Recent trend in applications of polymer materials to stents

Review Article

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ABSTRACT

Stent-based polymeric material is a remarkable tool to deal with any obstructions represented in gastrointestinal (GI) tract or to be used to avoid ongoing dilation or surgery in patients with benign stenosis. The extended study of the efficacy and the safety of the stent for human body should be studied. In near future, it would be possible to use bioresorbable polymeric stent in hospital instead of using metallic stents. In this review, the advantages of bioresorbable polymeric stent over metallic stent, the stenting of polymeric stent at GI tract as well as the drug release mechanism of stent-based polymer are presented. The mechanism of drug release and many parameters affecting drug releasing process are listed. In vitro and in vivo studies of drug-eluting stent are also reported.

Keywords: Biodegradable polymeric stent; Drug eluent; Polymer material; Stenosis

Introduction

Up to date, metallic and polymeric stents have been used to palliate any symptoms of patients in gastrointestinal (GI) tract. Nevertheless, these stents have several limitations associated with stent migration, tumor ingrowth, and repetitive endoscopic procedures. Nowadays, with an advanced improvement of intellect in the field of polymers, polymer materials are considered as a noticeable tool to replace the traditional stents used since the stent-based polymeric materials possess the ability to eventually be degraded or absorbed under natural conditions represented in the host body and create no toxic substances that could induce any inflammation. However, the materials that are not biocompatible with body can induce many complications. Also, some chemicals released from the materials or metal corrosion can create the toxicity, resulting in local cell damage.

Polymeric Material for Stent

Metal stent vs polymeric stent

Practically, in order to relieve an obstruction due to a malignant or benign stricture, many types of stents have been medically used to deal with these problems for examples, metal stents and plastic stents. Considering on the metal stent, there are tons of designed varieties of them such as Wallstent (Schneider, Bülach, Switzerland), Palmaz-Schatz (Johnson & Johnson, Warren, NJ, USA), Wiktor (Medtronic, Minneapolis, MN, USA) and Gianturco–Roubin (Cook, Bloomington, IN, USA), and other designs.1–4 Commonly, materials used for creating metal stent made of stainless steel, tantalum as well as nitinol alloy.1–4,6 Tantalum, a flexible, shiny, and highly radio-opaque metal, has high resistance to corrosion and high ductility. It is more brittle than stainless steel. Current example of tantalum is Wiktor (Medtronic). Nitinol is a biocompatible and super elastic shape memory alloy consisting of 55% nickel and 45% titanium. Nitinol is difficult to produce because the composition change only one percent in alloy can dramatically alter transformation temperature. Although,
Biodegradable and bioresorbable polymers for stent

The biodegradable polymer is known as “biomaterials”, which is a non-living material used in medical application and designed to interact with biological systems. The noticeable properties of biomaterials consist of inert characteristic, do not induce any reaction in the host, long stability in the host, ability to chemically degrade or decomposed under natural conditions. Biodegradable tools are useful for temporary or short-term applications. A product produced from degradation of polymeric materials is able to be resorbed by cell activity such as phagocytosis. Also, the ideal polymeric materials for fabricating the stent should be strong enough to maintain its structure until surrounding tissue has healed, not triggered inflammatory or toxic response to host, metabolized after fulfilling its purpose, leaving no trace to be easily processed into the final product form, and easily sterilized as well. Promisingly, the biodegradable polymers are able to overcome the mentioned shortcoming of the metallic stent as its biocompatibility with the host tissue. Therefore, it might not generate any inflammation. Aside from biocompatibility, another interesting property is that the mechanical properties and degradation rates could be practically tailored to suit various applications by chemical modification of the molecular structure.

Poly-L-lactic acid (PLLA), Poly-D,L-lactic acid (PDLLA), polye-caprolactone (PCL), and polyglycolic acid (PGA), all polyesters, are the most frequently used materials for bioresorbable stents. The degradation time of PGA is around 6 to 12 months, whereas that of PLLA is more than 2 years. Some biodegradable/bioresorbable polymers, such as, polyesters, polyorthoesters, polyamides, and polyanhydrides, may able to modulate the local delivery of drug and also degrade through hydrolytic or other mechanisms. Furthermore, several factors that induce polymer degradation are having the products with more porosity, less crystallinity, and small size. The characteristics and degradation time of the polymers used for stent were depicted in Table 1. Mechanical properties of biodegradable polymers including tensile strength, modulus, and ultimate strain should be considered in order to be used to fabricate stents. For example, PLLA and PDLA exhibited a high tensile strength, but long degradation time (more than one year). In contrast, PGA has less tensile strength but faster degradation.

Xu et al. investigated the biodegradability of biodegradable polymer stent, which was poly(D,L lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL), and polyethylene terephthalate, polyurethane-urea, and poly(ethylene-co-vinyl acetate) and poly(n-butyl methacrylate) (PEVA-PBMA) blend. The stent containing nonresorbable polymers reduced restenosis rates but remained the delayed healing and very late stent thrombosis.

Stenting of Resorbable Polymer Stent in GI Tract

Esophageal stenting

In the case of metallic or plastic stents used in esophagus, they are limited as the restenosis can be induced. Therefore, if the esophageal stent made of the biodegradable polymer, the subsequent stent removal operation would not be necessary. Tanaka et al. investigated the radial force resistant of biodegradable stent. Table 2 itemized the radial force, which was referred to a pressure force required to reduce the diameter by half of the biodegradable stent and other commercially available metallic stents. Tanaka and co-workers attempted to use the machine-knitted poly(lactic acid) (PLA) stent instead of using the metallic stent. The PLA stent

Table 1 Characteristics of Bioresorbable Polymers

| Polymer | Glass transition temperature (Tg, °C) | Modulus (GPa) | Degradation time (mo) |
|---------|-------------------------------------|--------------|----------------------|
| 50/50 PDLGA | 45–50 | 2.0 | 1–2 |
| 75/25 PDLGA | 50–55 | 2.0 | 4–5 |
| 85/15 PDLGA | 50–55 | 2.0 | 5–6 |
| PDS | −10–0 | 1.5 | 6–12 |
| PCL | 65–(−60) | 0.4 | > 24 |
| PDLLA | 55–60 | 1.9 | 12–16 |
| PLLA | 60–65 | 2.7 | 6–24 |
| PGA | 35–40 | 7.0 | 6–12 |

Table 2 Radial Force of the Machine-Knitted PLA Stent and Other Commercially Available Metallic Stents

| Stent | Diameter (mm) | Length (mm) | Radial force (gf) |
|-------|--------------|-------------|------------------|
| NT stent | 10 | 70 | 37 |
| Spiral Z stent | 10 | 60 | 67 |
| SMART stent | 10 | 60 | 57 |
| ACCUFLEX stent | 8 | 60 | 40 |
| ZA stent | 10 | 60 | 58 |
| WALLSTENT | 8 | 60 | 105 |
| Biodegradable polymer stent used (knitting PLA) | 10 | 60 | 117 |

Stents’ manufacturer information: NT stent (Terumo, Tokyo, Japan); Spiral Z stent (Cook, Bloomington, IN, USA); SMART stent (Cordis, Warren, NJ, USA); ACCUFLEX (Boston Scientific, Natick, MA, USA); ZA stent (Cook); WALLSTENT (Schneider, Bülach, Switzerland).

PLA, poly(lactic acid).
was applied in 2 patients with benign GI stenosis. The results showed that the PLA stents were successfully placed to the targeted site and there were no complications during stent placement. Interestingly, in both cases the restenosis had not recurred.

Repici et al investigated the efficacy and safety of biodegradable polymer stent, which was poly(p-dioxanone) (PDO), in 21 patients with refractory benign esophageal strictures. The results showed that 9 of 20 patients (45%) no longer encountered with dysphagia at the end of follow up period. In 2010, the comparative study of self-expanding plastic (Polyflex; Boston Scientific, Natick, MA, USA) and biodegradable stents (ELLA-CS, Hradec Kralove, Czech) to a patient with refractory benign esophageal strictures was published. The patients were separated into 2 groups; the first group (20 patients) was treated with self-expanding plastic and the second one (18 patients) was treated with biodegradable stents. The results exhibited that Polyflex stents were successfully placed in 19 of 20 patients, whereas ELLA-CS was placed in 16 of 18 patients. In Polyflex group, the stent removal was needed in 16 cases, 6 of 16 patients (30%) with dysphagia free after a median follow up of 385 days. For the second group, 6 of 18 patients (33%) were dysphagia free after a median follow up of 166 days. All in all, it might be concluded that the advantage of biodegradable polymer stent over self-expanding plastic stent was that biodegradable polymer stent do not need the stent removal process, but the symptom recurrence and complication during and after stenting need to be studied in details to improve the efficacy and safety of patients.

**Gastrooduodenal stenting**

Gastrooduodenal obstruction, which is an obstruction caused from advanced tumors, is a commonly problem founded in patient. It could be presented at stomach, pancreas, and duodenum as well. Traditionally, surgical gastrojejunostomy has been the palliative treatment, yet this technique is associated with various complications and morbidity. Therefore, in order to deal with this problem, the stenting is a noticeable method to probably replace the former one. Rejchrt et al investigated the placement of biodegradable stent in the lower GI tract. Three different designs, which were referred to flared at both ends, waved shape, and without flared ends, of biodegradable stents (ELLA-CS) used in this research were manufactured from woven PDO monofilaments and the available stent sizes are in diameter of 18 to 25 mm, with both ends flaring to 23 to 31 mm, and are in different lengths from 60 to 135 mm. The biodegradable stent could withstand the radial force for 6 to 8 weeks without any disintegration after implantation. After that, the disintegration of biodegradable stents was observed in the period of 11 to 12 weeks ensuing implantation. They reported 11 patients with stenosing Crohn’s disease. After that, the disintegration of biodegradable stent was not appropriate to use in this case. Therefore, it could be concluded that the waved design stent was not appropriate to use in this case.

Repici et al applied the PDO-based stent to treat 11 patients with postsurgical benign strictures located with 20 cm from anal verge, and refractory to mechanical or pneumatic dilation (at least 3 sessions) were also included in this study. The results showed that the PDO stent could be able to technically place in all patients, somehow 36% of stent migration in the patients within the first 2 weeks after stent implantation. Aside from this group, no stent migration was observed in the remnant (7 patients). The authors described that the majority of problem might be came from early migration of stent rather than an intrinsic failure in dilating strictures. Contrary to the results from the former one, Janik et al successfully inserted the PDO-based stent to three male patients with benign strictures after radiotherapy and resection of a retro-sigmoid carcinoma. They exhibited that no stent migration or occlusion presented in all cases. The stents were completely degraded in 4 to 5 months after implantation. According to reports mentioned above, the colonic strictures, Crohn’s disease, anastomotic colorectal strictures, and postsurgical colonic fistulas, could be medically treated using biodegradable stent. The biodegradable stent showed the efficacy to deal with strictures without any major complication, and it should be noted that the biodegradability of biodegraded stent is a remarkable property as the complication of removing stent after treatment would be avoided. However, the development in terms of stent design would be thoroughly concerned to avoid an early stent migration.

**Biliary tract stenting**

Insertion of stents to bile duct to support the reconstruction or to prevent stenosis is challenging as the CBD, using of T-tube (made of silicon rubber), or using plastic CBD stent (PE, PVC, PTFE, PU) are not able to effectively solve the problem, as common stents would probably induce hemorrhaging and biliary tract narrowing. The use of T-tube generally leads to several complications including biliary leakage, water-electrolyte disturbance, and using of plastic CBD stents is the source of many problems covered accumulation of bacteria-laden biofilms, infections, occlusion with sludge leading to recurrence of jaundice or cholangitis. Therefore, the researchers, nowadays, is putting an effort into developing a new material, which could be used to replace the materials represented, and biodegradable plastic stent is that one, as discussed in following example. Petrtyl et al initially investigated the feasibility of using stent-based biodegradable polymer, which was PDO stent (ELLA-CS), to 2 patients, who had undergone biliointestinal anastomosis for stone disease presented 2 years after surgery with intrahepatic biliary strictures causing new stone formation and chronic cholangitis, to prevent the recurrence of strictures. The results were satisfying.
because 2 years after stent implantation the patients still remained asymptomatic with normal liver function along with no further intervention required. Recently, Mauri et al. investigated the feasibility, safety, and outcome of patients treated with biodegradable biliary stents for benign biliary stenosis refractory. The PDO stents (ELLA-DV biliary stent; ELLA-CS) were applied to palliate symptoms of 10 patients with recurrent cholangitis caused from postsurgical biliary strictures. The result showed that the stent

![Diagram](image)

**Fig. 1.** Schematic represent of diffusion controlled drug coated stent. (A) Monolithic-matrix base Taxus stent (Boston Scientific). (B) Reservoir system-reservoir base Cypher stent (Cordis). Reused from the article of Raval et al (Braz J Chem Eng. 2010;27:211–25).

**Table 3 Factors Affecting Drug Release**

| Parameter                                                                 | Possible effect                                                                                     |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Basic properties of drug                                                 |                                                                                                   |
| Drug hydrophobicity/hydrophilicity                                       | Affects aqueous solubility, protein binding, tissue retention characteristics and local drug concentrations |
| Diffusion/dissolution characteristics                                    | Affects release kinetics                                                                           |
| Solubility in polymer matrix                                             | Affects release kinetics                                                                           |
| Solubility in medium                                                     | With higher solubility, higher drug release rate                                                    |
| Properties of rate controlling polymer                                   |                                                                                                   |
| Thermal properties (Tm, Tg)                                              | Affects degradation and hydrophobicity, drug release and drug solubility in the case of biodegradable polymers |
| Degree of crystallinity                                                  | Affects water penetration and drug solubility in the case of non-erodible polymers                   |
| For biodegradable polymer-initial molecular weight, copolymer ratio, absorption rate and time period, pH of dissolution medium | Affects degradation behavior and time                                                               |
| Processing parameter                                                    |                                                                                                   |
| Selection of coating process (dip coating, air brush)                    | Coating film property and drug eluent                                                              |
| Properties of solvent                                                    | Residual solvent effects, merging of coating layer, thus influencing release kinetics                |
| Solvent evaporation rate                                                 |                                                                                                   |
| Phase diagram of ternary system                                          |                                                                                                   |
| Coating design                                                           |                                                                                                   |
| Drug to polymer ratio                                                    | Effects on drug carrying capacity of polymer and drug elution rate                                  |
| Coating layer composition and thickness                                  | Affects diffusion of drug through film                                                              |
| Drug (initial solid phase) concentration and distribution inside the matrix | Describes initial burst effect and dissolution mechanism                                           |
| Microstructure of coating [spatial variation in physical and chemical composition] | Exhibits process condition and eventual effect on drug delivery kinetics                           |
| Top layer (drug free) thickness and hydrophobicity of polymer            | Regulates drug kinetics by lowering diffusion phenomena                                             |
| Mechanical properties of coating film                                    | Affects coating integrity during process like stent crimping and expansion, Improper coating may induce adverse and interrelated effects such as local inflammation and thrombosis and hinder homogeneous drug uptake |
| Stent design (system geometry)                                           | Affects extent of drug dose differentiation within arterial wall                                   |

Revised from the article of Raval et al (Braz J Chem Eng. 2010;27:211–25).
implantation to all patients was possible without immediate major or minor complications happened. In addition, the PDO stents in all patients were completely degraded in 6 months in follow up period. The use of biodegradable stent at biliary tract showed the advantages beyond the common stents used for CBD as it could be medically used to palliate symptoms of the patient without major or even minor complication.

Drug-Eluting Polymeric Stent

Biodegradable polymers are not only used for stents, but also able to use as drug carrier in drug-eluting stent. Generally, drug-eluting stents are composed of 3 main parts covering a stent platform, a drug carrier, and an active drug. The drug is blended with a bioresorbable polymer to regulate the release rate.

Mechanism of drug release kinetics for stent

The diffusion was defined as a majority of drug release mechanism of stent which can be classified as: (1) Monolithic system in which a drug is dispersed/dissolved in a polymer matrix and the release is controlled by diffusion through the polymer matrix (Fig. 1A). The drug release rate depends on initial drug concentration within polymer matrix. If the concentration of drug is lower the solubility limit in the polymer matrix, the drug dissolution in the matrix limits the release rates; however, if the drug concentration is higher the solubility limit in the matrix, the drug dissolution in the matrix limits the release rates. The example of this mechanism is the Taxus stent (Boston Scientific) consisted of poly(styrene-b-isobuthylene-b-styrene) triblock copolymer for the release of paclitaxel. (2) Reservoir system in which the drug is contained in the core surrounded by a thin polymer membrane and release to the environment controlled by membrane (Fig. 1B). The drug release rate is constant referred to zero order drug release profile at steady state and initial burst or time lag is occurred in the case of deviations in release rate. For example, the Cypher stent (Cordis, Warren, NJ, USA) in which sirolimus drug is loaded within the blend of PEVA-PBMA.

Factors affecting drug release

The main parameters in which affect the drug release from the stent are listed in Table 3. There are many other parameters that are possible for drug release mechanism, for examples, transport of drug through diffusion-convection, biological properties of tissue, and hydrodynamic condition at the implantation site and stent design.

In vitro and in vivo study of drug-eluting stent

Many research groups evaluated either in vitro or in vivo of efficiency to release a drug and degradation kinetics of stent-loaded drugs by using polymeric materials as a carrier for example, fluorouracil, paclitaxel, gemcitabine, carboplatin. In the field of drug-eluting stent for human, Suk et al fabricated a metallic stent covered with polyurethane contained paclitaxel, as shown in Fig. 2. Then, the stent was applied to palliate 21 patients with unresectable malignant biliary obstruction to technically evaluate the feasibility, safety, and efficiency of stent in practical applications, mean follow up was 329 days. The results showed that there were no paclitaxel-specific toxicities and low systematic concentrations resulting from paclitaxel absorption. In addition, another improvement of drug-eluting stent was the increase of numbers of patient survival, which improved compared with historical controls treated with conventional self-expandable metallic stents. However, an overall stent occlusion rate of 43% was observed.

Conclusion

Biodegradable polymeric stent is an attractive tool to replace the common stents represented, i.e., metallic- and plastic-stent. The remarkable property that makes biodegradable polymeric stent as an ideal stent in the future is the biodegradability. The novel stent could be eventually degraded and be resorbed in human conditions without creating any toxic substances. The degradation time of biodegradable polymeric stent also suits with the requirement for healing and reconstruction of tissue to prevent restenosis and symptom recurrence. However, the degradation rate of biodegradable polymeric stent should be thoroughly designed to avoid the stent-induced mucosal and parenchymal injury.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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