Expert Opinion

Stents as a platform for drug delivery

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Introduction: Drug delivery stents have proved their efficacy at preventing coronary restenosis and their potential in treating the occlusion or stricture of other body passageways, such as peripheral vessels and alimentary canals. The drug delivery systems on such stent platforms contribute to this improved therapeutic efficacy by providing improved drug delivery performance, along with reduced concerns encountered by current stents (e.g., in-stent restenosis, late thrombosis and delayed healing).

Areas covered: A wide variety of drug delivery stents (metallic drug-eluting stents, absorbable drug-eluting stents, and polymer-free drug-eluting stents for coronary and other applications) that are commercially available or under investigation are collected and summarized in this review, with emphasis on their drug delivery aspects. This review also gives insights into the progression of stent-based drug delivery strategies for the prevention of stent-related problems, or the treatment of local diseases. In addition, a critical analysis of the advantages and challenges of such strategies is provided.

Expert opinion: With an in-depth understanding of drug properties, tissue/organ biology and disease conditions, stent drug delivery systems can be improved further, to endow the stents with better efficacy and safety, along with lower toxicity. There is also a great need for stents that can simultaneously deliver multiple drugs, to treat complex diseases from multiple aspects, or to treat several diseases at the same time. Drug release kinetics greatly determines the stent performance, thus effective strategies should also be developed to achieve customized kinetics.

Keywords: bioabsorbable stents, drug delivery system, drug release kinetics, drug-eluting stents, gene delivery, in-stent restenosis, multiple drug delivery

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1. Introduction

A stent is a hollow cylindrical device that is used to support and keep strictured or obstructed body conduits or tubular organs open in order to allow the fluid to run through. Despite its modern connotation, which has been widely adopted in interventional therapy, the term stent traces back to a nineteenth century English dentist, Charles Thomas Stent (1807 – 85), who used it to describe a mold for inlay grafting [1]. Nowadays, stents have been widely used for the treatment of occlusion or stricture of tubular body structures, such as blood vessels [2-4], esophagus [5], biliary tract [6], pancreatic duct, urethra [7,8], colon, trachea/bronchus and nose [9], thanks to its desirable ability in providing mechanical support or expanding the lumen. Notwithstanding, in-stent restenosis is frequently encountered in stenting therapy as a result of tissue/body reactions (such as hyperplasia, inflammatory reactions and platelet aggregation) in response to tissue wall injury, the presence of a foreign body and/or benign/malignant overgrowth resulting from occlusive tumor [10,11].

More recently drug delivery stents emerged, and revolutionized the treatment of body conduit or tubular structure diseases by virtue of their dual functions of providing mechanical support and releasing drug to prevent restenosis or to treat

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Article highlights.

- A wide range of drug delivery systems have been applied on stents to elute drugs for preventing in-stent restenosis or treating local diseases.
- Drug delivery through metallic stents is usually achieved by polymer coating, polymer reservoirs, or non-polymer porous structures.
- Bioabsorbable polymeric stents incorporate drug in a coating or in the bulk, and release them in a controlled manner. The whole stents can be absorbed after a certain time.
- There is a great need for stents that can simultaneously deliver multiple drugs to treat complex diseases from multiple aspects or to treat several diseases at the same time.
- Gene delivery could presumably be realized in the next generation of stents to conduct gene therapy.
- Drug release kinetics greatly determines the stent performance, thus effective strategies should be developed to achieve customized kinetics.
- Mechanical performance is the basic function of a drug delivery stent and should be given priority over the drug delivery performance.

This box summarizes key points contained in the article.

malignancy positively. As such, drug delivery stents serve not only as scaffolds providing support for the occluded tubular organs or structures, but also as drug delivery systems for tissue healing, therapeutic management of benign/malignant stricture, or prohibiting the possible adverse reactions related to stent implantation. Thanks to the tremendous advances made over the past decade, drug delivery stents are widely used for the treatment of stenosis/stricture and occlusion resulting from diseased bodily tubular organs or structures.

Drug delivery stents are generally composed of three components: the stent platform, delivery system (carrier material and delivery construct), and the therapeutic agent [12]. They can be divided roughly into two categories: metallic stents and polymeric stents. Metallic stents are made from a variety of metals [13,14], such as 316L stainless steel, tantalum (Ta), cobalt-chromium (Co-Cr) alloy, nickel-titanium (Ni-Ti) alloy, magnesium (Mg) alloy and platinum-chromium (Pt-Cr) alloy; whereas the polymeric stents use biocompatible or bioinert polymers as the backbone. Among the metallic stents, the Mg alloy stent can be absorbed in the form of inorganic salts [14]. With regards to polymeric stents, biodegradable polyesters or polyanhydrides [15-17], polylactide (PLA), poly(lactide-*co*-glycolide) (PLGA), poly(ε-caprolactone) (PCL) and polysalicylate, to name but a few, were used extensively as backbone materials. They degrade eventually into small molecules (e.g., carbon dioxide and water) that can be metabolized and eliminated by means of the human metabolic pathway. The bioabsorbable stents may hold great promise in the next generation of drug delivery stents. In terms of bioactive agents, antiproliferative, antimetabolic, immunosuppressive, antibiotic and cardiovascular (e.g., antihyperlipidemic and antithrombotic) drugs have been used (**Table 1**). These drugs have proved effective at treating a variety of factors that result in restenosis. The action mechanisms of such drugs include: blocking cell proliferation; improving vascularization; killing tumors; and inhibiting bacterial adherence, inflammation and platelet aggregation.

The drug delivery function is a distinguishing feature of the drug delivery stents compared with conventional stents, and it may provide many advantages, including: i) avoiding excessive systematic exposure to drugs; ii) bypassing the first-pass effect, possessing high drug availability; and iii) achieving highly efficient diseased site-specific delivery. The local tissue drug concentration generated by a drug delivery stent can be thousands of times higher than those produced by traditional systemic routes; the drug concentration in target tissue could also be much higher than in the other tissues or liver [18]. For drug delivery, all kinds of delivery system consisting of carrier materials are usually applied on the metal platform (**Table 2**). They serve as drug reservoirs and release-limiting networks to carry sufficient amounts of drug and release drug in desirable patterns, so as to determine the drug delivery performance. Although carrier materials are not necessitated in some newly developed drug delivery stents [19,20], they are critically important for most drug delivery stents to carry drug and control drug release.

Without detailing all the aspects related to stents, this review aims to present an in-depth summary and analysis of the drug delivery aspects of drug delivery stents that are commercially available or under investigation, discuss the recent challenges and breakthroughs in developing drug delivery systems with better efficacy and safety, lower toxicity, and put forward some strategies for optimizing drug release.

2. Metallic stent-based drug delivery platforms

2.1 Drug-containing membrane-covered stents

A drug-containing membrane-covered stent usually consists of two parts, the bare metallic stent and a drug-containing membrane (also known as a stent sleeve or sheath) that is wrapped around the stent (**Figure 1A**). This type of stent is mainly developed and used for treating non-vascular benign/malignant narrowing [5,6], repair of vessel rupture, and coverage of thrombotic and degenerate plaques in old aortacoronary vein grafts, aneurysms and arteriovenous malformations [21]. However, they are rarely used in coronary diseases. Drugs loaded in the membrane include antitumor, anti-inflammatory and antibiotic agents as well as those for tissue healing. In esophageal, choledochal, tracheal and intestinal tumor treatments, they are used to keep patency and release antitumor drug to prevent the continued in-growth and overgrowth of tumor cells around the ends of the stent [22]. They are also preferable in the treatment of fistulas in a wide range of organs, such as arteriovenous,

Table 1. Summary of reported drugs delivered from drug delivery stents.

Drug type	Drug	Action mechanism/function	Stent application
Antiproliferative	Paclitaxel	Paclitaxel inhibits cell processes that are dependent on microtubule turnover, including mitosis, cell proliferation and cell migration [10]	Coronary (TAXUS™ stent, Boston Scientific [2]; Infinnium™ stent [4], Sahajanand); Biliary (a membrane-covered metallic stent [6])
	7-Hexanoyltaxol (QP2)	It is an antiproliferative and anti-inflammatory substance that interferes with the proliferation, signal transduction and migration of vascular smooth muscle cells, thus contributing to the reduction of neointimal growth [70]	Coronary (QP2-eluting Quanam QueST stent, Boston Scientific [70])
	Actinomycin	Actinomycin inhibits DNA-primed RNA synthesis and is used for the treatment of various malignant neoplasmas (e.g., Wilms' tumor, sarcomas, carcinoma of testis and uterus)	Coronary (Multi-Link Tetra™-D, Guidant [71])
	Angiopeptin	It reduces the tissue response to growth hormone, insulin-like growth factor and interleukin-1-mediated endothelial cell adhesion [72]	Coronary (angiopeptin-eluting BiodivYsio DD PC-coated stents [72])
Antimetabolic	Fluorouracil (5-FU)	Fluorouracil is commonly used against many cancers, namely, colon, stomach, breast and pancreatic cancers. Its active form (FdUMP) inhibits DNA synthesis by inhibiting the normal production of thymidine [46]	Esophageal (a 5-fluorouracil-containing PEVA membrane-covered metallic stent [5])
	Methotrexate	Methotrexate is a folate antagonist and is widely used in the treatment of proliferative diseases such as Crohn's disease, cancer, rheumatoid arthritis and psoriasis [73]	Coronary (a methotrexate-coated stent [73])
Immunosuppressive	Sirolimus (rapamycin)	Sirolimus blocks G1 to S cell cycle progression by interacting with and inhibiting the activation of protein mTOR [10]	Coronary (Cyper™ stent and Nevo™ stent [3], Johnson & Johnson; YUKON® stent [74], Translumina; Combo™ Bio-engineered stent [43], OrbusNeich; Supralimus™ stent [68], Sahajanand; IDEAL™ stent [17], Bioabsorbable Therapeutic)
	Biolimus A9	As a highly lipophilic derivative of sirolimus, Biolimus A9 inhibits T-cell and smooth muscle cell proliferation and was designed for use in drug-eluting stents [32]	Coronary (BioMatrix™ stent [25] and BioFreedom™ stent [32], Biosensors; Nobori™ Stent [74], Terumo Corp.)
	Novolimus	Novolimus is a metabolite of sirolimus and has a similar efficacy to the available -limuses [76]	Coronary (Elixir DESyne novolimus-eluting stent [76], Elixir Medical)
	Myolimus	As a macrocyclic lactone drug in the same family as sirolimus, myolimus has demonstrated impressive versatility, stability and a broad therapeutic index	Coronary (Elixir myolimus-eluting stent [77], Elixir Medical)
	Tacrolimus (FK506)	Tacrolimus is a hydrophobic immunosuppressive macrolide that inhibits several steps of the cascade of events leading to neointimal proliferation and prevents renal and liver transplant rejection	Coronary (Janus® tacrolimus-eluting stent [78], Sorin Biomedical); Urethral stricture [79]
	Zotarolimus (ABT-578)	As a more lipophilic analogue of sirolimus, zotarolimus blocks progression from G1 to S in the cell cycle and inhibits smooth	Coronary (Endeavor® stent [80], Medtronic; Zomaxx™ phosphorylcholine (PC) polymer-coated stent [81], Abbott, CA, USA)

Table 1. Summary of reported drugs delivered from drug delivery stents (continued).

Drug type	Drug	Action mechanism/function	Stent application
		muscle cell proliferation. It is also known to suppress a lymphocyte-mediated inflammatory reaction [80]	
	Dexamethasone	Dexamethasone is a steroid anti-inflammatory drug showing inhibitory effects on the systemic inflammatory responses [82]	Coronary (Dexamet™ stent [82], Abbott); Bronchial [83]; Transjugular intrahepatic portosystemic shunt tract [84]
	Everolimus	Everolimus, an analogue of sirolimus, is an immunosuppressive and antiproliferative agent [85]	Coronary (XIENCE™ stent [85] and BVS biodegradable stent [42], Abbott)
	Prednisolone acetate (PA)	PA is a water-insoluble steroidal drug and possesses anti-inflammatory and antiproliferative functions [86]	Coronary (a helical film-based biodegradable PLGA stents [86])
	Cyclosporine A	It is an immunosuppressive drug used in renal, cardiac, pancreatic and hepatic transplantations	Coronary (a metal stent coated with PLLA/ Cyclosporine A [87])
	Leflunomide	Leflunomide is a pyrimidine synthesis inhibitor that exerts potent anti-inflammatory and antiproliferative effects [29]	Coronary (a custom-made leflunomide-eluting stent based on YUKON® porous stent platform [29])
Antibiotic	Actinomycin D	Actinomycin D forms, via deoxyguanosine residues, a stable complex with double-stranded DNA and inhibits DNA-primed RNA synthesis [71]	Coronary (a custom-made actinomycin-eluting stent based on the Multi-link Tetra™ stent [71])
	Ofloxacin/ciprofloxacin	Ofloxacin and ciprofloxacin are members of fluoroquinolones and have broad spectrum antibiotic activities [8,88]	Urethral (bioabsorbable spiral/braided PLLA stents [8,88])
	Triclosan	Triclosan inhibits the highly conserved bacterial enoyl-ACP reductase, which is responsible for fatty acid synthesis and cell growth [7]	Urethral (Triumph® stent [7], Boston scientific)
	$AgNO_3$	It binds to intracellular proteins and nucleic acids of bacteria, resulting in the cellular distortion and loss of viability of the organism	Urethral (bioabsorbable spiral/braided PLLA stents [8])
	Echinomycin	It binds strongly to double-stranded DNA and acts as a molecular staple, sandwiching two base pairs within its U-shaped conformation [11]	Coronary (an echinomycin-eluting stent topcoated with a heparin-containing polymer [11])
Protein	Anti-CD34 Antibody	Anti-CD34 antibody can specifically capture $CD34^+$ cells circulating in the blood to form an endothelial layer that improves healing and provides protection against thrombosis and modulates restenosis [89]	Coronary (Combo™ Bio-engineered stent [89], OrbusNeich)
Gene	A recombinant adenovirus DNA	The adenovirus carries a nuclear-localizing β-galactosidase reporter gene. The *in vivo* expression of the reporter gene can demonstrate the success of gene delivery via the stent [57]	Intravascular (a bioresorbable microporous vascular PLLA/PCL stent [57])
	Green fluorescent protein (GFP) plasmid DNA	The cells expressing GFP can demonstrate the successful delivery and transcription of plasmid DNA [56]	Coronary (a customized PLGA-coated stent modified from the Crown™ stent [56])
	Plasmid DNA phVEGF-2	The plasmid DNA encodes human vascular endothelial growth factor (VEGF) and achieves reductions in neointima formation while accelerating, rather than inhibiting, re-endothelialization [54]	Intravascular (a modified BiodivYsio® stent with the phosphorylcholine polymer coating incorporated with phVEGF-2 plasmid [54])

Table 1. Summary of reported drugs delivered from drug delivery stents (continued).

Drug type	Drug	Action mechanism/function	Stent application
Cardiovascular/blood system agent	Cerivastatin	Cerivastatin can inhibit neointimal hyperplasia and reduce stent-induced inflammatory responses [13]	Coronary (a stainless steel stent coated with a thin layer composed of serivastatin and polymers [13]; a polymer-free cerivastatin-eluting stent [90])
	Atorvastatin	Atorvastatin is used for lowering blood cholesterol, stabilizing plaque and preventing strokes through anti-inflammatory and other mechanisms	Coronary (a atorvastatin-coated stent modified from the BiodivYsio™ stent [91])
	Abciximab	It blocks the final pathway of platelet aggregation, reacts to Vβ3 receptor of vascular smooth muscle cell and to Mac-1 of macrophage, and inhibits proliferation of vascular smooth muscle cells and inflammatory reaction [92]	Coronary (a abciximab-coated stent prepared by attaching abciximab onto the metal MAC™ stent surface [92])
Hormone/steroid	Mometasone furoate (MF)	It reduces postsurgical edema and inflammation [9]	Maxillary sinuses (a bioabsorbable self-expanding PLGA stent [9])
	17β-estradiol	17β-estradiol can inhibit intimal proliferation and accelerate endothelial regeneration after angioplasty, not delaying endothelial regrowth and avoiding the risk of late stent thrombosis [93]	Coronary (A 17-β-estradiol eluting stent modified from the BiodivYsio™ stent [93])

esophageal, tracheal, esophagorespiratory, urinary and external intestinal fistulas [23]. In this application, the integral membrane over the stent strut may function as a tube to substitute temporarily the perforated hollow body passageways, and concurrently release drugs to improve tissue healing.

A distinguishing feature of this type of stent is that only the outside of the membrane sheath contacts the tissue epithelium, with the inside facing the lumen. Hereby, drug release exclusively towards the tissue side is desired. In this regard, Guo's lab has introduced a featured drug-free backing layer on the adluminal side of the drug-loaded membrane [5]. The introduced backing layer has little drug permeability and therefore prevents drug release towards the lumen. This membrane delivers drug efficiently to the tissue without loss of drug from its lumen side.

These stents, however, may undergo significantly higher migration rates. Another shortcoming lies in poor longitudinal flexibility. These could be partly resolved by the application of multiple discrete membrane segments on a single stent to allow part of the metal strut not to be covered, thus improving the flexibility and anchoring ability at the tissue site [24]. Although used in the common bile duct, this type of stent is particularly not suitable for the intrahepatic biliary tree or airways, where the membrane of the stent may block the side branches and disable their normal functions, for example, drainage of bile.

2.2 Drug-polymer layer-coated stents

For this type of stent, the metal struts are coated with thin drug/polymer mixture layers (**Figure 1B**). At present, they are the most used drug delivery stents in clinical applications. It is the polymer coating that carries drug and controls the release of drug from the stent. To achieve good deliverability and *in situ* performance, therefore, several criteria for the polymer coating should be fulfilled: i) good mechanical properties in terms of flexibility and elasticity; ii) stable and long-lasting adherence to the stent surface (suitable for durable coating); iii) good drug release controllability; and iv) the polymer itself or its degradation products should have good biocompatibility. The polymers used in this type of stent could be durable or biodegradable (**Table 2**). The first generation of drug-eluting stents, including the Taxus® (Boston Scientific, MA, USA), Cypher® (Johnson & Johnson, NJ, USA) and Firebird® (Microport Medical, Shanghai, China) stents, all use durable polymers. More recently, many inert polymers with better biocompatibility have been applied, for example, the fluorinated copolymer on XIENCE™ everolimus eluting stent (Abbott) and BioLinx™ polymer system on the Endeavor Resolute™ stent (Medtronic, MN, USA). Even though durable polymer-coated stents have proved successful in reducing restenosis, they still encounter limitations, such as endothelial dysfunction, chronic inflammatory reactions and late thrombogenicity. In this regard, stents coated with biodegradable polymers are of great advantage. Many new drug delivery stents, such as the commercially available BioMatrix® stent

Table 2. Summary of drug carrier materials used on reported drug delivery stents.

Material type	Carrier material	Stent application	Coating characteristics
Durable polymer	Poly(ethylene-co-vinyl acetate) (PEVA) plus poly(*n*-butyl methacrylate) (PBMA)	Coronary (Cyper™ stent [94], Johnson & Johnson)	The coating has two layers, of which the sirolimus-containing base layer is composed of PEVA and PBMA and topcoated with a drug-free PEVA layer [94]
	Poly(styrene-block-isobutylene-block-styrene) (SIBS)	Coronary (TAXUS® stent, Boston Scientific) [2]	The SIBS coating contains paclitaxel
	Polyurethane	Coronary (a customized echinomycin-eluting metal stent [11])	The bare stent surface is precoated with polyurethane (PU) containing the antiproliferative echinomycin, then topcoated with a heparinized polymer layer
	Phosphorylcholine (PC)-based polymers	Coronary (Endeavor® stent [80], Medtronic; Zomaxx™ phosphorylcholine (PC) polymer-coated stent [81], Abbott; Genous™ Bio-engineered R stent™, OrbusNeich; a gene-eluting Iliac Arteries BiodivYsio stent [54])	The hydrophilic phosphorylcholine coating shows excellent blood and tissue compatibility and is designed to serve as the delivery matrix
	Poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP)	Coronary (XIENCE™ everolimus-eluting stent [95], Abbott)	The coating utilizes a two-layer coating system composed of an acrylate primer and a fluorinated copolymer drug reservoir [95]
	PLA plus Poly-*N*-butyl methacrylate	Coronary (Elixir DESyne Novolimus™-eluting stent, Elixir Medical) [76]	Both polymers are applied to the surface of the stent, without a primer polymer coating underneath, using a proprietary spray process [96]
	BioLinx™ polymer system (blend of a hydrophilic C19 polymer, polyvinyl pyrrolidone (PVP), and a hydrophobic C10 polymer)	Coronary (Endeavor® Resolute stent [67], Medtronic)	The C19 polymer elutes drug quite rapidly, PVP in the blend offers the initial drug burst and enhances the overall drug elution rate. C10 polymer also provides adequate hydrophobicity and rigidity to the blend [67]
Biodegradable polymer	PLA(PLLA or PDLLA)	Coronary (BioMatrix™ stent [24], Biosensors; Nobori™ stent [75], Terumo Corp.; JACTAX HD stent [15], Boston Scientific; BVS stent, Abbott; Axxess™ Plus stent, Devax; Excel™ stent, JW Medical)	—
	PLGA	Coronary (Nevo™ stent, Johnson & Johnson; MAHOROBA® stent [97], Kaneka Corp.; Conor CoStar™ stent, Johnson & Johnson ; Stellium™ stent, DISA Vascular [63]; eucaTAX stent, Eucatech [16]); Urology (a series of biodegradable stents [36])	—
	PLLA plus PCL	Intravascular (a bioabsorbable microporous stents delivering recombinant adenovirus DNA [57])	The adenovirus DNA is incorporated throughout the whole stent matrix
	BioPoly™ (a biodegradable copolymer combination of PLLA and PLGA)	Coronary (BioMime™ stent [98], Meril)	—

Table 2. Summary of drug carrier materials used on reported drug delivery stents (continued).

Material type	Carrier material	Stent application	Coating characteristics
	SynBiosys™ polymer (a poly(ether ester) block copolymer composed of blocks of dl-lactide, glycolide, ε-caprolactone and polyethylene glycol	Coronary (Sparrow® stent [99], CardioMind)	—
	A mixture of biodegradable polymers PLLA, PVP and PLGA	Coronary (Supralimus® stent [68], Sahajanand)	The coating has two layers. The base layer consists of PLLA, PLGA (50/50), PVP and 35% of sirolimus; the outer layer is only PVP
	A mixture of biodegradable polymers PLA, PVP, PLGA, PLACL	Coronary (Infinnium™ stent [4], Sahajanand)	The drug is coated in 3 different layers of the coating, and each layer has a different release profile
	Salicylate-based poly-anhydride ester	Coronary (IDEAL™ stent [17], Bioabsorbable Therapeutics)	The drug is coated on the fully bioabsorbable backbone [17]
	Blends of PLLA and poly (4-hydroxybutyrate) (P4HB)	Coronary (a laser-cut balloon-expandable slotted polymer tube stent and a metal stent with a bioabsorbable PDLLA/P4HB/sirolimus coating [16])	The drug is incorporated throughout the fully degradable stent backbone, or incorporated in the coating on the metal stent surface [16]
	ReZorb™ Polymer (a tyrosine-derived polycarbonate polymer)	Coronary (ReZolve™ bioresorbable stent [16], REVA Medical)	The balloon-expandable stent incorporates a new mechanical locking mechanism that may potentially address the issue of acute stent recoil [16]
Inorganic substance	Hydroxyapatite (HA)	Coronary (a polymer-free sirolimus-eluting metal stent with a microporous hydroxyapatite coating impregnated with a sirolimus formulation [100])	The coating is composed of a microporous hydroxyapatite underlying coating [100]
	Al_2O_3	Coronary (a tacrolimus-eluting Al_2O_3-coated stent [34])	The Al_2O_3 coating has a nanoporous structure of ceramics, and the nanoporous aluminum oxide layer is incorporated with tacrolimus [34]

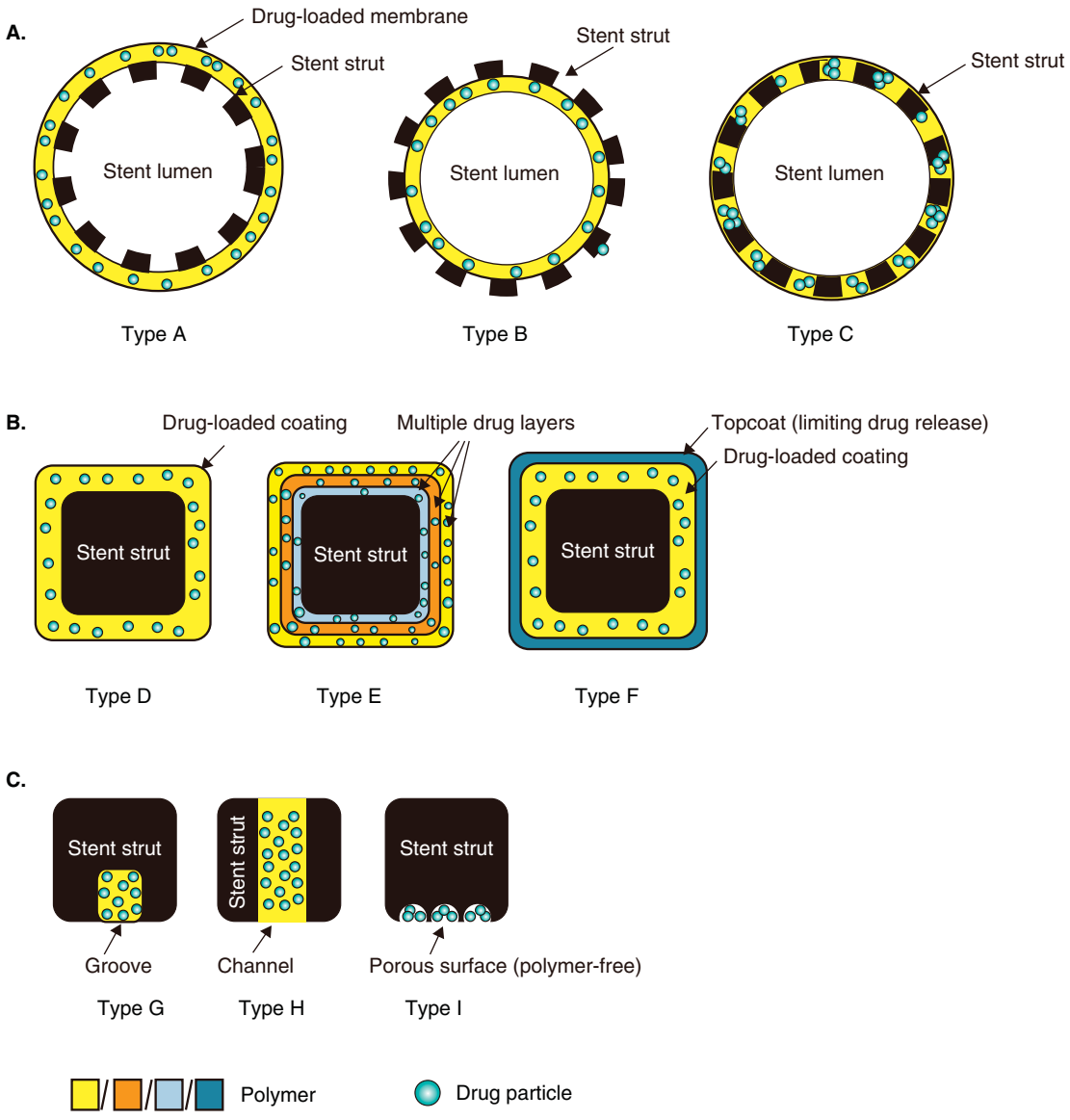

Figure 1. Schematic representation of various drug delivery systems based on metallic stents. A. Drug delivery systems based on stent-covered membranes. The drug-loaded membrane is covered around the outside (Type A), inside (Type B) or contains the stent mesh tube (Type C). **B.** Drug delivery systems based on drug/polymer coatings on stent struts. Type D: the metal strut is coated with a single drug/polymer layer. Type E: the metal strut is coated with several drug/polymer layers. Type F: the drug/polymer layer is topped by a drug-free topcoat. **C.** Drug delivery systems based on reservoirs on stent struts. Type G: the drug/polymer or drug alone is loaded in the grooves within metal strut. Type H: drug/polymer matrix is loaded in the reservoir. Type I: the drug is attached on the porous surface of the metal strut.

(Biosensors, Singapore) [25], Nobori™ stent (Terumo, Tokyo, Japan), Biomime™ stent (Meril, Gujarat, India), Sparrow™ stent (CardioMind, CA, USA), Supralimus™ stent (Sahajanand, Gujarat, India), Infinnium™ stent (Sahajanand, Gujarat, India), JACTAX HD stent (Boston Scientific, MA, USA) and Excel™ stent (JW Medical, Weihai, China), apply biodegradable polymer coatings which are generally based on polyesters including PLA, PGA, PCL and their copolymers. The biodegradable drug-loaded coatings release the incorporated drug while the polymers degrade into small molecules that are eventually absorbed. Drug release from the drug/polymer mixture-coated stent can be tailored by altering both the formulation and pattern of coating. The BioMatrix stent has an abluminal coating, which releases Biolimus A9 exclusively into the vessel wall. It is also worth mentioning the drug-eluting DREAMS (AMS-3) magnesium alloy stent (Biotronik, Berlin, Germany), which incorporates a fast degradable polymer matrix onto the magnesium alloy

backbone for slow release of antiproliferative pimecrolimus [14]. Unlike the permanent metallic stent, the magnesium alloy stent corrodes under physiologic conditions and is fully absorbed as magnesium ions [14].

Unlike the membrane-covered stents, this type of stent has much less drug surface area owing to the meshes between the metal struts. Handicaps derived from this could be non-uniform drug distribution on the stent surface and lower drug loading dose; these flaws may lead to a toxic tissue reaction or treatment failure, owing to much higher drug concentration in the coating-touching tissue but insufficient drug concentration in the stent mesh-located tissue. In another aspect, however, the smaller polymer area may reduce the degree of tissue response to the foreign polymers.

2.3 Drug reservoir-based metallic stents

Apart from the above-mentioned stent-based drug delivery systems, newly proposed reservoirs in the form of grooves, channels, wells and holes are applied for drug delivery (**Figure 1C**). The reservoirs are within the metal struts and filled with drug alone or drug/polymer mixture. Reservoir-based metallic stents are believed to have improved safety because of the significantly reduced polymer surface area. Another advantage of this stent type is that the reservoirs at different sites of the stent can be filled with different amounts of drug to improve drug uniformity or to achieve customized drug distribution for a specific application. Also, the drug distribution can be tailored further by rationally arranging the reservoirs. Polymers (e.g., PLGA and PLA) or other excipients can be used in the drug reservoir to immobilize the drug and, in another aspect, control the release of drug. The deep reservoir wells can contain multiple layers with different formulations to enrich the variety in drug release kinetics [26]. Besides, preferential vectorial delivery is achievable. For penetrating hole-based reservoirs (e.g., NEVO™ stent and doomed Conor™ stent, Johnson & Johnson, NJ, USA), for example, using a slowly degrading polymer on the adluminal side and faster degrading PLGA layers on the abluminal side could orientate drug release towards the tissue wall [26]. In addition, filling the different reservoirs with various drugs holds the promise of simultaneous delivery of multiple drugs. The multiple drugs can have similar effects and be delivered in the same direction for synergetic treatment, or different effects and delivered independently (in different directions) for diverse treatments. However, polymer is not always needed in the reservoir. For the OPTIMA™ JET tacrolimus-eluting stent (CID, Saluggia, Italy), tacrolimus is loaded into the groove reservoir by a proprietary process that melts the drug and allows the drug to coagulate and adhere to the reservoir as a tablet [27], and the drug is released slowly for ~ 3 months owing to its hydrophobic nature [28].

2.4 Polymer-free drug delivery stents

Notwithstanding polymer-based drug delivery stents achieve marked reduction of in-stent restenosis, they have also been proved to be involved with safety concerns, such as late stent thrombosis in arterial applications, reactive or inflammatory response, delayed healing and treatment failure due to the polymers used for stent coating [20,29]. Thus, some researchers have tried to avoid these issues by not using polymers and developed drug delivery strategies by means of polymer-free stents that have rough or microporous surfaces serving as reservoirs for drug (Type I in **Figure 1C**). The simplest approach used for attaching a drug to the metal surface is to dip the stent in the drug solution followed by evaporating the solvent. An interesting study utilized the natural adhesion property of paclitaxel to Co-Cr alloy and successfully prepared a paclitaxel coating on the smooth Co-Cr alloy surface at a dose of 6.2 μg/cm^2 stent surface area; the release was sustained for up to 56 days [30]. The polymer-free ACHIEVE™ stent (Cook, IN, USA) is prepared by Cook's proprietary coating process, which enables the coating of paclitaxel on the 316L stainless steel surface at a dosing density of 3.0 μg/mm^2 [19].

The dip-dry coating method may encounter two problems: premature loss of the attached drug during stent deployment and low drug loading dose [19]. To address the issues, some strategies create microstructures on the stent surface. The micropores on the surface enable drug deposition and retard drug release without the obligatory need of a polymer. For example, the YUKON® Choice stent (Translumina, Hechingen, Germany) carries sirolimus via its microporous surface (called PEARL Surface) (**Figure 2A**), and allows for individualizable, dose-adjustable and multiple on-site coating of drug [20]. This surface-porous stent platform has also been used to carry leflunomide [29] and dual drugs of sirolimus and antioxidant probucol [31]. Similar to the micropore technology, a mechanically modified textured surface without polymer has been used on the BioFreedom™ stent (in development by Biosensors, Singapore) to incorporate and release Biolimus A9™ (**Figure 2B**) [32]. Another polymer-free drug delivery strategy used on the Amazonia Pax® stent and NILE®-Pax stent (in development by MINVASYS, Paris, France) uses a microdrop spray crystallization process (proprietary Pax Technology®) to generate a semicrystalline pure paclitaxel coating on the abluminal surface (**Figure 2C**).

With revolutionary drug-releasing reservoir (groove) design, the OPTIMA JET tacrolimus-eluting stent delivers drug entirely to the vessel wall, optimizing device safety and efficacy [27]. A proprietary process brings the drug to a point of simultaneous melting in each of the reservoirs, without addition of any polymer. About 50% of the drug is released in 30 days, and the remaining drug is completely released in ~ 3 months.

Biocompatible micro-/nanoporous inorganic coatings composed of hydroxyapatite and aluminum oxide (Al_2O_3) are applied on the sirolimus-eluting VESTAsync™ stent (MIV Therapeutics, Vancouver, Canada) [33] and a tacrolimus-eluting 316L stainless steel stent [34], respectively. The former hydroxyapatite coating, which has its micropores filled with sirolimus/oil formulation, was expected to be stable for a period of between 9 months and 1 year and then crack and

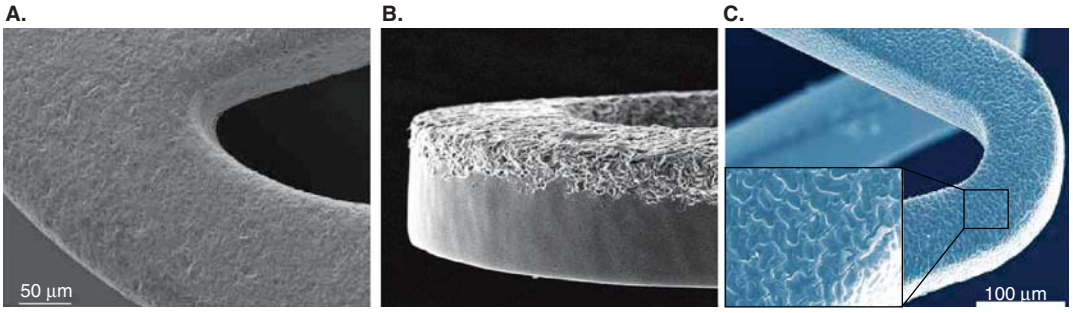

Figure 2. Representative porous surfaces of non-polymer drug delivery stents. A. The microporous surface of YUKON® Choice stent strut loaded with sirolimus. **B.** A microscopic view of a strut on a BioFreedom™ stent (the textured microstructure on the abluminal surface is loaded with Biolimus A9™). **C.** The polymer-free abluminal paclitaxel coating on the Amazonia Pax® Co-Cr alloy stent platform.

totally disappear. The latter porous Al_2O_3 coating is formed by *in situ* electrochemically converting the precoated aluminum layer on a 316L stainless steel stent via an oxidative reaction.

3. Bioabsorbable polymeric stent-based drug delivery platforms

Bioabsorbable polymeric stents refer to stents that are made of bioabsorbable polymers. Different from the biodegradable polymer-coated metal stents (described in Section 2.2) that are now popular in clinical applications, the bioabsorbable polymeric stents are made completely of biodegradable polymers and do not contain any metals. They have the potential to remain *in situ* for a predicted period and then degrade into small molecules that can be metabolized and removed from the body by means of normal metabolic pathways; because of the good compatibility and bioabsorbability, bioabsorbable polymeric stents may not irritate implantation tissues and can avoid the concerns involved with the permanent presence of conventional metallic stents. An ideal bioabsorbable polymeric stent is expected to disappear spontaneously after it completes the treatment mission of offering mechanical support and agent-based therapy, not necessitating a second surgery for removal after their periods of action. So far, a variety of drug-loaded fully degradable stents have been developed and investigated for vascular and non-vascular (bile duct, urethral and prostate) applications [35]. The widely used biodegradable polymers are polyesters (poly(l-lactide) [PLLA], poly(dl-lactide) [PDLLA], PLGA, PCL and polyhydroxybutyrate-valerate copolymer [PHBV]) and poly(anhydride esters) [35]; fibers [36], films [37] and tubes [38] are generally used as the transitional product for further fabrication of biodegradable stents with complicated geometries.

With regards to the drug loading performance, bioabsorbable polymeric stents as the platform for drug delivery can be loaded with larger amounts of drug than drug-coated metallic stents because their entire polymeric backbone can be loaded with drug [35]. However, polymeric stents may have mechanical properties that are inferior to those of metallic stents. To improve the mechanical properties, new polymers, a new polymer processing procedure and new geometry could be used. Without radiopacity, most bioabsorbable polymeric stents demand a radiopaque marker or radiopaque additive to help visualize through MRI or computed tomography CT when used in clinical practice. At present, only one bioabsorbable stent, the BVS stent (Abbott), has CE mark approval; several other promising ones [39], such as REVA stent (REVA Medical, CA, USA), Ideal™ stent (Bioabsorbable Therapeutics, CA, USA) and Combo™ Bio-engineered stent (OrbusNeich, Hong Kong, China), are still undergoing preclinical or clinical trials.

3.1 Drug-polymer layer-coated stents

Like the drug-polymer layer-coated metallic stents, the drug-polymer-coated polymeric stents also carry drug through the biodegradable coating (Type A in **Figure 3**). Most of the reported bioabsorbable stents belong to this category. The first drug delivery bioabsorbable polymeric stent could be credited to an Igaki-Tamai stent coated with a tyrosine kinase antagonist, ST638 [40], followed by a double-helical PDLLA stent releasing paclitaxel over a period of 4 weeks [41]. As other examples, the BVS bioabsorbable everolimus-eluting stent (in clinical trials by Abbott) was composed of a bioabsorbable polymer backbone of PLLA and a PDLLA coating containing everolimus [42]. The release of drug was controlled by the PDLLA coating matrix, which is absorbed more rapidly than the PLLA backbone. The ReZolve™ bioresorbable coronary stent (in development by REVA Medical, CA, USA) uses a proprietary radiopaque tyrosine-derived polycarbonate polymer (ReZorb™ Polymer) as the stent backbone, and the incorporated Limus compound in the coating is completely released within 3 months [39]. OrbusNeich's fully absorbable sirolimus-eluting stent, which combines an adluminal endothelial progenitor cell (EPC) capturing coating for rapid endothelial coverage with an abluminal sirolimus drug coating for the control of neointimal proliferation, provides protection against thrombosis and

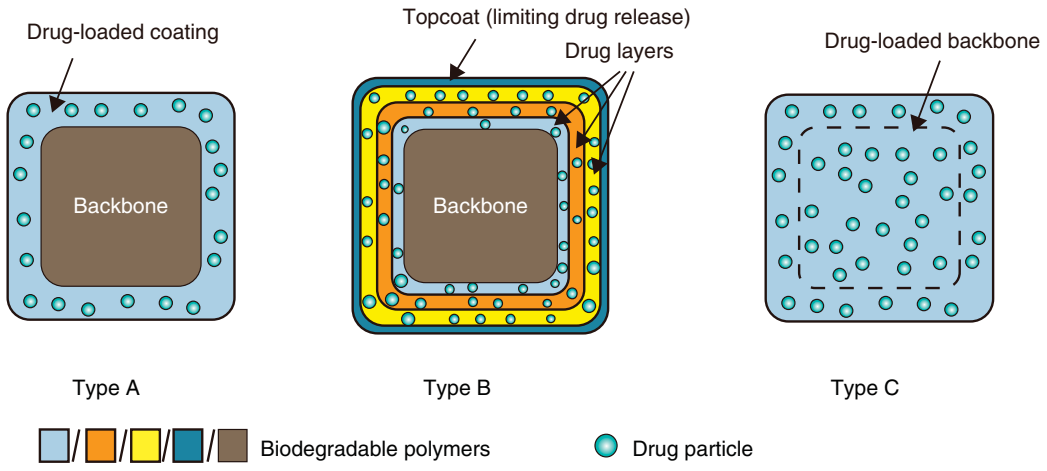

Figure 3. Schematic of three typical drug loading patterns for both bioabsorbable and non-degradable polymeric stents. Not only the polymer coating but also the backbone of the polymeric stents can be loaded with drug.

modulates restenosis [43]. Mikkonen *et al.* developed a series of self-expandable biodegradable drug-eluting stents based on PDLLA wires with a 7-µm-thick drug-incorporated coating [44]. In parallel, Li *et al.* engineered a self-expanding bioabsorbable stent with PLGA fibers and coated the fibers with a bioabsorbable formulation containing mometasone furoate (MF) for sinus mucosal uses [9].

3.2 Monolithic drug-containing stent matrix

This category of stent is characterized by the incorporation of bioactive agents in the stent bulk, that is, drug is dispersed in the entire stent matrix (Type C in **Figure 3**). This drug loading mode enables large drug loading dose, but deteriorates mechanical properties. With regards to drug release, they allow drug release to occur either before or with the progressive degradation of polymer matrix. Two common methods used for the preparation of stent matrices are the polymer/drug mixture heat molding method and the polymer/drug solution casting (precipitating) method. A balloon-expandable multiple-lobe-based stent was prepared by weaving PLLA fibers into a four-lobe configuration. The drug-incorporated fibers were melt-extruded from PLLA and curcumin blends [45]. However, owing to the thermal instability of most drugs, the fabrication of a drug-loaded stent matrix via conventional heat molding is problematic for biodegradable polymers (e.g., PLA and PLGA) that have high softening/molten temperatures. Some special processing technologies have been reported, allowing the incorporation of thermosensitive agents into a bioresorbable polymeric matrix. Vogt *et al.* adopted the CESP (controlled expansion of saturated polymers) process and prepared a paclitaxel-loaded double-helical PDLLA coronary stent at a low processing temperature of ~ 37°C [41]. Otherwise, the polymer/drug solution precipitating method is also applicable. A slotted tube stent based on polymer blends of PLLA and poly(4-hydroxybutyrate) (P4HB) was prepared by laser-cutting the polymer tube, which was formed on a mandrel by dipping in the polymer/drug solution [16]. Using the polymer/drug solution-casting method, Venkatraman and co-workers prepared PLLA or PLGA films containing paclitaxel/sirolimus in the bulk, and used the films to fabricate helical stents [37].

3.3 Multilayered film-based stent platforms

To enrich flexibility in drug release kinetics, a promising strategy is endowing a stent matrix with a unique structure of multiple layers (Type B in **Figure 3**). The layers could have different formulations and be arranged in changeable patterns, thus enabling adjustable or programmable drug release. Lei *et al.* have reported a series of multilayered PCL films for stent application (**Figure 4**) [46]. The multilayered films were composed of two or three layers that had different drug loading doses or various contents of PEG additive. The multilayered films had distinct release kinetics with the films with a single layer. Venkatraman and co-workers engineered PLLA/PLGA bi-/trilayer-film-based stents and investigated their drug (sirolimus/paclitaxel) loading efficiency and controlled release behaviors [37,47].

4. Non-degradable plastic stent-based drug delivery systems

The stents discussed here refer to unexpendable, undegradable hollow plastic tubes that are used mainly in the biliary or urethral systems. The commercially available or investigated drug delivery plastic stents generally deal with encrustation with bile or urine, biofilm formation, infection due to bacterial colonization, as well as malignant obstruction. Antibiotics, antitumor drugs or those for preventing encrustation are impregnated in the drug-loaded stent coatings. The anti-infective triclosan-eluting Triumph® stent has an inhibitory effect on bacterial adherence [48]. Heparin bonded on the Endo-Sof™ Radiance™ ureteral stent (Cook Medical, IN,

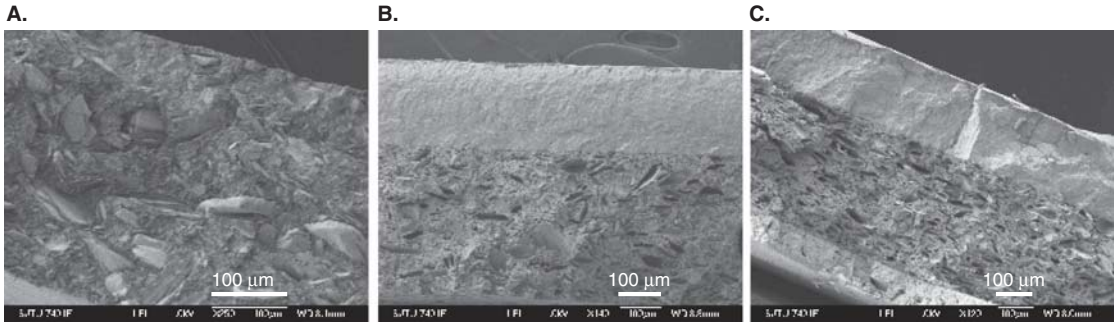

Figure 4. Multilayered poly(ε-caprolactone) films containing 5-fluorouracil drug particles. A. Single drug-containing layer. **B.** Bilayered film with a drug-free blank layer and a drug-containing layer. **C.** Trilayered film with a drug-free blank layer, a main drug-containing layer and a drug-containing topcoat layer.

USA) reduced bacterial encrustation and salt precipitation on the stent surface [49].

5. Multi-drug delivery systems based on stents

The concept of multi-drug delivery stents involves delivering more than two therapeutic agents through a single stent. The multiple drugs delivered can be with similar or totally different action effects. For the drugs with similar action mechanisms, their combined deliveries can enhance the action effect produced by each alone; whereas for those with categorically different action mechanisms, their synchronous deliveries can treat a disease from different angles or treat multiple diseases at the same time. In coronary applications, the combined deliveries of antiproliferative drugs (such as paclitaxel and sirolimus) with antiplatelet deposition drugs (e.g., clopidogrel, aspirin and abciximab) and/or antithrombotic drug (e.g., hirudin, bivalirudin, low-molecular-mass heparin) through a single stent would be very advantageous in simultaneously preventing vascular smooth muscle proliferation, neointimal hyperplasia and stent thrombosis. For example, the Synchronnium™ stent (Sahajanand, Gujarat, India) simultaneously elutes sirolimus and heparin to prevent neointimal hyperplasia and thrombosis; the Zodiac™ stent (Abbott, CA, USA) elutes simultaneously dexamethasone and zotarolimus for combined therapies; a dual drug-eluting stent elutes sirolimus and genistein through its five coating layers, which contain an alternating blend of sirolimus and genistein [50]. In parallel, a polymer-free dual rapamycin- and probucol-eluting stent (dual drug-eluting stent [dual-DES]) was developed based on the surface-porous YUKON stent platform [31]. The multiple reservoir-based dual drug-eluting SymBio™ stent (Johnson & Johnson, NJ, USA) was prepared by filling antiproliferative paclitaxel and anti-inflammatory pimecrolimus into alternate intra-strut reservoirs on the stent [51], and it avoids drug interactions and allows independent releases of the two drugs in independent vectorial directions. Huang *et al.* prepared a dual drug-eluting stent by spray coating the bare Co-Cr stent with a biodegradable polymer layer containing antiproliferative sirolimus and antithrombotic triflusal to treat restenosis and thrombosis, respectively [52]. With two partitioned coatings, both the Genous™ Bio-engineered R stent (OrbusNeich, Hong Kong, China) and OrbusNeich's fully absorbable coronary stent combine an anti-CD34 antibody cell capture coating on the luminal surface and an abluminal coating of a biodegradable polymer matrix coating [43] for rapid achievement of endothelial coverage and to control neointimal proliferation.

6. Gene delivery systems based on stents

Gene therapy is the insertion, alteration, or removal of genes within an individual's cells and biological tissues to treat or prevent disease. It is considered a promising treatment option for several diseases (including genetic disorders, cardiovascular diseases and cancers). As the most common form of gene therapy, transferring genetic material into specific cells is being broadly investigated. In stenting, the transferred genes are used to alter the expression of existing genes that lead to abnormal cell proliferation, or to produce cytotoxic proteins or product-activating enzymes to kill tumor cells [53]. What is advantageous is that the drug delivery stents can efficiently deliver genes to the stent-touching tissues in a local fashion. So far, there have emerged some strategies for delivering genes through stents. The most reported DNA delivery systems rely on their positively charged coatings, which make possible the adsorption of negatively charged DNA by electrostatic reactions. The positively charged phosphorylcholine has been used as the coating material on the BiodivYsio stent for adsorbing DNA [54]. The amount of adsorbed DNA can be increased by stacking DNA layers and positively charged coating materials in a layer-by-layer fashion [55], and the release of bound DNA takes place with replacement by negative ions present in the physiological environment. Also, the traditional drug loading strategies can be applied to macromolecular DNA. As an example, the dip-dry coating method was adopted to coat the metallic stent with a DNA/polymer

matrix layer, which was formed by repeatedly dipping the stent in the emulsion (composed of DNA Tris buffer solution and PLGA chloroform solution) [56]. As ordinary polymer networks may hinder the release of DNA (usually with large molecular size), a nano/microporous polymer matrix with high permeability is preferable as the loading matrix [57]. In addition, the DNA molecule is unstable in the physiological environment, thus it would be better for it to be released in the form of DNA/vector complexes, which are more stable. The reported DNA vectors include modified viruses and polycations, for example, poly-l-lysine (PLL), poly(ethylenimine) (PEI) and cationic lipids [58]. Although less investigated, gene delivery stents may advance greatly with the stimulation of future progress in gene delivery systems and drug delivery stents.

7. Drug release from stents

It has been widely accepted that, apart from the efficacy and dose of a drug, drug release kinetics also has direct relevance with the treatment effect [59], because biological responses are determined by the local drug concentrations in target tissues or cells. Ideal drug release kinetics for a drug delivery stent is expected to maintain the tissue drug concentration above the effective level and below the toxic level for a desirable period of time [60]. Many drug delivery stents, nevertheless, have been preclinically or clinically tested to be ineffective. The ineffectiveness is, in great part, attributed to the poor drug delivery performance, especially inappropriate dose and drug release kinetics. Too large a dose may induce severe local toxicity, whereas an insufficient dose cannot produce an effect. For example, among the four investigated doses (0.6, 1, 2 and 4 μg paclitaxel/mm^2 of the stent surface area) for the TAXUS® stent (Boston Scientific, MA, USA) the highest dose (4 μg/mm^2) resulted in severe adverse effects (e.g., endothelial cell loss and fibrin accumulation), while the lowest dose (0.6 μg/mm^2) induced neointimal hyperplasia; only one acceptable dose (1 μg/mm^2) was applied to the product after preclinical and clinical trials [2]. The dosing strategies, which are usually screened and optimized in the preclinical and clinical trials according to disease characteristics [60], are not the focus in this review. Below, the aspects related to the characterization and adjusting strategies of drug release are described and assessed. The drug release kinetics of a stent is determined by several formulation factors, namely the drug's physicochemical properties, the delivery system and the carrier material.

7.1 Drug release kinetics

In general, drugs are released from stents in the following ways: diffusion of drug molecules out of the carrier matrix; drug freeing with the dissolution or degradation of carrier matrix; and direct drug dissolution from the surface of stents (for polymer-free drug-alone-coated stents). Under some circumstances, the drug release could be dominated by a combination of such mechanisms.

For inert matrix-based stents [2], drug release is driven by dissolution of the incorporated drug particles into molecules and the subsequent diffusion of drug molecules out of the matrix into the external release media. When the drug concentration is below the drug solubility in the matrix (namely the drug is dispersed in molecular form), drug release is driven by direct diffusion of drug molecules. The diffusion distance and drug diffusion coefficient, which is dictated by the partitioning coefficient and the free void among polymer chains in the matrix, determine the release rate. Owing to the increasingly lower diffusion rates resulting from the longer diffusion distances for the drug molecules from the matrix surface to the inner regions, the macroscopic drug release shows progressively decreasing rates. Therefore, the slopes of the release profiles for such systems are steep at the initial stages and then gradually become gentle with increasing time [5,46]. In addition, an inert drug-free topcoat can be applied to limit drug release from the drug-loaded matrix, which in turn functions as a drug reservoir, and such a system has the potential to achieve zero-order drug release kinetics.

For most polymer-free metallic stents [19], the drug is attached directly on the metal surface. The drug release kinetics from this category of stents relies just on the dissolution behavior of the drug in the environmental media. Generally, the more hydrophobic and adhesive the drug is, the more slowly the drug will be released. Theoretically, zero-order kinetics driven by a Case II drug transport mechanism [61] will be observed. Nevertheless, non-uniform drug deposition combined with the specially modified stent surface structures may lead to initially fast and later slow drug release [20].

In terms of drug releases from biodegradable coatings, they are generally driven by complex mechanisms that are contributed by the diffusion of the drug as well as the degradation and erosion of the polymer matrix. For those polymer (e.g., PCL) matrices with high drug permeability with lower polymer degradation rates, drug release is dominated by the diffusion mechanism and shows diffusion-controlled release kinetics, which is characterized by gradually decreasing release rates [46,62]; whereas for those (e.g., PLGA and PDLLA) with low drug permeability and high degradation rates, drug release may be dominated by a combination of a diffusion mechanism and a degradation mechanism and generally produce typical three-phase release profiles contributed by an initial burst, a diffusion-controlled release, and a degradation-controlled drug release [47,63]. For polymer matrices with absolutely no drug permeability, the drug release kinetics is determined completely by the degradation behaviors.

The application of new carrier materials and new drug delivery systems may endow the stents with more complicated drug release kinetics, which may be a result of a combination of factors, or interactions of many different factors.

7.2 Strategies for adjusting drug release

Many approaches, such as the selection of carrier materials, optimization of formulation variables and design of delivery

systems, can be adopted to adjust the drug release. As different types of carrier material may generate distinct release profiles (**Figure 5A**), the selection of carrier materials can be an effective way to optimize drug release. Exclusively for the matrices based on copolymers, such as PLGA, poly(ethylene-*co*-vinyl acetate) (PEVA) and poly(lactide-*co*-caprolactone) (PLACL), the drug release kinetics can be altered by changing the ratios of the co-monomers consisting of the polymer molecule [64]. For example, highly adjustable drug release from the stent coatings was achieved by varying the PEG length and the co-monomer ratio of LA:CL on the multiblock structures of hybrid polyurethanes (**Figure 5B**). In optimization of the formulation, a simple way to modify drug release kinetics could be by changing the drug/polymer ratio in the formulation (**Figure 5C**) [2,5], which was adopted in the development of the TAXUS stent [2]. For example, increasing the drug/polymer ratio will diminish the retarding effect of polymer, thus promoting drug release and generating a higher local drug concentration [2,5,46]. Besides, the use of additives (e.g., hydrophilic substances) in the polymeric matrix [46] and changing the coating matrix thickness [2,65] could be other approaches to regulate drug release. The additives may increase the drug permeability of the polymer matrix owing to plasticization effects; otherwise, hydrophilic additives may dissolve and diffuse quickly out of the matrix when exposed to water and thus leave microcavities or channels to promote drug diffusion [46,62]. The preparation methods and processing parameters of the delivery systems on stents can also influence the drug release kinetics. It has been reported that the types of solvent and solvent ratios of a multisolvent system can affect remarkably the drug release profiles of the stent coating prepared by the solution method (**Figure 5D**) [2].

The strategy of applying multiple layered stent coatings has proved their effectiveness in controlling and modulating drug release [46,66–68]. The coatings consist of multiple layers, and each layer has a different formulation and generates a different drug release profile. These strategies allow for the production of highly adjustable or even programmed release kinetics, by elaborately designing the formulation of each layer in the coating. With three different layers of combined drug and biodegradable polymers, the Infinnium stent releases paclitaxel in a bimodal release pattern, leading to three programmed release rates during three separate time stages [66]. Other drug delivery stents with multiple layer drug coatings include the trilayer Zodiac stent, bilayer Synchronnium stent and five-layer genistein-sirolimus dual-eluting stent [50]. The controversial burst release contributes, on the one hand, to rapid elevation of drug concentration to effective levels; on the other hand, it may cause side effects. By utilizing multiple layers, burst release can be either created by introducing a top layer with fast drug release or eliminated by covering the drug layer with a release-limiting layer. With a drug-free water-soluble PVP layer, the Supralimus stent prevents premature release of sirolimus from the base layer [68].

8. Balancing drug delivery and mechanical support

A drug delivery stent technically has two functions, namely, providing mechanical support and delivering drugs. Between the two functions the former is the basic one, thus the component used for providing mechanical support should be the primary part of a stent. However, the introduction of a drug delivery system or modification of the stent geometry for loading a drug may have more or less influence on the mechanical property of the original stent. For example, the drug-incorporated membrane-covered metallic stent may have inferior flexibility compared with the original bare stent. The impairment of mechanical properties (in terms of extensibility and collapse pressure, etc.) of the stent resulting from the incorporation with drug is significant, especially for monolithic polymer matrix-based stents [46,69]. In general, the larger the amount of drug loaded, the better the drug delivery ability will be, but meanwhile the more mechanical properties will be compromised [5,46]. For these reasons, to develop a drug delivery stent with desirable performances, comprehensive considerations of influencing factors on both drug delivery performance (including drug loading ability and drug release kinetics) and mechanical performance should be made, with the priority given to the mechanical support performance.

9. Expert opinion

Stenting has developed into the most effective therapy for occlusive diseases. Thanks to the introduction of drug delivery stents that have drug delivery ability, the treatment of body conduit or tubular structure diseases has been revolutionized. Many drug delivery stents have demonstrated their success in treating local disease. The drug delivery stents serve as both a mechanical device supporting the occluded structures and a drug delivery system offering pharmacotherapy, showing great efficacy in re-establishing and maintaining patency. Theoretically, stents could act as universal drug delivery platforms for the treatment of a variety of occlusive diseases. However, many challenges are encountered in translating drug delivery stents from academic research to clinical applications. These obstacles facing the treatment efficacy of current DESs are in large part related with the long-term safety (e.g., late-stent thrombosis and delayed endothelialization in coronary applications; and encrustation and biofilm formation in biliary/urethral applications) as well as poor drug delivery performance, especially feeble drug localizing, inappropriate dosing and poor drug release controllability.

It is a systematic project to develop effective drug delivery stents. First of all, the selection of stent platform is fundamentally important. Stents with better geometry, good tissue compatibility and long-term safety are preferable. In this respect, new strut/drug carrier materials (e.g., absorbable metals and biodegradable polymers) with better compatibility could be

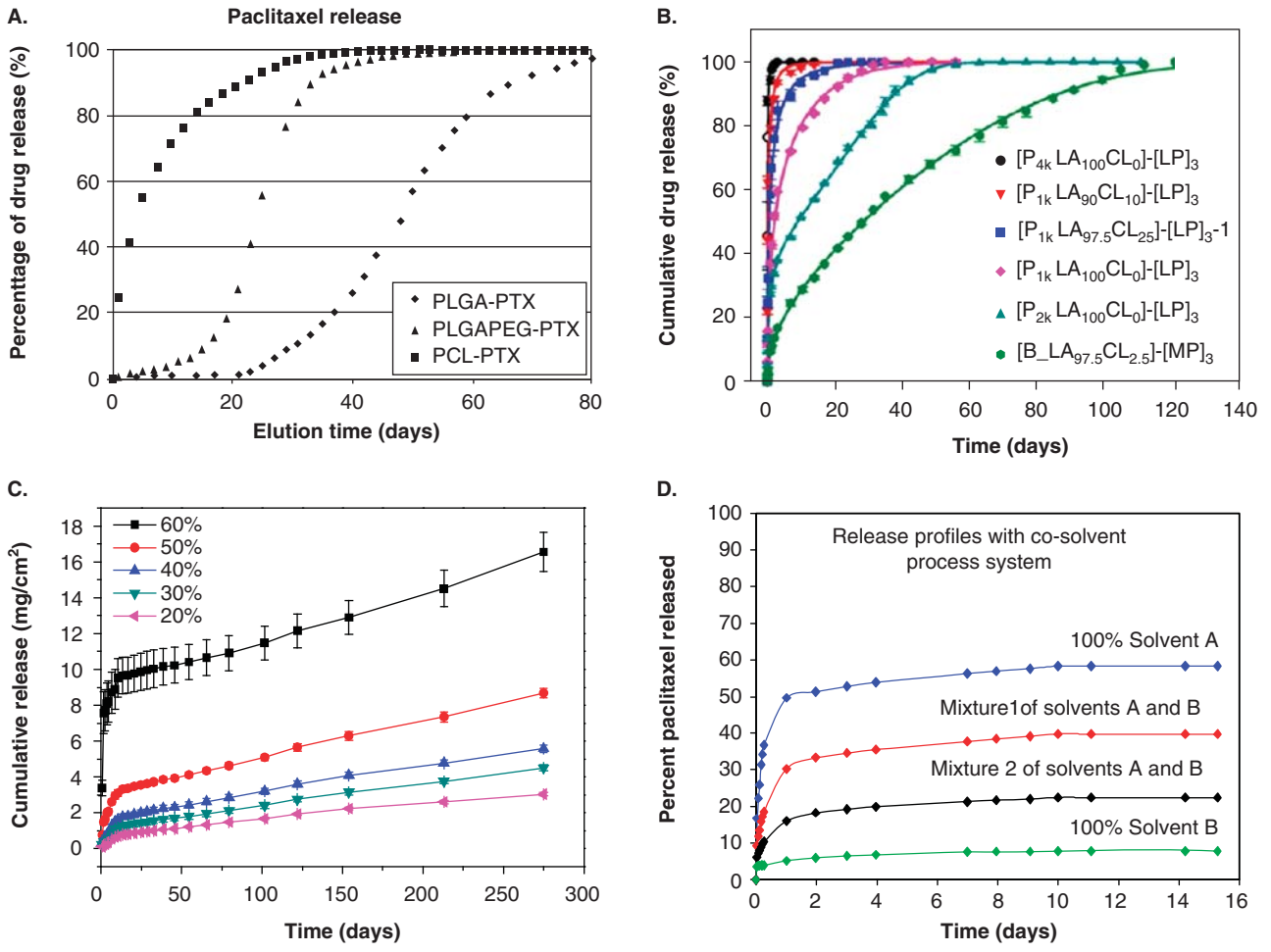

Figure 5. Strategies reported for adjusting drug release kinetics of drug delivery stents. A. The distinct release profiles of paclitaxel from three films with different polymer compositions: pure PLGA; PLGA with the addition of 10 wt% PEG (PLGA-PEG); and pure PCL. **B.** Release profiles of paclitaxel from the thermoplastic polyurethane stent coatings with different multiblock structures. **C.** A wide range of release profiles of 5-fluorouracil from stent coatings with varying drug loading doses. **D.** Paclitaxel release profiles modified by varying the solvent ratios in the co-solvent systems for preparing SIBS stent coatings.

Reproduced with permission from **A.** [59] **B.** [64] **C.** [5] **D.** [2].

used; alternatively, drugs for preventing reactive responses or inflammation can be delivered. Second, the good understanding of disease mechanism will help in the selection of proper drug and the design of efficient drug delivery systems according to the disease characteristics. Finally, in the drug delivery aspect, most of the available stents use polymers just as drug release retarder, and the release of drug lacks programmability or customization. It would be ideal for a stent to carry a sufficient amount of drugs and release them in a customized manner for a desirable duration. In the process of drug release, dynamic change of drug release behaviors according to the individual, dynamic disease-developing stage may be desirable.

Fully bioabsorbable drug delivery stents, with their inherent advantages of temporary presence over permanent stents, appear very promising in future applications. However, some criteria should be fulfilled for their practical applications: i) good deliverability (balloon-expandable or self-expandable) through practical procedures; ii) maintenance of required radial strength for a certain time for the completion of healing or therapy; iii) customizable drug release and biodegradation behavior; and iv) can be visualized by standard MRI and CT when they are clinically implanted.

In terms of the active agents to be delivered, future drug delivery stents are expected to fulfil simultaneous delivery of multiple drugs and to deal with the delivery of biotech drugs, such as proteins and genes. In theory, multiple drug delivery stents would be superior to the conventional single drug delivery stents, because the multiple drugs delivered make possible the treatment of disease from

different angles or treatment of multiple diseases at the same time. Gene or protein delivery via stents is still in its infancy; the successful integration of gene delivery systems with stent platforms demands a deep understanding of the advances in gene delivery systems and the upgrading of drug-carrying stents.

An individualized drug delivery stent, which takes into account the individual patient's condition and tissue biology as well as lesion characteristics, would have better long-term efficacy and safety. For individualized treatment, the geometry, construction and drug delivery properties of a stent are anticipated to be highly adjustable.

Although there are a number of commercially available drug delivery stents, most of them are for coronary applications. New drug delivery stents are also needed for the local management of stricture or occlusion due to tumors, injury, infection, and so on, in non-vascular conduits or tubular organs (including the esophagus, bile/prostate/pancreatic duct, urethra and trachea/bronchus). For promotion of the development of stents for such applications, many innovative strategies and lessons can be learnt from the successes of coronary stents.

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Declaration of interest

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