A	45

[a] N/A, no application; PLA, polylactic acid; PLGA, poly(lactide-*co*-glycolide); PVP, polyvinylpyrrolidone; PLC, poly(lactide-*co*-caprolactone); PLLA, poly(L-lactic acid); PDLLA, poly(D,L-lactide); PDLLGA, poly(D,L-lactide- coglycolide).

Table 3. Primary Polymer-Free Stents

stent name	drug dosage	coating method	manner or mechanism of controlled release	drug release rate (days)	coating thickness[a]	refs
VESTASyncTM (MIV Therapeutics, Alexander, Georgia, USA)	sirolimus (2.9 $\mu g/mm^2$)	a nanothin-microporous hydroxyapatite surface; impregnated with a polymer-free sirolimus (immerse)	a nanothin-microporous hydroxyapatite surface/dissolve	in vitro: 100% (90)	0.7 μm	49
Nano+ (Lepu Medical, Beijing, China)	sirolimus (2.2 $\mu g/mm^2$)	abluminal nanoporous cavities filled with sirolimus	the nanoporous (average diameter of aperture: 400 nm) surface of the stent/diffuse	60% (3); 75% (7); 83% (14)	N/A	50
Bicare (Lepu Medical, Beijing, China)	sirolimus (1.6 $\mu g/mm^2$)/probucol (0.8 $\mu g/mm^2$)	sirolimus and probucol coat the stent (electrochemical method)	nanoporous cavities (400 nm in depth)/diffuse	in vitro: sirolimus 53% (7); 70% (14); 80% (28) and probucol 14% (7); 18% (14); 22% (28)	N/A	51
Cre 8 (CID Saluggia, Italy)	sirolimus (0.9 $\mu g/mm^2$)	an ultrathin (0.3 μm) passive carbon (i-Carbofilm) coats the stent and sirolimus is loaded into abluminal reservoirs	the amphilimus formulation, constituted by sirolimus with an excipient composed of a long-chain fatty acid mixture to modulate the drug release	in vivo: 50% (18); 100% (90)	≤1 μm	52
Zilver stent (Cook Medical, Bloomington, Indiana, USA)	Paclitaxel (3 $\mu g/mm^2$)	polymer-free paclitaxel coating on the outer surfaces of the self-expanding nitinol stent	diffuse	in vivo: 95% (1); details see 3.1.3	N/A	53, 54
Yukon (Translumina, Hechin-gen, Germany)	Sirolimus (195 ± 33 $\mu g/cm^2$)	microporous surface (sand-blasted); sirolimus (inkjet technology)	the microporous of stent/diffuse	ex vivo: 67% (6); 100% (25)	N/A	55
BioFreedom BES (Biosensors Europe SA, Morges, Switzerland)	Biolimus A9 (15.6 $\mu g/mm^2$)	selectively microstructured surface holds drug in abluminal surface structures	microstructured surface holds/diffuse	80% (28); 100% (90); in vivo: 98% (30)	N/A	56
Janus Carbostent (Sorin Biomedica, Saluggia, Italy)	tacrolimus	tacrolimus is loaded into the grooves, and then the stent is passively coated with carbofilm	grooves/diffuse	50% (30)	N/A	57

[a] N/A, No application.

polymer-free stents usually adopt the following two mechanisms for storing the drug and achieving the controlled drug release: (1) through constructed nanoporous cavities on the stent struts or (2) using prepared nanopores to connect to other substances.

The VESTAsync-eluting stent is prepared with a nano thin microporous hydroxyapatite surface coating instead of a polymer, and the pores are then impregnated with lipid-sirolimus (2.9 μg/mm) vs the 7.8 μg/mm in the Cypher stent. The drug release rate is nearly the same as in the Cypher stent in the first hour. After that, the drug release rate of VESTAsync-eluting stent slows to less than half the rate of the Cypher.[49]

The Bicare stent and the Nano$^+$ stent were developed by Lepu Medical with a surface modulation to create nanoporous cavities that allow initial drug retention followed by controlled drug release. The Bicare stent has a sirolimus release rate of 70% and a probucol release rate of 18% at 14 days, compared with the Nano$^+$ stent, which has a sirolimus release rate of 83%, and the Yukon stent, with a sirolimus release rate of 67% eluted at 6 days.[50,51] The Cre8 stent, in the new generation of polymer-free coronary stents, has two primary features, including the presence of reservoirs on the stent's outer surface that are devoted to the containment of the drug and a coating that promotes rapid cellular growth constituted of a permanent ultrathin and high-density turbostratic carbon film called i-Carbofilm. The Cre8 stents are based on an Amphilimus formulation, in which sirolimus is formulated with a mixture of long-chain fatty acids that function as a polymer-free carrier. The sirolimus is released from the reservoirs created on the abluminal stent surface. This device can prolong drug elution, with only 50% of the total drug amount released in approximately 18 days and 100% of the drug released in 90 days.[52]

The Zilver paclitaxel stent is a unique polymer-free stent different from the above two strategies, which has a polymer-free PAT coating (3 μg/mm^2) on the outer surface of a smooth electropolished finish stent strut neither nanoporous cavities nor nanopores to connect to other substances. In a normal porcine artery model, despite stents delivered about 95% of the PAT within the first 24 h after stent implantation, drug levels were retained at about 20% of the peak level through 14 days and stranded detectable through 56 days in the vessel wall.[53] The latest research shows that prolonged vascular healing and sustained peristent inflammation may be present even at 12 months after Zilver paclitaxel stent implantation.[54]

3.2. Drug.

The type of drug selected may also affect the release rate. The parameters of the drug release system are closely related to the intrinsic qualities of the drugs, especially in physiological conditions. These qualities include the drug diffusion coefficients and dissolution constants in the coating on surface of the stents, the drug binding/uptake rates, and the amount of the transmural convection in the blood vessel wall.[58] The drugs used for DES usually include PAT, sirolimus and its derivatives, which are lipophilic drugs. To improve the drug's distribution and to decrease its release into the peripheral circulation, the drug-polymer matrix, including the Biolimus A9 and the biodegradable PLLA, are only coated on abluminal surface of the Nobori coronary stent. Compared with the Cypher stent, in addition to the difference in the polymers, the primary difference between the Biolimus A9 and sirolimus (Cypher) is the substitution of hydrogen at 40-O position, which increases the drug's lipophilicity. On the basis of the drug release curve, the Nobori stents release 45% of the drug in 30 days, whereas the Cypher stents release 85% of the drug.[6,29] Biolimus A9 was also used on the BioMatrix-Flex stent and the Axxess stent. The release rate of the Biolimus A9 is 45% in 30 days.[28,43]

High or extremely high drug doses have something to do with toxic effects, which include augmented fibrin deposition, intraintimal hemorrhages, mural thrombus, medial necrosis and excessive arterial expansion. These toxic effects may result in stent thrombosis and the pathological changes of neointimal tissue. On the contrary, an insufficient dosage may decrease the antirestenotic benefit.[59] Lamichhane et al. have recently investigated the effects of solvents (ethanol, DMSO, and their mixtures), the drug concentrations (PAT, 2, 3, 4, 8, and 12 mg/mL) and the coating methods (dip and spray) on the drug-loading capacity of stent. A solvent mixture of 75:25 v/v Et—OH:DMSO was determined to be optimal for obtaining a smooth and homogeneous PAT coating. Depending on the PAT concentration used in the coating solution, the total amount of the drug loaded on the stents ranged from 3.2 to 71.1 μg and from 27.2 to 249.6 μg for the dip and spray coating methods, respectively.[60] The PAT (with doses of 0.2, 0.7, 1.3, 1.4, 2.7, and 3.1 μg/mm^2 stent surface area) that is released from the nonpolymer-based stents significantly decreased the 6-month diameter stenosis only at the highest loaded drug dose compared with the BMS. A reduction in all of the angiographic parameters of restenosis occurs in a dose-dependent manner. The % diameter of the stenosis is in the range of 14% for the highest dose to 33% for the lowest dose.[61]

3.3. Coating Methods.

The suitable surface modification of the stent should meet the following conditions: (1) impede the inflammatory reaction, thrombosis formation, intimal hyperplasia, and excessive proliferation of the VSMCs; (2) expedite the endothelialization to form the complete endothelium layer on the surface of stent within the first month; and (3) be biocompatible with the exposed stent surface after the elution.[62] On the basis of the technological principle of material surface modification, there are physical methods and chemical methods.

3.3.1. Physical Methods.

The physical methods include immersion, dipping, spraying, electrostatic dry powder deposition, layer-by-layer (LbL) assembly coating, and electrospinning, for example. For the spraying method, the instability between the coating and the stent material often results in a serious burst-release phenomenon that limits its application,[63] such as in the Promus Element, Promus and BuMA stents. Electrostatic technology allows an electric field to overcome the surface tension of the droplet at the nozzle under the influence of the voltage, leading to the random deposition at the receiver to form a uniform coating.[64]

Electrostatic dry powder deposition technology was used to prepare the sirolimus drug-eluting stents. The sirolimus was encapsulated in polymeric PEVA/PBMA microparticles. The average diameter of sirolimus microparticles is 3 μm. Once power is applied, the microparticles begin "melting" to form a uniform continuous film on the stent surfaces. The coated stents showed continued release behavoir over 25 days.[65] The LbL assembly technology uses nanotechnology and can be widely used in DES because of its advantages of mild reaction conditions, wide range of biomolecule selection, ease of preparation, and independent requirements of the materials' structure.[66]

On the basis of the modification of the polymer matrix, combining the ultrasonic atomization spraying and the

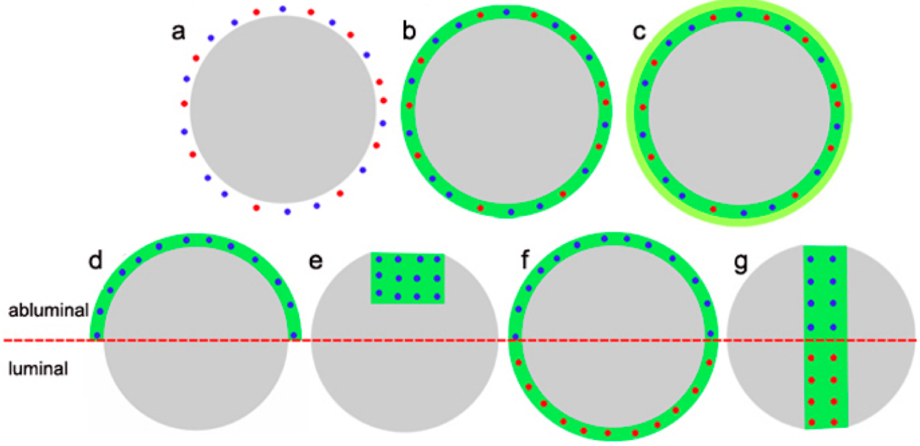

Figure 1. Integration system of the drugs and polymers used in drug-eluting stents. (a) Nonpolymer-based PAT particles, (b, c) stent coating consisting of an antiproliferative drug and polymer as the drug layer with or without the top layer as the shield layer, the mural release system (d) in the smooth stent strut and (e) in the grooves/reservoirs stent, the bidirectional release system (f) in a smooth stent and (g) in grooves/reservoirs stent. The red color represents the endothelialization-promoting drugs, the blue color represents the antiproliferative drug, the dark green and light green represent the different polymer coatings, and the gray represents the cross-section of a stent strut.

electrostatic LbL adsorption of oppositely charged polyelectrolytes and proteins, the platelet membrane glycoproteins monoclonal antibody SZ-21 and chitosan multilayer composite system are prepared on the stent surface. SZ-21 is released from the coated composite matrix for approximately 2 weeks, with 50% of the SZ-21 still remaining on the 5-bilayer-coated stents and 60% remaining on the 10-bilayer-coated stents. In contrast, only 10% of the SZ-21 remained on the coated stent wires when the immersion method was used. Therefore, when the stent is coated using the LbL self-assembly technology, the burst release of the SZ-21 is decreased.[67]

3.3.2. Chemical Methods. The chemical methods include acid/alkaline treatment, anodic oxidation, silanization, etc. For the drug release, the strongly bound molecules are released from drug stents at a sustained rate, while the weakly bound molecules are burst released.[68] However, the chemical reaction covalently binds the polymer or drugs to the surface of the stent materials to generate different groups as the basis of the secondary reaction, which usually requires different surface treatments, such as an anodic oxidation, acid/alkaline treatment, or silanization, for example.[69] The surface roughness of the stent materials is influenced by the different pickling times, which increases gradually with the increase of the acid pickling time. The increased roughness leads to the increase of support for the contact area and is conducive to improvements in the adhesion force and mechanical properties. After the BMS undergoes an acid treatment (obtain −OH) and 3-glycidoxypropyltrimethoxysilane silanization (obtain $-NH_2$), antihuman VE-cadherin antibody or antihuman CD34 antibody (100 μg/mL) is directly linked to the surface-activated stents, which can capture endothelial progenitor cells (EPC) over a sustained length of time and promote endothelialization.[70] The most common secondary reaction is used to form the required amino groups on the stent surface, such as silicon alkylation (such as 3-aminopropyl-triethoxysilane or γ-aminopropyltriethoxysilane) or a different cross-linking agent (N-(3-(dimethylamino)-propyl)-N′-ethylcarbodiimide (EDC)).[71,72]

Dopamine, as the key molecule in mussel adhesive protein, recently has attracted widespread attention. The polydopamine (PDA) coating shows a high affinity for various substrates and is a promising platform for secondary reactions.[73] Using dopamine-mediated biomolecule immobilization, the multifunctional coatings can be prepared through two methods: (1) the synthesis of a biomolecule-dopamine conjugate (heparin) and its assembly by the catechol groups of dopamine and (2) the Schiff base reactions or Michael addition between the catechol groups of dopamine with thiols or amine of biomolecules.[73] The polydopamine-modified surfaces lead to remarkable cell-material interactions, which increase the proliferation, viability and migration of ECs, and decreased SMCs proliferation. The inhibition of the SMCs proliferation may have something to do with the surface catechol content.[74] Undoubtedly, to promote the endothelialization of stents, the mussel-inspired PDA layer provided a meaningful and inspiring strategy for surface modification.of stents.

3.4. Drug Storage and Elution Direction. Over the past decade, stent coating technology has noticeably improved. It has evolved from a single drug coated onto the stent surface through a single method, to stents coated with a drug or several different drugs through one or multiple methods.[7] Figure 1 shows some typical drug delivery methods. Nonpolymer-based PAT particles on the strut showed that up to 40% of the drug could be released during the stent delivery release (Figure 1a).[75] However, a drug release system that lacks a polymer is not a wise choice. A stent coating containing an antiproliferative drug and a polymer as a drug layer with or without a top layer as the shield layer is the most typical strategy for the first generation of DES (Figure 1b, c), which often shows the drug burst release phenomenon (Table 1).

To achieve a more effective role for the pharmacological inhibition of restenosis, we have designed directional drug delivery by coating the antiproliferative drug on the abluminal (outer) surface of the stent only so that the luminal (inner) surface of the stent can be a bare metal surface (the mural release system) or have a different coating (the bidirectional release system) to enhance endothelialization or reduce platelet adhesion.[6] The abluminal coating can minimize the exposure of the polymers to the luminal area of the blood vessel, which can ensure that the drug−polymer matrix is in contact with the blood vessel wall, whereas the bare-metal strut is retained in the luminal area.[29] The mural release system is used not only in smooth stents struts, such as the BioMatrix-Flex, Nobori, Excel, Axxess, MAHOROBA, Synergy, and Inspiron stents (Figure 1d, Table 2), but also in the grooves/reservoirs stents for the storage of drugs, such as in the Infinnium, Firehawk, and Jactax stents (Figure 1e). This bidirectional release system is used in a few smooth stents, including the Combostent and Orsio stents, which have shown promising results (Figure 1f, Table 2).[33,37] Our laboratory has studied this bidirectional release system using a two-sided coating method, in which the SZ-21 that was used as the antithrombotic drug was coated on the luminal surface by the dip-coating method and the sirolimus that was used as the antiproliferative drug was coated on the abliminal surface by an ultrasonic atomization spray. Another bidirectional release system is a stent reservoir that extends across the full thickness of a strut (Figure 1g), such as the Conor stent, which is loaded with PAT within a PLGA matrix by depositing individual drops within each hole. The complete elution time of the bidirectional elution is more rapid (10 days) than the mural elution (30 days). An in vivo study also indicated that the inhibition of the in-stent neointimal hyperplasia was better in the long-release groups.[43] Furthermore, for the sake of a fixed-point release drug from this reservoir stent, the antiproliferative drugs can be placed on the abluminal surface of the stent reservoir, whereas the endothelialization drugs are placed on the luminal surface.

3.5. Hemodynamics.

As noted previously, stents have both an abluminal surface and a luminal surface. The former is directly contact with the blood vessel wall, and the latter is characterized by the changing blood flow. In stent-based drug delivery, both the diffusion owing to the drug concentration gradients and the solvent-driven flow in the vessels' lumen govern the drug distribution and mass transport.[76] The drugs at the mural surface play the part of the secondary sources of tissue absorption. The degree of the drug's deposition and penetration into the tissue not only finally affects the effectiveness of drug but also may cause possible side effects.[77] Because of the effects of the scaffolding on the local arterial geometry, stent implantation induces changes in the coronary artery hemodynamics and may induce obvious alterations in the spatial shear stress distribution, particularly at the stent edges.[78] Furthermore, the flow magnitude, direction, and strut geometry will directly impact the stent-based drug delivery.[79]

A multiscale and multidomain advection−diffusion model has been formulated to describe the drug dynamics in the polymer matrix. This model accounts for the tissue's microstructure, macrostructure, and local hemodynamics.[80] In a dynamically changing blood flow field, the drug absorption will be lesser in magnitude but larger in extent to that of the steady standing recirculation zones, and the DES's effectiveness may get greater with an increase in the flow pulsatility as opposed to that under a steady flow.[81] Kolachalama et al. have elucidated how the interplay of local flow and strut geometry determine the difference in the sizes of the two recirculation zones (distal and proximal to the stent strut) and the asymmetrical distribution of the drug. Using computational fluid dynamic modeling tools, their investigation showed that the proximal zone was about 3-fold shorter than the distal zone but held a nearly 7-fold higher mean luminal drug concentration than the distal zone. Consequently, the drug delivery from the proximal zones is more efficient than from distal zones under a bidirectional flow.[77] Therefore, stent design improvements, such as in the shape and thickness of a strut and its mechanical properties, are essential for the future development of DES.

3.6. Other Factors.

In addition to the polymers, drugs, coating methods, drug storage and elution direction, and hemodynamics, other factors, such as the coating thickness, pore size in the coating, and release conditions (release medium, pH value, temperature), also affect drug release. Even if a single factor is altered, the drug release curve may also change slightly.

The drug loading capacity is restricted primarily by the stent size and surface area, coating thickness and loading capacity per unit area. Through the incorporation of chitosan with SZ-21 (SZ-21/CH), a biocompatible coating for DES was constructed using the LbL method. The preparation of the 5 and 10 layer coatings have different thicknesses, the $(\text{SZ-21/CH})_5$ and $(\text{SZ-21/CH})_{10}$, respectively. In vitro, the release kinetic of the SZ-21 indicates that the SZ-21 residues on the stent surface are 60% (5 days) and 45% (10 days) in the $(\text{SZ-21/CH})_5$ group and 75% (5 days) and 60% (10 days) in the $(\text{SZ-21/CH})_{10}$ group.[66] Therefore, an appropriate increase in the coating thickness can slow the release of the drug.

The influence of the release medium on drug release was demonstrated with a dual DES, which is coated with multilayers of Duraflo Hep and sirolimus.[82] The stent was coated using 3 layers of Duraflo Hep and 2 layers of sirolimus by the LbL method. In vitro the prepared DES was immersed into a release medium of PBS (pH 7.4) without or with 10% or 20% (v/v) ethanol. Because sirolimus and duraflo Hep are practically insoluble in water, Duraflo Hep was not detected in the PBS medium without ethanol. However, in the presence of ethanol, a near-zero-order release was exhibited. The release rate of the Duraflo Hep has been associated with the ethanol concentration. With 10 days of immersion, a higher release percentage (18%) was observed in the PBS containing 20% ethanol compared with the 11% release in the PBS containing 10% ethanol.[82]

To make the heparin and fibronectin (Hep/Fn) films on the amino-silanized Ti surfaces, we invented a technique that combines electrostatic interaction and covalent immobilization. The silane-based surfaces were functionalized by the covalent immobilization of the Hep/Fn mixture.[71] Before the immobilization, 100 μg/mL of Fn and 5 mg/mL of Hep in PBS were premixed with a ratio of 1:1 (v/v) under different conditions, i.e., pH 4 (electrostatic attraction conditions), pH 7 (physiological conditions), and with EDC/NHS cross-linking, respectively.[71] Although the quantity of Hep immobilized on the pH 4 samples was not the largest amount, the pH 4 samples displayed the longest activated partial thromboplastin time and lowest quantity of platelets, which indicated a better blood compatibility on pH 4 samples than on pH 7 and EDC/NHS samples.[71]

4. STRATEGIES FOR IMPROVING DRUG RELEASE CONTROL

4.1. Stent Design.

Stent design includes two aspects, i.e., improvements in the strut geometry and in the stent surface topography. On one hand, the geometry of the stent struts is nearly rectangular on a cross-section and usually 80−170 μm high. Numerical modeling with idealized stent strut geometries forecasted that reducing the strut height or altering the cross-sectional shape will decrease the size of the recirculation zones and in turn decrease the prothrombotic fibrin deposition and increase the endothelial anticoagulant thrombomodulin expression, which further inhibits the formation of late stent thrombosis.[83] On the other hand, the progress of micro- and nanotechnology have permitted to produce the fine geometries on the surfaces of metal and polymeric biomaterials with the necessary micro- and nanostructured features, which are simple, rapid, reliable, reproducible, and cost-effective.[84] There are four basic nanotopography geometries, including nanogratings, nanopost arrays, nanoislands, and nanopits (Figure 2).[84]

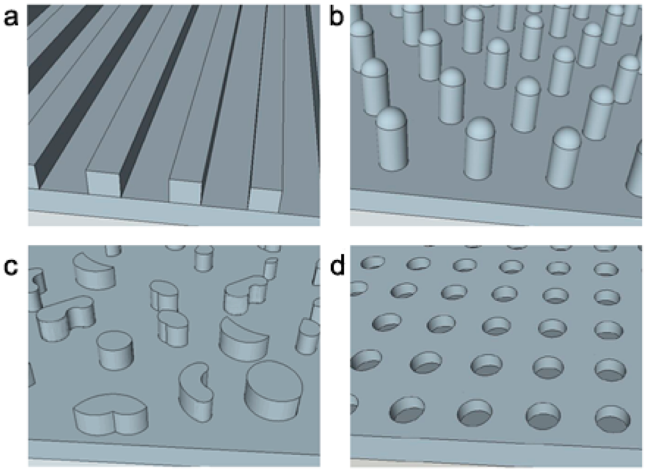

Figure 2. Schematic depictions of nanotopography geometries, including (a) nanogratings, (b) nanopost arrays, (c) nanoislands, and (d) nanopits.

Many DESs are simple. The stents are coated with a drug–-polymer matrix, which delivers the drug from the polymer matrix. However, several new stents incorporate reservoirs, which do not deliver the drug from the polymer matrix but instead from a reservoir per se. In general, this type of stent incorporates hundreds of reservoirs, grooves, or micropores into the stent struts. To improve the polymer coating, researchers specifically manufacture the micropores on the surface of the BMS.[85] Nonpolymer DES's often use this stent platform. There is a major difference in the reservoir design between the defunct stents and the contemporary reservoir DES. The former, such as the Conor stent and the Costar stent, use reservoirs that are created using a laser and extend across the full thickness of a strut (Figure 3a).[11,85] The latter, such as the Jactax stent, NEVO stent, and Cre8 stent, etc., use grooves that are scored on the outer surface of the strut (Figure 3b) and therefore only partially use the strut thickness.[44,45,52,86] The Cre8 stent has been introduced in the previous polymer-free section. The Firehawk stent employed an abluminal groove, which was filled with a biodegradable PLA polymer combined with sirolimus. Animal experiments have indicated that nearly 75% of the drug was eluted in 30 days and that 90% of the drug was eluted in 90 days.[42]

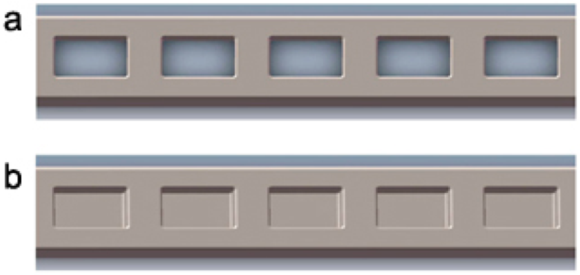

Figure 3. Schematic depictions of reservoir-based DES. (a) The reservoir extends across the full thickness of a strut, and (b) the grooves are scored on the outer surface of the strut.

The structural design can also safeguard the drug during the implantation process. In comparison with the integrally coated DES, the grooves' design forms nanoscale or micrometer-grade holes for the drug or polymer adhesion to the materials and increases the surface area of the materials.[85] More importantly, the reservoirs are embedded on the outer stent surface. The drugs loaded into the reservoirs are released directly to the blood vessel wall and are not washed away by the bloodstream.[57]

A microlevel roughness of the stent surfaces was modeled by grit blasting with glass beads and alumina (Al_2O_3) powders to increase the surface area and provide more sites for the drug or polymer to adsorb than would be available on flat surfaces. The previous study showed that the growth of VECs on microrough surfaces is excellent.[87] However, rough surfaces also enhance the aggregation, adhesion, and activation of blood platelets and can induce thrombosis. The surface of platelets exhibits an electronegative charge. If the surface of a material also shows a net negative charge, because of the repulsion between the same charges, the platelets would not adhere to the surface of the material.[88] Hence, microrough surfaces modified with the $-COOH$ or $-SO_3H$ groups have also been used in drug delivery studies of stents.

Lancaster et al. prepared four bare microrough surfaces by grit blasting using Co–Cr alloy plates with four types of abrasive powders, e.g., glass beads (50 or 100 μm) and alumina powders (50 or 110 μm), respectively. They also modeled four self-assembled monolayers (SAMs) coated microrough surfaces by depositing a $-COOH$ terminated phosphonic acid monolayer on four bare microrough surfaces, and a PAT solution was then deposited on the eight microrough surfaces using the microdrop deposition method.[47] An in vitro study indicated that the glass bead grit-blasted bare microrough surfaces exhibited burst release behavior, while Al_2O_3 grit-blasted surfaces exhibited constant release kinetics. All of the SAM-coated surfaces showed a biphasic drug release behavior that is an initial burst release followed by a slow and constant release. The SAM-coated Al_2O_3 grit-blasted surfaces extended the constant release of PAT (close to 1 μg/day) significantly during the second week of the elution test. However, at different time points, the magnitude of the drug released have no notable differences between the roughened surface prepared using Al_2O_3 (50 or 110 μm) or glass (50 or 110 μm). The reason for this result is that the flat alloy surfaces had been covered by $-COOH$ terminated phosphonic acid SAMs. There is lots and lots of hydrogen bonding interplay between the $-OH$ groups of the PAT and the $-COOH$ groups of the SAMs. Therefore, the stability of the PAT on these modified surfaces increased.[47]

4.2. Application of Absorbable Stents. The traditional stents have the risk of preventing surgical revascularization, vascular inflammation, and neoatherosclerosis, which were caused by a foreign body within the artery.[89] Bioresorbable vascular scaffolds (BVSs) are a relatively new technology that is introduced to overcome these drawbacks. BVSs can sustain the vessel structures for a certain time until they gradually forfeit their mechanical support because of biodegradation and finally disappear. In addition, BVS may also be designed to have a drug coating layer to deliver antiproliferative agents to depress neointimal hyperplasia.[90]

4.2.1. Polymer Stents. Bioresorbable polymeric materials contain bioresorbable polyesters, polyurethanes, polyanhydrides, polyorthoesters, poly(amino acid), poly(ester amide), and tyrosine-derived polycarbonates. Among them, polyesters have been widespreadly applied in medical devices, which include PCL, poly(D-lactide) (PDLA), PLLA, PDLLA, polyglycolide (PGA), poly(trimethylene carbonate), and their copolymers.[91] Currently available polymer-based BVSs tested in clinical trials as shown in Table 4. The ABSORB everolimus stent is the only drug-eluting BVS that is currently undergoing clinical trials. PLLA has been widely used as the material for the development of various BVS. Both the first generation (ABSORB Revision 1.0) and the second generation (ABSORB Revision 1.1) have the same backgone of PLLA, 1:1 mixture of an amorphous matrix of PDLLA and 8.2 μg/mm of everolimus. Their drug release rate were similar.[92,93]

The most popular used synthetic polymers are polyesters. However, their degradation via hydrolysis of ester bonds in the polymer chain can release acidic degradation products to lead to a strong inflammatory response. Because of the poor wettability and lack of cellular attachment, their hydrophobicity can be also unfavorable in tissue regeneration applications. Polyurethane (PU) is an attractive candidate for scaffold fabrication, which shows moderate biocompatibility and excellent mechanical flexibility and mechanical properties.[94] On the basis of bioactive glass and hydroxyapatite, porous polyurethane NPs scaffolds were prepared that were surface-coated with a uniform polymeric layer, embedded with thermo-stable PU-based NPs, comprising an antiinflammatory drug indomethacin (IDMC). In vitro drug release indicates that approximately 15−20% of the drug released within the initial 3 h of incubation, followed by a constant IDMC release during the first week of incubation (65−70% of the loaded-drug), without further release detected in the following days.[95] However, the effect of PU used for the preparation of the coronary stents still need further experiment.

4.2.2. Metal Stents. For the bioresorbable metal scaffolds, most studies have been focused on magnesium (Mg) and iron (Fe) and Mg- or Fe-based alloys.[91] Magnesium metal is popular in coronary stents because of its excellent properties, including a high strength to weight ratio, excellent vibration and shock absorption, good thermal and electrical conductivity, a high damping capacity, and electromagnetic shield performance.[96] Currently available magnesium-based biodegradable stents tested in clinical trials as shown in Table 4. The main disadvantage of Mg and Mg alloys is their rapid corrosion behavior before injured tissues heal. Therefore, a solid and slower degradation of surface coating is requisite, which can not only alleviate degradation rate of magnesium stents, but also can better regulate the release of the drug. To optimize the biodegradation rate and the drug release rate, we adopted a new method in the design of a Mg-based stent, which mainly aimed at fabricating a microarc oxidation/PLLA (MAO/PLLA) coating mixture on the magnesium alloy AZ81 substrate. The microcracks and microholes on the surface of the MAO coating were effectively sealed by the PLLA to give controllable biodegradation.[97] The coating containing one PLGA/PAT layer and one pure PLGA blank layer also functions to provide controlled biodegradation rate of the stent. The drug release rate of PAT showed nearly linear sustained-release kinetics with no obvious burst releases: 7.5% (15 days), 10% (30 days), and 20% (50 days), whereas 80% PAT was released on 25 days without a top blank PLGA.[97]

Table 4. Bioresorbable Vascular Stents Take Drug That Are under Preclinical and Clinical Evaluation[a]

stent name	strut material	drug (concentration)	coating method	manner or mechanism of controlled release	drug release rate (days)	coating thickness (μm)	strut thickness (μm)	resorption time (months)	refs
absorb BVS A/B (Abbott Vascular, Santa Clara, CA, USA)	PLLA	everolimus (8.2 μg/mm)	stent coated with a thin layer of a 1:1 mixture of an amorphous matrix of PDLLA incorporated with everolimus	slow elease membranes Hydrolysis, diffusion and dissolution	80% (28)	N/A	150	24	92
ReSolve/ReZolve (REVA Medical, San Diego, CA, USA)	tyrosine poly carbonate with iodine	sirolimus	coating material is absorbable polymer with sirolimus (abluminal)	hydrolysis, degradation and erosion	100% (>30)	N/A	114−228	48	92
IDEAL BTI (Xenogenics Corp.; Canton, MA, USA)	the backbone consists of polylactide anhydride mixed with a polymer of salicylic acid with a sebacic acid linker	sirolimus (8.3 μg/mm)	the backbone of the stent is coated by a drug layer of sirolimus and salycilate	hydrolysis, degradation and erosion	elution over 30 days	N/A	200	9−12	100
Xinsorb (Huaan Biotechnology, Laiwu, China)	PLLA	sirolimus (8 μg/mm)	PDLLA mixed with PLLA, carrying sirolimus, was coated on the stent struts	degradation and erosion	ex vivo: 80% (28)	N/A	150	N/A	101
DREAMS 1 (Biotronik, Berlin, Germany)	Mg alloy	paclitaxel (0.07 μg/mm^2)	PLGA containing paclitaxel	slow elease membranes, degradation,dissolution	N/A	1	120	9	102
DREAMS 2 (Biotronik, Berlin, Germany)	Mg alloy	sirolimus (1.4 μg/mm^2)	PLA containing sirolimus	slow elease membranes, degradation,dissolution	N/A	7	125	4−6	103

[a] N/A, no application; PLLA, poly(L-lactic acid); PDLLA, poly(D,L-lactide).

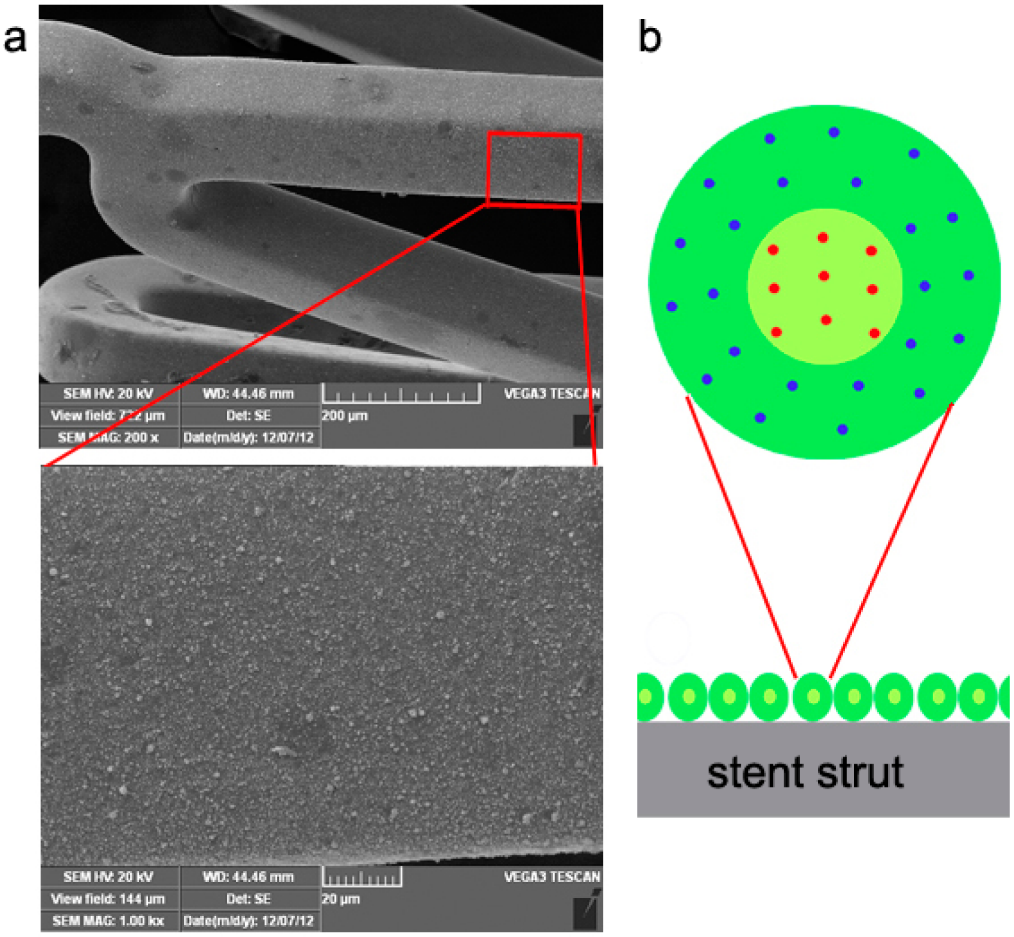

Figure 4. (a) SEM of the DES and (b) the nanoparticle structure diagram of the stent's coating surface. The red color represents the endothelialization-promoting drugs, and the blue color represents the antiproliferative drug.

A protective surface coating strategy based on the electrodeposition of self-assembled colloidal NPs may stably load and release drugs in a controlled manner. The substrate functionalized with colloidal particles containing a vitamin obvioustly improved the attachment, proliferation, and spread of NIH-3T3 cells (a mouse embryonic fibroblast cell line).[98] In addition, a lot of magnesium alloy surface coating methods can been used to control the release of drugs.[96,99]

4.3. Development of New Polymers. At present, the polymer is still considered an essential component of a DES. Developing new polymers is also considered very important in promoting the development of DES stents. A novel type of biodegradable nanostructured hybrid polymers, called polyhedral oligosilsesquioxane thermoplastic polyurethanes (POSS TPUs), has been designed, which shows enhanced mechanical properties and has been used in PAT-loaded stent coatings.[104] The polyurethanes possess the characteristics of alternating multiblock structure. The hybrid polyurethane family can effectively control the drug release rate by variations in the polymer glass transition temperature, degradation rate, and incremental thickness rate.[104] Another nanocomposite polymer is polyhedral oligomeric silsesquioxane poly(carbonate-urea) urethane (POSS−PCU), which can function as a component of artificial organs, as a coating for NPs, and as a platform on which bioactive molecules can be attached, the latter of which has been used in DES coatings with covalently attached anti-CD34 antibodies.[105,106]

To screen a stent coating or platform material, Busch et al. have investigated the impact of the VSMCs, VECs, and platelets with various biostable polymers and biodegradable polyesters. The biostable polymers include PBMA and PEVA. The biodegradable polyesters include PLLA, poly(3-hydroxybutyrate) (P(3HB)), poly(4-hydroxybutyrate) (P(4HB)), and a polymeric blend of PLLA/P(4HB) in a weigh ratio of 78/22%. Both PLLA and P(4HB) inclined to a more thrombotic potential, whereas only the PLLA/P(4HB) obtained wonderful endothelial markers of biocompatibility and a lower thrombotic response.[107] Therefore, the PLLA/P(4HB) is a distinctly promising material for vascular stents coatings. A shape-memory terpolymer has also been studied as an antirestenotic drug carrier for DES. Using the zirconium acetylacetonate $Zr(Acac)_4$ as an initiator of ring-opening polymerization, a terpolymer was synthesized from L-lactide, glycolide, and oligotrimethylene carbonate. The terpolymer has shape-memory properties and was used to obtain double layer matrices composed of the drug-free matrix and the PAT-containing layer.[108] An in vitro study established that the polymer's degradation proceeded regularly. All of the matrices released very small amounts of the drug and provided even PAT release profiles during 15 weeks of degradation with no burst effects. The double-layer system allowed for the modification of the amount of the drug released, which may be useful in developing self-expanding drug-eluting stents that are tailored for different clinical indications.[108]

4.4. Application of Nanocarriers. The cell can absorb nanocarriers more easily than larger molecules. As the currently available bioactive compounds, nanocarriers with excellent biological and physicochemical properties can be successfully used as delivery tools. Some nanocarriers, such as liposomes (80−300 nm), solid lipids NPs (80−300 nm), dendrimers (1−10 nm), polymers (10−100 nm), silicon or carbon materials (1−5 nm), and magnetic NPs (10−300 nm), have been tested as drug delivery systems to control the release of a drug.[109] A drug may be taken up or covalently adhered to the surface of nanocarriers or be wrapped into the nanocarriers. Although there are many types of nanometer carriers, this review primarily introduces the NPs, nanoporous and nanofibers.

4.4.1. Nanoparticles. A number of recent studies have focused on the preparation of different NPs that have the ability to carry different drugs or biomolecules and to achieve the effects of a slow drug release. In the light of a time-programmed opinion of biofunctionality for blood vessel stents, heparin/poly(L-lysine) nanoparticles (Hep/PLL NPs) were prepared by an intermolecular electrostatic interaction and then immobilized on a polydopamine-coated titanium surface. An in vitro study indicated that the NP-immobilized surface showed a rapid Hep release behavior at the start, with a cumulative release amount reaching 7.8 ± 1.5 μg at day 10 and a residual Hep amount of 5.2 ± 0.6 μg. Then, the Hep release curve reached its plateau, with 3.8 ± 0.5 μg remaining on the NP-immobilized surface after 28 days.[10] In addition, a small particle size and good particle stability can effectively slow the drug release. NPs have a much larger surface area compared with a solid film structure. The high intermolecular binding force in NPs may provide better control of a sustained Hep release.[110]

Combining the grooves and NPs, Yang et al. have obtained a better drug release effect.[111] Using a multistep emulsion technique, the bilayered PLGA (50/50) nanoparticles (BL-PLGA NPs) were prepared. BL-PLGA NPs contains VEGF plasmids in the outer layer and PAT in the inner core. A stent was coated with BL-PLGA NPs to ensure the early release of the VEGF gene and a slow release of the PAT. The early release of the VEGF gene in the outer layer would facilitate re-endothelialization, whereas the slow release of the PAT in the inner core would inhibit the VSMCs proliferation. To determine the BL-PLGA NPs release from the stent, Rhodamine B was loaded onto a NPs-coated stent. The fluorescence intensity of the Rhodamine decreased gradually but remained at a detectable level after shaking in PBS for 30 days, which suggested the stability of the BL-PLGA NPs coating layer and its better slow-release effect.[111] In our lab, a uniform nanoparticle-coated stent has been prepared using coaxial electrostatic spraying technology (Figure 4), and this type of a nanoparticle-coated stent can carry many types of drugs and has a good slow-release effect.[112]

4.4.2. Nanoporous. The strategy of using nanoporous carriers to control drug release is based on modifying the nanopore/nanotube structures, controlling the pore openings and using polymeric micelles as the drug nanocarriers.[113] The novel polymer-free paclitaxel-eluting stent (nano-PES) possesses a nanoporous surface. Compared with the polymer-based sirolimus-eluting stent (SES), nano-PES can more effectively and more rapidly deliver and release the drug to the local coronary artery, which are beneficial to the rapid endothelialization of the nano-PES. Therfore, nano-PES showed a rapid surface coverage and less fibrin deposition, and inflammation.[114] Currently, nanotubular titania (TNT) and nanoporous anodic alumina (NAA) are most commonly used due to their outstanding properties, such as mechanical robustness, stability, chemical resistivity and inertness, nontoxicity, excellent biocompatibility, high surface area, and controllable nanotube thickness (1−300 μm) and diameters (10−300 nm)). The TNT and NAA nanopores have emerged as reliable contenders for these applications.[115] The nanoscale topography on metallic Ti stents was prepared through an alkaline hydrothermal route. This type of nanostructured Ti surface is antithrombogenic, can promote endothelialization, and may be a cost-effective alternative to using drug-eluting stents or polymer-coated stents to overcome ISR.[116]

A nanobiohybrid hydrogel-based endovascular stent device has also been developed. The hydrogel consists of fibrin matrices, which were assembled layer-by-layer on the stent surface, with alternate layers carrying endosomolytic Tat peptide/DNA NPs or hybrid NP-CNT. The hybrid NP-CNT is that NPs hybridized to poly(acrylic acid) wrapped single-walled carbon nanotubes, which is formed by the electrostatic bond (ionic bond). The NP-CNT can work as a reservoir to carry, protect, and deliver the VEGF, pro-angiogenic, Angiopoietin-1, gene-carrying NPs to the target site. This method provides the flexibility of changing the release profile of the NP from the stent by adjusting the concentration of the CNTs.[117]

4.4.3. Nanofibers. Polymer nanofibers have attracted much attention due to their unique properties, such as a small pore size, high porosity, large surface area, superior mechanical properties and the ease of adding surface functionality compared with other materials.[118] Some polymers have been electrospun into ultrafine fibers.[119] Their high surface to volume ratio can increase drug loading, cell attachment, and mass transfer properties. The drug release profile depends upon the drug diffusion in the carrier polymer and the degradation rate of the polymer.[120]

The critical experimental parameters for determining the size and shape of the electrospun fibers include the concentration, viscosity and surface tension of the polymer solution, air gap distance, applied voltage, and solution delivery rate. The distribution state of the drug in the fibers can be controlled through changing experimental parameters and the drug release behavior is improved accordingly.[121] Oh et al. prepared a nanofiber (NF) stent combined with NPs, in which Eudragit nanoparticles (ES-NPs) were used as a carrier of β-estradiol. Using a quasi-emulsion solvent diffusion technique, ES-NPs and 4 modified types were prepared. Among them, NP-CHA (ES-NPs containing a chitosan layer were first added into H_2O, and then was blended with HFIP (1:1(v/v) with 15% PLGA) exhibited a constant release kinetics. During the first week, the release of β-estradiol gradually increased and then reached the balanced state, which showed no burst release phenomenon.[122]

4.5. Improvement of Coating Technology. To date, a variety of coating methods have been developed for use with DES. Nevertheless, these available methods have been used to a limited extent in practical applications because of an inadequate loading dose and low deposition rate, complicated programming, and imperfect positioning of the stent, and coatings that are not robust enough to withstand in vivo long-term exposure.[123] Therefore, the improvement of the coating technology is also a very important aspect, including the development of new coating technology, optimizing the existing coating processes, combining different coating methods, etc.

Wang et al. prepared a PDA for a stent surface modification by combining a self-polymerization and electrochemical method.[107] In their work, a facile and rapid approach for the surface modification of metallic and electroconductive substrates with complex three-dimensional shapes was developed through the electropolymerization of dopamine (ePDA). Compared with the classical approaches, the electrochemical method exhibited a higher deposition rate and was more efficient in utilizing the dopamine. The deposition kinetics of the classical PDA coating differed under different conditions, e.g., in the self-polymerization of the PDA at a pH 8.5 in the presence of O_2, the coating thickness increased rapidly during the initial 0.5 h and then gradually tended to plateau. In contrast, using electrochemical methods, the ePDA in deoxygenated solutions at a pH 7.4 always exhibited a much higher coating thickness (over 5 times).[124] Another study generated structural nanocomposites using a combination of electrospinning and electrospraying to prepare core−sheath fibers, in which Eudragit1 L100−55 and PVP were used as the core and sheath matrices, respectively.[125] In vitro, the core−sheath fibers exhibited dual drug release kinetics with a burst release of 35.1% in an acidic medium and a constant release of 62.2% in PBS medium (pH 6.8).[125] This advanced strategy greatly develops the applications of the electrohydrodynamic atomization processes in generating novel structural nanocomposites for complex and time-ordered drug release behavior.

5. CONCLUSIONS AND REMARKS

This review primarily discussed the various factors influencing drug release, including the polymers, drugs, coating strategy, drug storage and elution direction, hemodynamics, and other factors. The review also presented strategies for controlling the drug release rate, which include preparing grooves in the surface of the stent, using nanoscale carriers, developing new polymers, and improving coating technology.

In the future, the greatest challenge of DES primarily lies in maintaining a balanced relationship between inhibiting ISR and promoting re-endothelialization. Most of the research has attempted to capture molecules as a stent coating to capture the stem cells, such as EPCs, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs), to repair the endothelial damage. However, it should be recognized that the specific surface markers of the stem cells are not fully understood, and how the stem cells directly differentiate into specific cells and the mechanisms of differentiation remains unclear. These difficulties hinder the development of this technology.[126] In view of the VECs injury, the most promising and effective developments are in biomimetic surface engineering, which includes the two aspects of mimicking the extracellular matrix function and mimicking the endothelial function.[127] The antiproliferative drugs have no specificity, which not only inhibits the VSMCs proliferation but also prevents the VECs proliferation, and inversely delays the endothelialization. It is very significant to control the drug release behavior from DES to conform to the time-programmed pathological change and to apply a stage-adjusted remedy. The following are some strategies for controlling drug release: (1) Use grooves and cavities on the stent struts made by laser engraving. In this case, the stent needs to have a good biocompatibility and mechanical properties with appropriate ductility and flexibility. (2) Construct nanocarriers, such as NPs, nanoporous, and nanofibers. Nanocarriers provide a greater surface area to store drugs and minimize the chances of local drug toxicity. For the core−shell structure nanocarrier, the drug placed in the shell will be released first, while the inner drug loaded in the core will be released afterward. This drug-carrying mode is more suitable for the in vivo pathologic repair process. (3) Combine new biological absorbable stent material and drug carriers with the drug or biological molecules as well as the relevant gene NPs, which can specifically inhibit the VSMCs proliferation. (4) Develop a new coating technology and optimize the existing coating methods to achieve an excellent binding force and smooth surface coating.

In any case, drug release is a very complicated process, and there are numerous interference factors in both in vivo and in vitro conditions. There is an urgent need for the achievement of reasonable drug release behaviors. To achieve the time-ordered release of DES, a novel controlled slow-release DES is an important development direction to pursue. Therefore, we need to understand the mechanisms of ISR and combine new scaffold materials, drug, drug carrier, and coating technology to prepare an ideal controlled slow-release DES. In addition, real-time monitoring systems for drug release are also particularly important to accurately quantify the drug release rate.

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