

# Biodegradable stent

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## ABSTRACT

The bare metal stent (BMS) used in the blood vessel caused the restenosis after the operation due to formation and proliferation of neointimal. Recently, as a method to overcome the problems of BMS, drug eluting stent (DES) is developed and being applied to human body which has drug reducing restenosis applied on the metal surface. DES has the advantage of greatly reducing the restenosis after the operation; however, metal stent remains in the body after the drug is released causing issues such as late thrombosis and restenosis so that currently the attention is increasing for biodegradable materials that reduce restenosis and thrombosis by degrading as a certain amount of time passes after the drug is released by the stent material. In this review, the study trend of biodegradable stent will be explained.

**Keywords:** Stent; Biomaterials; Biodegradable; Bioabsorbable

## 1. INTRODUCTION

In 1977, Gruentzig of Switzerland successfully executed percutaneous transluminal coronary balloon angioplasty in stricture lesion to open up a new era of coronary artery [1]. This method dilates the balloon to widen the stricture lesion, which brings about the improvement of blood flow with the dilatational balloon to expand the narrowed coronary artery. Acute obliteration during or right after the operation, however, may cause death or acute myocardial infarction, because 30% - 40% of restenosis within 6 months occur from constriction and neointimal hyperplasia of coronary artery after the balloon dilatation [2,3].

In the early 1990s, bare metal stent (BMS) was operated on the stricture lesion of coronary artery with the stent on the balloon and wire mesh on the inner wall of

coronary artery to expand the coronary artery [4]. The insertion of BMS had lower restenosis occurrence rate than balloon expansion, and the stent played the role of supporting the blood vessel inner wall to prevent the contraction of the coronary artery reducing the restenosis rate to 20% - 30%. Stent insertion reduced the critical shortfall of balloon expansion which was the stricture of coronary artery with acute recoil, but mechanical blood vessel damage was caused in the expansion process and neointimal was formed to cause in stent restenosis [5,6]. In order to prevent in stent restenosis, many researches were conducted, and sirolimus originally developed as immunosuppressant and paclitaxel used as anticancer drug were reported to effectively suppress formation of neointimal [7,8]. The problem was, however, systemic injection of such drugs interfere with maintaining the local drug concentration in the stent, and is prone to serious side effects. In order to overcome such problems, the research to insert the drug on the stent surface and locally release the drug was conducted. As the result, drug-eluting stent (DES) was born, but this also has the issue of drug release control and being unable to maintain appropriate drug concentration.

In order to overcome such limitations of the existing stents, the development of biodegradable DES was suggested, which is expected to bring a dramatic change in treatment of coronary arterial diseases. This review intends to discuss the design of the stent using biodegradable biomaterial and the technological development trends.

## 2. BIODEGRADABLE STENT MATERIALS

For stent materials, whether to expand with a balloon or if the self-expansion using shaped memory characteristics shall be employed should be considered. Balloon expandable stents must be able to maintain the form once expanded, and the stent using self-expansion must have sufficient elasticity to expand. The ideal characteristics

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of a stent material are shown in **Table 1**. In this section, the research trend of biodegradable stent production using polymer, metal, and ceramic is introduced.

## 2.1. Polymer

The synthetic polymer of poly-L-lactic acid (PLLA) is biodegradable biomaterial with its repetition unit hydrolyzed into lactic acid, and eventually decomposed to water and carbon dioxide and absorbed to metabolism. In Igaki and Tamai groups, the PLLA of molecular weight 183 kDa was used to develop a stent of thickness 170  $\mu\text{m}$  in the zig-zag helical coil form strut. The stent of Igaki and Tamai group is self-expansion by heat and when applied to clinical experiments, the operation on coronary artery lesion reported restenosis rate of 10.5% after 6 months [9]. After such successful cases, the researches on stents using biodegradable polymers were actively conducted.

Abbott vascular group also used PLLA to produce a BVS (bioresorbable vascular scaffold) stent with interconnected linear bridges with the thickness of 150  $\mu\text{m}$  strut in the form of zig-zag hoops, which expands using a balloon. The stent surface is coated with poly-D,L-lactic acid (PDLLA) and everolimus (a rapamycin derivative) to develop DES [10]. BVS stent used everolimus to effectively reduce inflammatory reaction.

Blindt group developed a double-helical type stent with paclitaxel using PDLLA of molecular weight of 240 - 250 kDa [11]. The stent was produced using controlled expansion of saturated polymers so that it has excellent mechanical stability, and as the result of 3 months of experiments *in vivo*, the comparison of the stent with (49%  $\pm$  4%) and without (71%  $\pm$  4%) paclitaxel reported that coronary stenosis was significantly reduced.

The tyrosine-derived polycarbonate was used to develop a stent with the slide and lock design and strut thickness of 150  $\mu\text{m}$  [12]. The slide and lock design stent has excellent radial strength with a locking structure when expanded. Also, due to its radiopacity, the materialization with X-ray and fluoroscopy is reported to be possible.

Niels Grabow group blended PLLA and poly(4-hydroxybutyrate) in the mass ratio of 78/22% to produce a stent in the slotted tube form [13]. This stent has elastic modulus and tensile strength reduced by 52% and 20% respectively compared to PLLA alone, but the elongation

to break increased by 16 times. Also, stent was prepared in the water of 37°C for 5 minutes, and then was quickly expanded within a minute using the balloon under the pressure of 8 bar. And *in vitro* biodegradation, the molecular weight after 48 weeks was reported to have dropped to 82%.

In Liu group, poly( $\epsilon$ -caprolactone) (PCL) of molecular weight of 80 kDa was used to produce a stent that expands by balloon; the components of this stent were geometrically designed and assembled as self-lock so that it is reported to have excellent resistibility against the pressure of the external blood vessels when expanding. The surface of the stent was applied with poly(D,L-lactic acid-co-glycolic acid) (PLGA) and paclitaxel at room temperature using the spray coating method. The release of paclitaxel was confirmed for over 60 days *in vitro* [14]. Also, PLLA and PLGA were used in the bi-layer format of elastic memory to develop a self-expanding stent at 37°C [15].

And Lauto group developed a self-expanding stent using chitosan, a natural polymer, in an experimental stage. The chitosan film was used to produce in the helical coil form, which was reported to completely expand within 3 minutes [16].

## 2.2. Metal

BMS is a permanent implant which causes not only stent thrombosis and chronic injury but also the risk of increasing the formation of neointimal. Thus, researches on development of biodegradable metal stent material were actively conducted, and recently pure iron and magnesium alloy are receiving much attention as the biodegradable stent material [17].

Pure iron (over 99.5%) has high elasticity modulus and excellent radial strength to make a stent with thin strut [18]. And iron is theoretically expected to easily break during or after the expansion due to its yield strength and tensile strength being similar, but as the result of *in vivo* experiment, the strut with the thickness of 100 - 120  $\mu\text{m}$  was expanded with the pressure of 3 - 10 atm and no destruction of stent was observed at all [19]. Iron is oxidized to ferrous iron and ferric iron by the phagocytosis of nearby tissues. Ferrous iron reduces the proliferation of smooth muscle cells *in vitro* tissue culture so as to suppress the formation of neointimal and it was reported that local toxicity does not occur [20].

Another biodegradable metal of magnesium alloy was first used as the orthopedic implant, but recently it is receiving much attention as the cardiovascular implant [21]. AE21 and WE43 among magnesium alloys are emerging as the cardiovascular stent material [22,23]. AE21 is composed of 97% magnesium, 2% aluminum, and 1% of rare earth metals (Ce, Pr, Nd), and WE43 is composed of >85% magnesium, <5% yttrium, <5% of

**Table 1.** Ideal properties of biodegradable stent materials.

Good biocompatibility
Sufficient flexibility
Sufficient radial strength with minimal recoil
Adequate radiopacity for visualization
Ability to facilitate drug delivery

zirconium, and <5% of rare earth metals. The biodegradation of magnesium involves hydrolysis of magnesium chloride in physiological environment, decomposing to the hydrogen gas and magnesium hydroxide, and the biodegradation period is about 60 - 90 days. Magnesium has generally low elasticity modulus and low radial strength so that it is difficult to support blood vessel walls. Therefore, the thickness of the strut increases. Also, it has low ductility and therefore is easy to break, and its radiolucent quality makes it impossible to materialized with X-ray and fluoroscopy; however, recently the stent that can be materialized using intravascular ultrasound and MRI was reported [24]. Biotronik produced a stent with magnesium alloy of WE43 and clinical experiment was conducted, but the results were disappointing [25]. Currently, such biodegradable metal material requires further research on the development of processing technology and the interaction of biology and material.

### 2.3. Ceramic

Besides polymer and metal, ceramic also has the potential possibility as the stent material. Iridium oxide is a ceramic material with excellent biocompatibility, and supplies hydrogen peroxide when coated on the stent surface [26]. It was reported that the iridium oxide sprayed on the metal stent releases hydrogen peroxide which converts to water and oxygen to reduce inflammatory reaction and catalyzes the proliferation of endothelial cells [27]. The nonconducting and amorphous hydrogenated silicon-carbide (SiC) is well known for its antithrombogenic characteristics [28]. The stent sprayed with SiC is receiving much attention as the material to reduce restenosis by reducing the accumulation of platelets, leukocytes, and monocytes [29]. Currently ceramic materials are mostly used as the stent coating materials rather than the material of the stent struts [30].

## 3. MECHANICAL PROPERTY FOR BIODEGRADABLE STENTS

The biodegradable stent materials mentioned in the above section are under research to add the unique characteristics of each material and elastic/biodegradable characteristics. There are many biodegradable stent materials reported. In this section, the elastic/biodegradable characteristics of polyester-based material among the biodegradable stent materials shall be explained.

### 3.1. Polymer Mechanical Property

The polymer receiving much attention as the biodegradable stent material is mainly polyester. PLLA composed on L isomer forms the secondary combination between

polymer chains so that the crystallinity is greater than PDLLA composed of D and L isomers [31]. High-crystallinity polymer generally has strong union between molecules so that it can easily break at room temperature, but has the advantages of high tensile strength and diverse processing methods compared to low-crystallinity polymer. Also, polymer chain has excellent mobility so that under certain force, the chains optimize themselves and arrange. If the viscoelastic polymers are quickly increased, the rearranging time of the chains are shorter so that they become brittle; on the other hand, if they are slowly increased, the chains are rearranged so that they can be easily deformed. The physiochemical characteristics of the commercial biodegradable polymers are shown in **Table 2** as follows [32-46]. Also, the glass transition temperature ( $T_g$ ), an important physical characteristics in the polymers, was summarized.  $T_g$  is a special characteristic for amorphous material such as polymer, and refers to the characteristic of phase transition from glass phase to rubber phase according to the temperature. As the temperature rises, the molecules divide the kinetic energy due to the heat so that the union between the molecules is destroyed and the mobility of the chain increases. Especially  $T_g$  is related to the strength of polymer at the room temperature or the body temperature. PLLA with  $T_g$  of 60°C - 65°C exists as glass phase near the body temperature. Thus, PLLA is thought of as a brittle polymer. PLLA, which has the highest  $T_g$  among the general biodegradable polymers, has high tensile strength and would be an appropriate choice for the researchers who are looking for a brittle material.

### 3.2. Polymer Degradation

The molecular chains of polyester stent materials should contain easily bond-cleavage segments sensitive to water or enzyme, that is to say, hydrolytically or enzymatically degradable stent can be designed. Natural polyesters are enzymatically degradable, while synthetic polyesters tend to hydrolytically degrade [47]. Meanwhile, the dominantly utilized materials in the most manufactured stents are synthetic polyesters. Hydrolytic degradation of synthetic polyesters occurs in the middle of the chain or at the end of the chain. The random scission where the decomposition occurs in the middle of the chain is dominantly observed in the early stage of polymer decomposition, and as the number of polymer chains increase as the polymer decomposes, the chain-end scission is more dominant where the hydrolysis occurs at the end of the chain. The products of the decomposition depend on the molecular structure of the polymer, and decomposition products with excellent biocompatibility are promoted.

PLLA is decomposed to lactic acid, poly (glycolic acid) (PGA) to glycine, and PCL to organic acid such as

**Table 2.** Properties of biodegradable polymers [32-46].

Polymer	$M_n$ (g/mol)	Tensile Strength (MPa)	Glass Transition Temperature ( $^{\circ}$ C)	Modulus <sup>a</sup> (GPa)	Degradation Time <sup>b</sup> (Months)
PLLA	~100 K	55 - 80	60 - 65	2.8 - 4.2	>24
PDLLA	~20 K	25 - 40	55 - 60	1.4 - 2.8	12 - 16
PCL	50 - 100 K	20 - 35	-65 to -60	0.4	>24
PGA	~140 K	<70	35 - 40	~7	6 - 12
85/15 PLGA	~80 K	40 - 55	50 - 55	1.4 - 2.8	5 - 6
75/25 PLGA	~100 K	40 - 55	50 - 55	1.4 - 2.8	4 - 5
50/50 PLGA	~100 K	~36	45 - 50	1.4 - 2.8	1 - 2
75/25 PCLA	~100 K	~8	Amorphous	0.3 - 1.4	22
20/80 PCLA	~50 K	~5	Amorphous	0.3 - 1.4	16
PLLA/P4HB	-	~36	~34	1	<12
Poly Carbonate	~450 K	~230	~93	~3.1	>14

<sup>a</sup>Tensile or flexural modulus. <sup>b</sup>Time to complete resorption. PLGA: poly(D,L-lactic acid-co-glycolic acid), PCLA: poly( $\epsilon$ -caprolactone-co-D,L-lactic acid), PLLA: poly(L-lactic acid), PGA: poly(glycolic acid), PLLA/P4HB: poly(L-lactic acid)/poly(4-hydroxybutyrate), Poly carbonate: poly(trimethylene carbonate).

6-hydroxyhexanoic acid; most decomposition products are converted to carbon dioxide and water through metabolism reactions. Factors contributing to the biodegradation of polymers include molecular weight, molecular structure, hydrophobicity, pH, crystallinity, and melting point; generally the contact with water or water infiltration accelerates the biodegradation. The polymer of crystalline structure with well-organized molecules delays the internal ester unit and water reaction, and thus the biodegradation speed will be slowed down. For example, PCL is a hydrophobic polymer with high crystallinity with biodegradation period of 1 - 2 years. And polymers such as PLGA are amorphous and less hydrophobic than PCL so that the biodegradation period is a few months.

#### 4. DRUG FOR BIODEGRADABLE STENTS

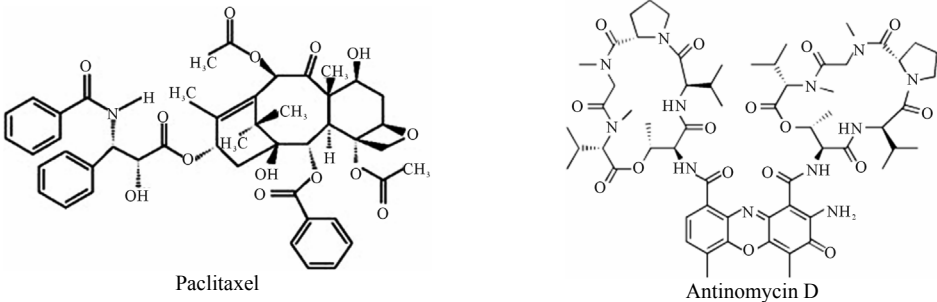
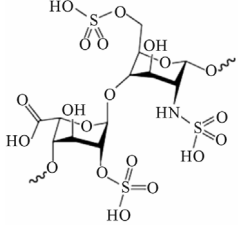
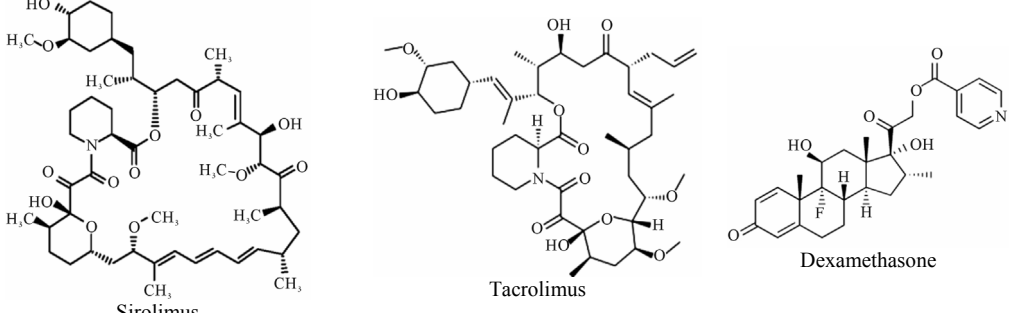
Methods of using drugs were suggested to suppress the inflammatory reaction caused by stent and the formation and proliferation of the neointimal occurred by proliferation of smooth muscle cells. When applying biodegradable stents, various drugs are included to locally release them over a long term to reduce the restenosis (**Table 3**). Depending on the composition of drugs and polymer stents, the release of the drugs and timing can be controlled. Drugs that suppress the excessive proliferation of smooth muscle cells to reduce the restenosis include heparin, paclitaxel, and sirolimus, and there are many other drugs that are expected to be used for reduction of restenosis [48]. Heparin effectively reduces thrombosis

and formation of neointimal, and paclitaxel and sirolimus mainly interrupts the formation of neointimal with the effects of antiproliferative. In this section, the characteristics of representative drugs applicable to biodegradable stents shall be introduced.

##### 4.1. Heparin

Heparin is a type of acidic polysaccharide with sulfate, mainly used as a material reforming the blood vessel surface as an anticoagulant. Heparin combines with anti-thrombin III in the blood to suppress the activation of thrombin and other blood coagulation factors (X, XII, XI, IX), exhibiting anti-thrombosis reactions and anti-proliferation reactions to directly suppress platelets and migration of smooth muscle cells [49]. Such characteristics are believed to reduce the occurrence of restenosis, and in reality, many researches using heparin-coated and containing stents are being conducted. The method of introducing heparin into the stent includes physical adhesion, ionic bond, and copolymerization, but the physical adhesion and ionic bond have lower stability than copolymerization so that they are easily removed from the surface. Thus, it is used by copolymerization with polymers such as poly(vinyl alcohol) and poly(methyl methacrylate) [50]. Beside such, there is a method of using biodegradable PLGA microsphere to release heparin [51] and poly(ethylene glycol) is added in the production of polymer-heparin film as the plasticizer to control the release of heparin from biodegradable PLGA [52]. The heparin-containing stent was reported to effectively reduce the formation of neointimal and thrombosis through

**Table 3.** Potential drug candidates for biodegradable stents.

Classification	Drug Candidates
Antineoplastic	 <p>Paclitaxel</p> <p>Antinomycin D</p>
Anticoagulant	 <p>Heparin</p>
Immunosuppressants	 <p>Sirolimus</p> <p>Tacrolimus</p> <p>Dexamethasone</p>

animal experiments [53].

#### 4.2. Sirolimus

Sirolimus is a naturally occurring macrocyclic lactone type, which is a drug first approved by FDA in 1999 for the prevention effects of rejection after kidney implant [54]. As one of the immunosuppressants, it binds with the intracellular receptor protein of blood vessel smooth muscle cells to disturb cell cycle, suppressing the migration and proliferation of smooth muscle cells of blood vessels [55]. Sirolimus, also as an immunosuppressant, contributes to the prevention of restenosis by suppressing the inflammatory reaction after blood vessel damage. Cypher of Johnson & Johnson is a DES with the mixture of poly(ethylene-co-vinylacetate) and poly(n-butyl methacrylate) in the ratio 67:33 sprayed on the stent surface where sirolimus and parylene C were sprayed, first approved as the DES stent by FDA in 2003 [56].

#### 4.3. Paclitaxel

Paclitaxel is widely used as an anticancer drug, espe-

cially being recognized for its effects on breast cancer and ovarian cancer [57-59]. Paclitaxel encourages the polymerization of tubulin which has an important influence on the cell proliferation process, in turn abnormally stabilizing microtubule and rendering it dysfunctional to suppress cell proliferation. Such influence suppresses the cellular replication of smooth muscle cells and destructs the cells [60]. Also, paclitaxel has strong lipophilicity so that it is easy to be absorbed in the cell, and has the advantage that the medicinal effect can last long within the cell. Boston Scientific, following Taxus and Cypher, applied paclitaxel in mixture to the poly(styrene-b-isobutylene-b-styrene) triblock copolymer as a DES approved by FDA in 2004.

### 5. CONCLUSION

The history of coronary artery interventional procedure begun by coronary artery balloon dilatation in 1977 was the continuation of much effort and challenge, and overcoming such. Afterwards, from BMS to DES, the coronary artery interventional procedure has achieved bril-

liant advancements, but still issues such as thrombosis and restenosis are present. For DES, encouraging results were reported in the early-mid period clinical experiments compared to the metal stents [61]; however, the results with the concerns for late thrombosis due to the stent remaining in the body after the release of the drug are being suggested [62,63]. While there is no accurately clarified mechanism regarding the phenomenon, excessive inflammatory reaction is caused due to the drugs and healing process is blocked to cause the formation of new inner membrane. Beside such, various complex reasons exist and currently the theoretical knowledge and understanding on the pathological physiology are falling short. As a rational method to overcome the faced issues, the DES which completely decomposes by using biodegradable material should be developed. The biodegradable BVS stent currently in research was recently applied to 45 patients in 2 clinical occasions, and the encouraging result of 4.4% of heart-related side effects and no thrombosis was announced [64]. Also, unlike the DES using metal, it has the advantage of leaving no implant in the body after the artery is healed. Such completely decomposable biodegradable stent is expected to become a new standard of the treatment of coronary artery diseases. In the future, the development of advanced biodegradable materials and fusion among metal, polymer, and ceramic materials shall overcome the limitations of the existing DES and overcome the thrombosis and restenosis currently suggested as problems.

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