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Emerging Trends in Biliary Stents: A Materials and Manufacturing Perspective

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Abstract

Biliary stent technology has come a long way since its inception. There have been significant advancements in materials used, designs, and deployment strategies. Options have expanded from plastic and metallic stents to a wider variety of materials and manufacturing technologies to offer several options to clinicians, including self-expandable metallic stents and bioresorbable stents. Bioresorbable biliary stents are still in the early stages of clinical adoption. This review encompasses the materials currently used for biliary stents and the significant developments in the past few years in the resorbable materials for use as biliary stents. We critically discuss the emerging trends in the development of new resorbable materials for fabricating biliary stents. We then assess the developments in drug-eluting stents and advanced manufacturing technologies that could be leveraged for biliary stents. Challenges in the paths for translation for the future, such as pre-clinical and clinical trials, are highlighted. Finally, we present future directions that could drive the biliary stent market to meet the increasingly complex and diverse clinical needs of patients.

Keywords: biliary stents; polymers; medical devices; bioresorbable stents; drug-eluting stents; advanced manufacturing

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1. Introduction

The common bile duct (or simply bile duct) forms a vital part of the biliary system, which transports bile stored in the gall bladder into the duodenum (upper part of the small intestine). It is a small tubular structure (7.5 to11 cm long and 6 to 8 mm wide on average) formed by the union of common hepatic ducts emerging from the liver and cystic duct from the gall bladder, which finally empties into the duodenum. Bile is a greenish-yellow alkaline fluid and performs the major functions of aiding in digestion by the breakdown of fats and excretion of waste products from the liver to the duodenum. The composition of bile is rather complex, comprising 95% water, and the balance is a variety of solid constituents such as bile salts, bilirubin, amino acids, cholesterol, and enzymes, etc.

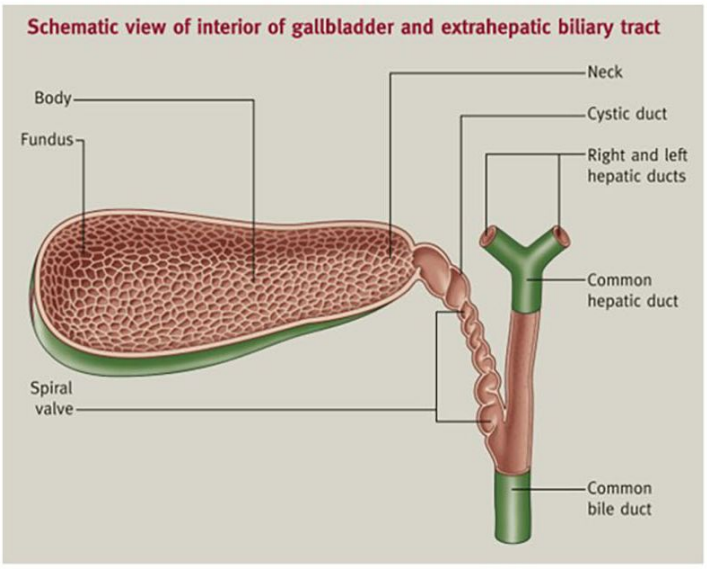

Figure 1: Schematic of common bile duct anatomy[1], Reproduced with permission from Elsevier, Copyright 2020

Due to a variety of clinical pathologies, there can be narrowing or structuring of the lumen of the bile duct causing an obstruction to the normal bile flow. Strictures in the bile duct can either be benign or malignant. Benign biliary strictures (BBSs) primarily result

due to injury to the bile duct, iatrogenic reasons such as common bile duct (CBD) stone disease, post-surgical complications following cholecystectomy, orthotopic liver transplantation and inflammatory causes such as chronic pancreatitis and primary sclerosing cholangitis (PSC). On the other hand, malignant biliary obstruction (MBO) can occur due to biliary tract and pancreatic cancer. Biliary strictures, whether benign or malignant, can have quite diverse repercussions ranging from cholestasis and jaundice to recurrent cholangitis. They can also lead to impaired liver functionality, secondary biliary cirrhosis and ultimately death without proper clinical intervention.

The treatment options available clinically for reversing the biliary obstruction are either a surgical procedure or placement of stents through endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous interventions (percutaneous transhepatic biliary drainage; PTBD). ERCP is unanimously regarded as the best option due to its safer profile and fewer complications.[2]

Biliary stents are tubular medical devices typically made of non-degradable plastic or metal and used to establish the patency of a blocked or occluded bile duct. Endoscopic stenting represents the most common of treating biliary strictures. Stents may also be used to treat bile leaks and seal anastomoses arising due to benign or malignant causes, among other biliary disorders.

This review encompasses the continually evolving field of stent technology in the context of biliary stents. A few reviews have been published in this field such as the one focusing on the different kinds of materials used in the fabrication of biliary stents[3], and another one only on a specific class of materials, i.e., fully covered metallic stents (FCSEMS) used for the treatment of specific pathologies[4], etc. The other class of reviews in this field tend to focus on the clinical aspects of biliary stenting, highlighting the clinical scenario.[5, 6] This review is unique as it discusses broadly about the clinically available stents with an

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emphasis on materials, with a detailed focus on the evolving next-generation stents in terms of materials, manufacturing strategies, and associated clinical outcomes. In view of the recent breakthroughs in biomaterials and associated manufacturing technology that can lead to new generations of such devices, this review aims to highlight the challenges of the current devices and opportunities for the near future for bioengineers and physician-scientists. We first discuss the progressive changes in the class of biomaterials employed as stents. Next, manufacturing techniques used to fabricate stents are briefly compared. We then discuss some latest developments such as drug-eluting stents and complementary technologies such as tissue engineering that have the potential to change the way stents are currently looked at. We finally end with some future directions to go about in making next-generation biliary stents.

2. Materials Currently Used for Biliary Stents

2.1 Plastic Stents

Plastic stents are the first to become widely available for clinical use to seal bile leaks and treat benign strictures. In fact, the first-ever reported biliary stent placement was a plastic back in the late seventies.[7] They are still popular primarily because of their lower cost, ease of placement, and wider availability compared to metallic ones. Some commonly used materials used to fabricate these endoprostheses are polyethylene (PE), polyurethane (PU), and Teflon/ polytetrafluoroethylene (PTFE). They are usually available in diameters of 3 to 5 mm, being limited by the accessory channel of the endoscope. They are therefore prone to occlusion frequently in about three to six months after stenting.[8] The primary cause for occlusion is microbial biofilm formation leading to sludge accumulation in the narrow lumen. Vaishnavi *et al*. systematically characterized the chemically complex biofilms formed on the stent surface and elucidated that smaller diameter stents, longer dwelling times (beyond six months), and the presence of cholangitis at the time of insertion lead to increased biofilm

formation[9]. This early stent occlusion leads to severe complications such as recurrent jaundice and ascending cholangitis accompanied by stone formation[10]. Hence, a widely adopted alternative is using multiple plastic stents with progressively increasing diameters at different time intervals with the idea that gradual and continuous stricture dilation would induce better tissue remodeling. Though it is more effective, multiple endoscopic procedures are needed (at least thrice a year), leading to patient non-compliance, and often stricture dilation is also not sufficient [11]. There have been some approaches to increase stent patency, such as the use of drug-loaded polylactide (PLA) coatings on PU stents. Still, these are only limited to in vitro tests with minimal information on local or systemic toxicities *in vivo*[12]. Plastic stents are generally limited to cases where the life expectancy of patients is less than a year.

2.2 Self-Expandable Metallic Stents (SEMS)

SEMSs were introduced in the early 1980s to reduce the number of endoscopic procedures needed for plastic ones by exerting immediate self-expansion (up to 10mm). They comprise metal mesh cylinders that are designed mostly by laser cutting and some by braiding or knitting. They are usually delivered in compressed form, constrained in a delivery device with an outer diameter of 8.5F or smaller, which is withdrawn, and the stents recover to their original shape over time. [13-15] Some commonly used materials in SEMS are platinol (platinum core with nitinol casing), stainless steel, and nitinol (an alloy of nickel and titanium). Metal stents, in general, are shown to have longer patency over plastic ones owing to their larger lumens. They are typically used in the case of malignant biliary strictures owing to their larger diameters and higher recovery forces. There are three common variations in metal stents: uncovered, partially covered, and fully covered SEMs. Uncovered metal stents (UCSEMS) are the earliest in use but are found to be more prone to tumor ingrowth (TI) due to characteristic wire-mesh structure, which embed in the tissue wall and occlude the stent

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induced by either sludge accumulation or epithelial hyperplasia. Hence, removal becomes necessary, which sometimes might be difficult.[8] There have been some approaches to reduce sludge formation and tissue hyperplasia, such as coating of silver nanoparticles in the nitinol stents that were then implanted in rabbit extrahepatic bile ducts and resulted in an observable decrease in submucosal fibrosis and inflammation compared to bare stents.[16] But these are only limited to in vitro tests and small animal testing. To address this issue, partially covered and fully covered SEMSs (PCSEMS and FCSEMS, respectively) were developed with a thin polymeric membrane to prevent TI. The polymer coating used could be polytetrafluoroethylene, polyurethane, silicone, etc. But even PCSEMSs exhibited hyperplasia [17], and FCSEMSs are more prone to migration and even blockage at smaller biliary branches due to the non-embedding body of the stent [15]. Though FCSEMSs have higher patency than UCSEMSs, the polymer coating might act as a substrate for bile sludge accumulation, and hence, even FCSEMSs report high occlusion rates. [18] It is also known that the mechanical properties of SEMS directly affect its clinical outcomes though this relation is not clearly understood yet. Among the mechanical properties of SEMS, radial force (RF) and axial force (AF) are the most important in determining its performance. Isayama *et al*. reported that while RF decreases as the braided stent continues to expand to its original dimensions after being deployed, AF, which is relatively less explored, was also found to lead to a lot of adverse events like kinking, sludge formation, and migration if it was too high.[19] These parameters need to be more carefully considered to design anti-migration properties in next-generation SEMSs. Nevertheless, it requires additional interventions to replace the stent if it is occluded, which involves increased costs and pain to patients. Hence, the use of SEMS is currently restricted to the treatment of malignant biliary obstruction (MBO). They are not preferred for benign strictures owing to difficulties in repositioning and/or removal post- deployment.[20]

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Table 1: List of commercially available biliary stents

Sl no	Material	Manufacturer	Model Name	Highlights
1	Platinol	Boston Scientific	WallFlex^{R}	• Hard to remove • Self-expanding • High incidence of cholestasis
2	Nitinol	Cook Endoscopy	Zilver^{R}	
3	Nitinol	ELLA-CS	SX-ELLA^{R}	
4	Nitinol	TaeWoong Medical	LCD^{R}, Niti-S^{R} S type, Niti-S^{R}D type	
5	PTFE	Endo-Flex	PTFE-Strong	Can be bended, straight, or curved
6	Soft blend	Hobbs Medical	Biliary stent	Curved and double pigtail
7	PU	GI Supply	ViaDuct	Winged straight
8	PE and PU blend	Cook Endoscopy	Cotton Leung SofFlex	Curved
9	PE	Cook Endoscopy	Zimmon	Double pigtail

Figure 2: Different classes of materials used currently to fabricate biliary stents

3. Next-generation stents

3.1 Bioresorbable Stents

Both plastic stents and SEMS have their share of disadvantages; plastic stents are prone to accumulation of biofilm leading to infectious complications, such as cholangitis, and need

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multiple exchanges. On the other hand, SEMSs are limited by their difficult removal after placement and their tendency to cause hyperplasia leading to stent occlusion or inflammation[21]. The associated long-term complications, hence, may include secondary blockage if the stent is left long or the need for a second surgery for removal[22]. Consequently, bioresorbable stents are promising as they avoid the need for any additional interventions, thereby minimizing hospitalization times and healthcare costs. They can combine the advantage of mesh design (which is typical of a SEMS) that allows for a large diameter lumen, thereby resulting in longer patency while offering degradability. The spontaneous resorbability would be an attractive option in patients with poor follow-up, and the possibility of stent migration is reduced, too[23]. However, they need to meet the stringent mechanical properties for at least eight weeks post-implantation to seal the anastomosis and be flexible enough for easy implantation. More importantly, they must fully resorb in approximately six months without triggering an excessive inflammatory response via degradation products. Now, the materials used could be resorbable metals/alloys or polymers.

3.1.1 Resorbable Metals/Alloys

Magnesium (Mg), iron, zinc, and their alloys are among the most favorable metals studied as resorbable medical implants, including stents. Mg alloys have recently gained a lot of interest as resorbable orthopedic fixation devices and coronary stents, with some of the products being commercialized, such as DREAMS 1 G and DREAMS 2 G, etc. Though the biocompatibility and degradation behavior of Mg-based implants are quite well understood in bone and blood environments, studies on the use of Mg-based stents in the biliary system are yet to be explored.

Metallic implants, in general, resorb via corrosion through rather complex mechanisms that generate a wide variety of degradation products. More importantly, the rates and products of

corrosion may differ fundamentally between *in vitro* and *in vivo* conditions[24]. Chen *et al.* evaluated the degradation of Mg-6Zn alloy [25], its effects on apoptosis of bile duct epithelial cells both *in vitro* and in rabbits[26]. The results found in both the cases were indeed quite contradicting; there was apoptosis and necrosis of primary mouse extrahepatic bile epithelial cells *in vitro,* whereas no prominent effects on inducing apoptosis were observed *in vivo*. The reasons were the very different corrosion rates in both the conditions and the influence of different constituents present in bile. The alloy exhibited a very high corrosion rate *in vitro* compared to *in vivo*. Liu *et al.* studied in *vitro* degradation of pure Mg and WE43 alloy in human bile over 60 days to be acceptable[27], but detailed *in vivo* studies are warranted as the complex bile environment can significantly alter the results. Liu *et al*. evaluated the *in vivo* biodegradation of AZ31 alloy (3 wt% Al, 1 wt% Zn, and balance Mg) stents on placing in rabbit common bile ducts. Stents retrieved post-1-month implantation maintained their shape and morphology, highlighting improved corrosion resistance than Mg-6Zn alloy, while after three months, the stents had severely corroded with some parts peeled off and structure damaged. The stents had completely degraded after six months with very few residues remaining, and histological examination also revealed acceptable biocompatibility[28]. Apart from the obvious benefits of avoiding a second surgery, Peng *et al.* studied if the degradation products of pure Mg wires have any gallbladder tumor-inhibiting potential and found that a higher concentration of Mg^{2+} and OH^- ions inhibited gall bladder cancer cell proliferation and induced apoptosis. They also reported that Mg wires significantly reduced tumor mass after 24 days of implantation in nude mice[22]. However, *in vivo* studies for longer durations involving stents made of the Mg and other degradable metals such as Zn, Fe, and their alloys are essential to assess their efficacy and clinical outcomes. Special emphasis should also be laid on assessing the long-term toxicity of all possible degradation products.

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3.1.2 Resorbable polymers

To overcome some of the shortcomings posed by non-resorbable stents, such as a second surgery required for their removal, the choice of resorbable polymers is clearly advantageous. A lot of the resorbable polymers are already in use for the large-scale production of medical devices, including scaffolds, sutures, drug delivery systems, and stents. As far as resorbable polymeric biliary stents are concerned, most used polymers are polyglycolic acid (PGA), polylactide (PLA), polycaprolactone (PCL), polyglycolide (PGA), polydioxanone (PDO or PDX), and their copolymers, etc.

Important requirements for an ideal stent in biliary reconstruction would be sufficient expansion forces, resistance to sludge attachment and migration, minimum inflammation and damage to the duct wall, and the ability to resorb in a timely manner to allow for tissue remodeling. *In vitro* testing of all these properties provides an essential preliminary assessment of the material properties for initial screening based on which *in vivo* testing can be undertaken, which are typically expensive and time-consuming. The degradation studies are mostly performed with the polymer immersed in human/animal bile and sometimes in phosphate-buffered saline (PBS) at 37°C. It is critical that degradation occurs in a controlled fashion and should be optimally slow to allow for enough mechanical support to hold the narrowed duct open for the initial time of placement. Ideally, degradation time should match the healing time of the bile duct, but on average, a time frame of six to eight months is considered optimal. The mechanisms of *in vivo* degradation of these polymers are studied to some extent using experiments as well as modeling in the case of vascular stents[29]. Broadly, the aliphatic polyester class of polymers degrades in a two-step process, chemical hydrolysis, wherein the water molecule breaks apart the random ester bonds in the polymer chains into oligomers and monomers, followed by enzymatic degradation that breaks down the chains into smaller fragments[30]. In addition to hydrolytic degradation, the surrounding biological

molecules that encounter the stent may also influence its degradation. In the biliary environment, several enzymes in the bile like proteinase K and lipase PS, etc. have been found to accelerate the *in vitro* degradation of PLA and PCL-based stents. Enzymatic degradation again proceeds in a two-step process, the enzyme approaching the polymer surface followed by the enzyme initiating the hydrolysis. The exact time of complete degradation of these polymers depends on a variety of factors, including the chemical structure, molecular weight, polydispersity, and crystallinity, etc.

PDO stents degrade in three to six months, have superior flexibility, and retain their mechanical properties longer than most other polymers such as PLA[31]. PDO degrades by random hydrolysis of its ester bonds into glyoxylic acid. Similarly, PLA degrades into lactic acid, which is then metabolized through normal pathways (Krebs cycle) into carbon dioxide and water[32]. PLA usually takes 2 years on average for complete degradation *in vivo*. Also, the advantage of resorbable polymers is that the degradation rates can be suitably tuned to some extent by copolymerizing the appropriate polymers. The complete degradation time varies from four to five weeks for poly(L-lactide-*co*-glycolide) (PLGA), more than twelve weeks for a block copolymer of PLA and polyethylene glycol (PEG)[33] to six months for poly(L-lactide-co-ε-caprolactone) (L-LA/CL 50:50)[34]. A copolymer of three polymers, namely PLA, PCL, and PGA, i.e., poly (lactide-co-glycolide-co-caprolactone) /PLGCL was synthesized, used for bile duct reconstruction in a porcine model, and was absorbed completely in 6 months[29]. However, more detailed investigations are required to compare the degradation profiles of the copolymers and identify their degradation products.

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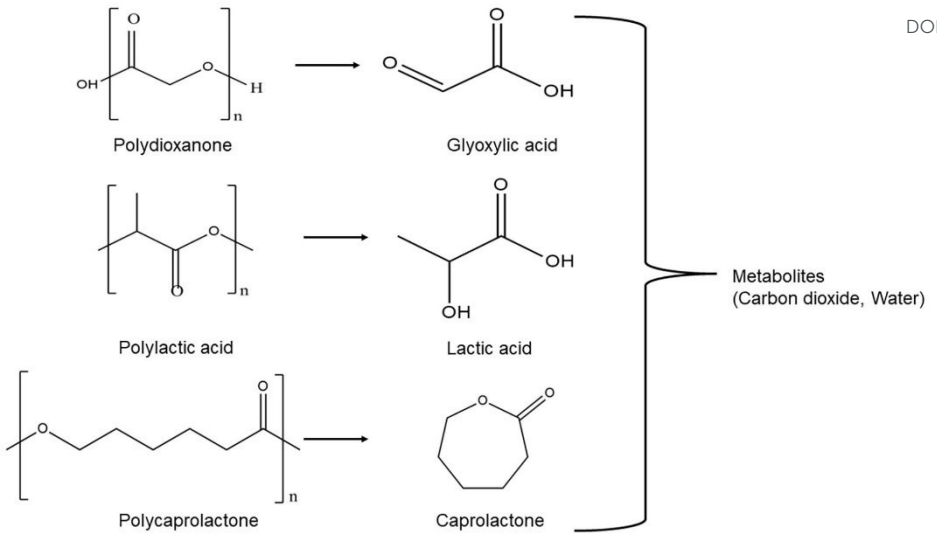

Figure 3: Degradation of different polymers into respective monomers

Table 2: Comparison of properties of different resorbable polymers for biliary stent

Sl no	Polymer	Mechanical Properties	Degradation profile	Reference
1	PLGA	TS=55 MPa, E=2.25 GPa	Canine model: 5 weeks	[35]
2	PLLA	E=7.5 GPa	Porcine model: 6 months	[36,37]
3	PLGCL	-	Porcine model: 6 months	[38]
4	PDO	E=1.75 GPa	Porcine model: 13 weeks	[36,39]
5	PLA-b-PEG-b-PLA	-	*In vitro*: 6 months	[33]

Among the mechanical properties, tensile strength, modulus, maximum elongation, and radial force are important. The radial force of early PLA stents was much lower compared to SEMS but that has been mitigated through advanced manufacturing, e.g., braiding. For self-expanding braided resorbable stent of poly-l-lactic acid (PLLA), the diameter recovery to original increases with the diameter of the delivery device, decrease in fiber diameter while radial pressure stiffness of the right designs was comparable to metallic ones[40]. Also, the evolution of mechanical properties as the stent degrades over time is crucial to maintaining patency. For instance, PLLA monofilaments retained mechanical properties for eight weeks

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without any brittle fracture[36] while the block copolymer of PLA-b-PEG-b-PLA for 10 weeks[33]. To assess the sludge attachment on the surface, PLLA and PE stents were immersed in human bile for 56 days and the amount of sludge on PLLA was less compared to PE due to the self-clearing mechanism of PLLA owing to its degradation[41]. This behavior highlights another potential advantage of a resorbable stent, that is, it inhibits bacterial adherence owing to its degradation over time which sheds off the bacterial load.

In an interesting study by Kwon *et al.*, a comparison was made between PGA, PDO, PDO-PLLA (sheath-core), and PDO-Mg (sheath-core) stents for their *in vitro* properties as well as *in vivo* efficacy in porcine models[42]. While the PDO stent degraded into smaller fragments by 18 weeks, in the PDO-PLLA stent, the PLLA core was still intact with the PDO sheath peeled off. This unique approach of placing two different materials with varying degradation profiles was successful in minimizing the adverse effects of stenting. The PGA stent degraded rapidly due to its low radial force. The PDO/Mg sheath-core also degraded within eight weeks due to the very thin wire of the outer PDO, which led to very fast degradation of the inner Mg. The PDO-PLLA stent was fractured in 16 weeks in the *in vivo* study, but the thin fragments did not cause any serious adverse events compared to the bare PDO stent, which fractured in 12 weeks and the fragments were thick enough to result in adverse events. This concept of having a bilayered structure of different polymers with varying degradation can be further extended to copolymers and polymer blends to yield more predicted and tunable degradation profiles.

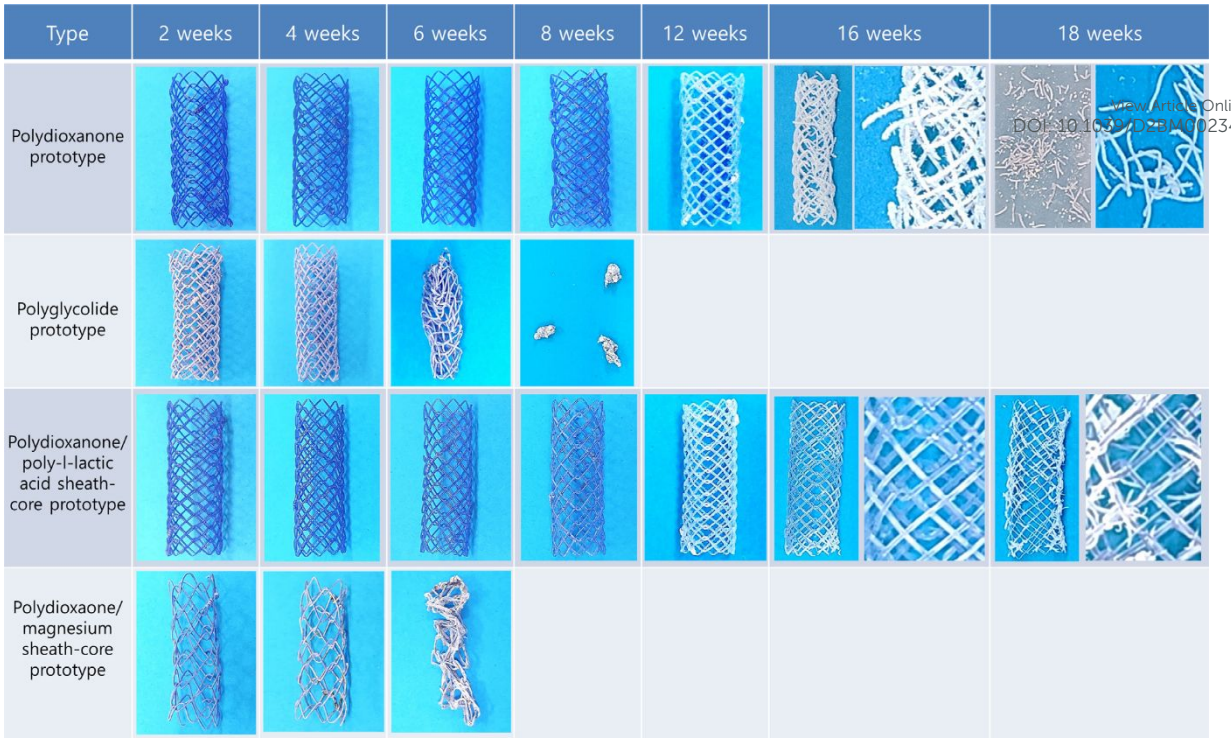

Figure 4: *In vitro* biodegradation of different resorbable materials for biliary stents: Effect of core-sheath design in controlling the adverse effects after stenting. PDO stent fractured in 16 weeks resulting in thick fragments and hence occlusion but PDO/PLLA sheath-core stent fractured into thin fragments without causing occlusion. PGA and PDO/Mg sheath-core degraded rapidly due to low radial force and thin diameter of the outer PDO sheath respectively. [42], Reproduced with permission from John Wiley and Sons, Copyright 2021

Table 3: Comparison of various materials used to fabricate biliary stents

Sl. No.	Class of Material	Advantages	Disadvantages	Clinical Outcomes	Ref
1	Plastic	• Less expensive • Easier removal and re-stenting • Ideal for shorter patency time (3 months)	• Needs frequent replacement after 3-6 months • Prone to occlusion leading to cholangitis and stone formation • Prone to migration • Infection, pancreatitis, bleeding	• Suitable for benign strictures • Useful in cases where the life expectancy of patients is lesser than 3-6 months	10, 20, 43

2	Metallic	• Longer patency (10 months) • Reduces overall hospital stays, costs, and pain to patients	• Retrieval is difficult • Occlusion by tumor ingrowth/overgrowth • Cleaning, additional stent placement upon inclusion • Higher initial costs	• Ideal for malignant strictures • Larger inner diameter reduces blockage in case of unresectable tumors	44-46
3	Resorbable	• Prevents additional procedures of restenting, etc. • Reduces biofilm formation due to self-cleaning property	• Long-term effects not well reported • *In vivo* degradation mechansims not fully analysed	• Expected to be patent for longer durations than plastic stents • Ideal for benign stenoses	47, 48

3.1.3 Tissue-engineered Bile Ducts

As the field of biomaterial science continues to advance rapidly, tissue engineering (TE) approaches also become more advanced, bringing the dream of tissue/organ regeneration one step closer to realization. Though *in vitro* liver tissue engineering has made great strides, presently, the models still lack the bile duct system. Recently, there have been some approaches to engineer biliary tissues, both intrahepatic and extrahepatic biliary tree *in-vitro* using biologically derived materials such as cellulose, synthetic polymers, and decellularized extracellular matrices (dECM). Natural materials, e.g., bacterial cellulose films, were used for biliary reconstruction in pigs and were completely resorbed over 47 weeks with inflammation and excessive fibrosis[49].

An elegant strategy to grow bile duct epithelial cells was devised by first converting human induced pluripotent stem cells (iPSCs)into hepatic spheroids, which can form ductal structures in the right 3D conditions. This would still require a long time and involves

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complex procedures. Lewis *et al*. 3D printed cholangiocyte-laden dECM (derived from the porcine liver) with sacrificial Pluronic F-127, which were later washed away to form aligned ducts in a pure ECM network[50].

TE can also be combined with 3D printing to yield more customized bio-biliary stents. A combination of natural and synthetic materials, namely PCL and gelatin methacryloyl (GelMA) were 3D printed into tubular constructs with ultrasmall superparamagnetic iron oxide (UPSIO) nanoparticles as a contrast agent to monitor the position and degradation of stent via MRI[51]. However, relevant cell lines were not used as only BMSCs were shown to maintain viability and proliferate on the scaffolds for only 13 days, and no animal testing was performed. In a study, polyvinyl alcohol (PVA) was printed and crosslinked into porous tubular stents, coated with PCL- $BaSO_4$ at the ends, and later cholangiocyte-laden collagen gels were matured on them for two weeks[52]. This tight cell layer aids in tissue integration and reduces bacterial adherence to the stent surface and warrants further studies to determine the long-term stability of such materials and cell viability. A 3D printable bioink of thiolated-gelatin supplemented with peptide amphiphiles (PAs) was used to tailor the bioactivity and nanostructure, which allows for the incorporation of cholangiocytes. PAs trigger specific signaling pathways leading to the maturation of small cholangiocytes to mature to initiate the formation of rudimentary intrahepatic ducts[53]. However, this was only a preliminary study to explore the potential of PAs and still needs substantial efforts to mimic the formation of the functional duct and branching structures as seen in the native liver tissue architecture.

Sampaziotis *et al*. developed a challenging approach to isolate human cholangiocytes derived from the extrahepatic biliary tree, develop them into organoids and validate *in vivo* as they self-organize into bile duct–like tubes expressing biliary markers the following transplantation in mice without any tumor formation or differentiation into other lineages. They also tested the potential of ECOs to grow on PGA scaffolds and found their

functionality and marker expression maintained, now providing a bioengineered tissue resembling the biliary epithelium structurally and functionally. These PGA scaffolds populated with ECOs, when implanted into mice with incised gall bladder walls, exhibited full remodeling with a morphology resembling untransplanted counterparts and endogenous cells colonizing the scaffold. For common bile duct (CBD) reconstruction, they used ECOs populating densified collagen scaffolds which also maintained all biliary markers. This ECO populated collagen tube was inserted into excised CBDs of mice, and biliary reconstruction was achieved with minimal apoptosis and proliferation[54].

These studies certainly open new avenues in reconstructing bile ducts without using any stents but are currently only limited to understanding the regeneration process better.

3.2 Drug-eluting Stents (DESs)

Current biliary stents that are in wide use for treating malignant biliary obstruction (MBO) are only for ensuring proper bile drainage with no antitumor activity. Chemotherapeutic drugs are administered separately and are not localized, leading to systemic and undesired side effects with limited bioavailability. DESs combine stenting with chemotherapy to simultaneously prolong stent patency and improve the prognosis of related disorders. Additionally, stent occlusion can be caused due to microbial growth and biofilm formation and epithelial overgrowth, etc. Attempts at engineering DESs so far have mostly focused on FDA-approved single drugs, e.g., paclitaxel (PTX) and gemcitabine loaded in a polymeric membrane coated over metal stents. Jang *et al*. coated metal stents with a double membrane structure of PTFE on the inner layer and PTX-polyurethane- Pluronic F-127 as the carrier and placed them in the bile ducts of pigs. The optimal drug carrier concentrations maintained a sustained release up to 28 days in the pig models without any histological changes, but there were concerns with stent occlusion and migration[55]. To overcome these limitations, sodium

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caprate (SC), known to enhance the local antitumor effect, was added to inhibit occlusive tumor ingrowth, and antimigration flaps were added[56].

Sorafenib (SF) was studied as an anticancer drug by dissolving it with PCL as the carrier and then electrospraying it over metallic stents. This strategy was effective in inhibiting the proliferation of HuCC-T1 cancer cells and also in animal tumor xenograft model[57], but the drug release profile was not exhaustively evaluated.

Xiao *et al*. tested a combination of drugs, namely gemcitabine (GEM) and cisplatin (CIS) in poly-L-lactide-caprolactone (PLCL) matrix as the drug carrier prepared by mixed electrospinning. This drug-loaded PLCL membrane was coated over a covered Nitinol stent placed on a rolling collector. Both the *in vitro* cell experiments performed on human cholangiocarcinoma cells and *in vivo* tumor xenograft mouse model confirmed the antitumor activity of the drug-loaded nanofilms, and the dual-drug-loaded films showed a much better effect than the single-drug-loaded films. Also, the drug release was sustained over a period of 30 days with no initial burst effects. The film-coated stents were implanted in porcine biliary tracts, and histologically, there were no significant complications like ulceration, perforation, necrosis, or mucosal hyperplasia except for fibrotic reactions in the submucosal layer of stented segments.[58] However, the drug release rate was only tested in *vitro,* which could be significantly different in animal models and patients. The antitumor effect was also tested in mouse xenografts which is not representative of the complex tumor microenvironment in the biliary tract. Longer time scale studies in relevant large animals are required to validate the efficacy of these potential DESs.

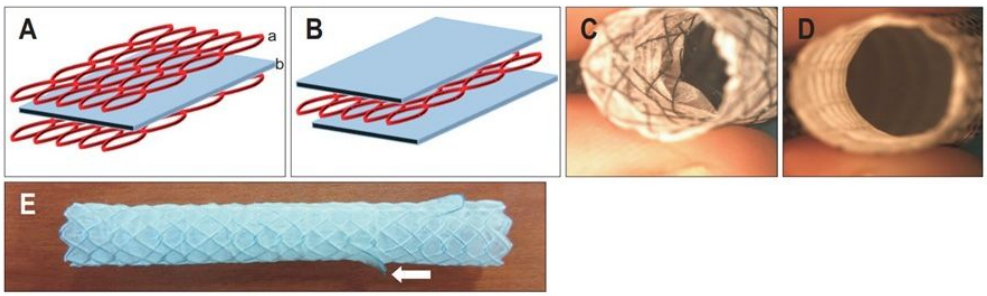

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Figure 5: Drug-eluting biliary stents. (c) Modification of PTX impregnated membrane over SEMS, the metallic mesh is flanked by membranes on either side, thereby preventing stent occlusion by food or sludge[59]. Reproduced with permission from Joe Bok Chung, Copyright 2018

3.3 Alternative Approaches

In one study by Schaub *et al*., the authors tried engineering bile duct formation by relying on trans-differentiation approach[60]. Hepatocytes were shown to convert into mature cholangiocytes and form a functional biliary system owing to their plasticity. Though this study seemed promising as the first-ever organ development de novo by mammalian trans-differentiation, the time needed to form a mature and stable bile duct is yet to be explored.

4. Testing in Animal Models

Resorbable stents made of common polymers have been tested in various animal models, which provide more relevant insights into their clinical efficacies than *in vitro* studies. Braided self-expanding stent made of PLA and barium sulfate as a radiopaque marker (BioStent, Bionx Implants, Blue Bell) has been tested in bile ducts of swine and reported to be functional for more than six months without integration with the duct or proliferation, but sludge accumulation was a concern [61]. The same stent was used for a large-scale animal (swine) study to seal bile leaks after cholecystectomy and was found easy to insert, dilated almost immediately to its original diameter after deployment, safe, and completely degraded in between 3 to 6 months[37]. PLLA stent of a different design, helical braided, was implanted in canine models and reported no sludge attachment 3 months after implantation due to the degradation, which clears off the sludge and hence could maintain patency longer in the bile duct [41].

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Copolymers such as PLGA showed complete absorption in canines in 2 to 3 weeks without any significant chronic inflammation, which marks their suitability for temporary therapeutic applications[35] while others such as lactic and glycolic acid and caprolactone copolymer stents maintained their patency in pigs for as long as 6 months after which they resorbed completely [34].

Table 4: List of resorbable polymers studied in animal models for biliary stents

Sl no.	Polymer	Type of stent/ Commercial product	Size and type of animals	Indications	Reference
1	PLA	BioStent (Bionx Implants, Blue Bell, Pa): braided	8 pigs	• Easy deployment • Good immediate self-deployment • No bile duct integration/ proliferation Sludge attachment	61
2	PDO	ELLA DV, ELLA CS	23 pigs	• Complete absorption in 13 weeks • Mild to moderate hyperplasia and inflammation by 13 weeks • Large accumulation of mucus by 8, 13 weeks but intensity of inflammation reduced by 20 weeks	39
3	PLCL-PGA	Biopatch: Porous PLCL scaffold reinforced with PGA fibers: not yet commercial	12 pigs	• Degraded in 5 weeks without any foreign matter • Neo-bile duct regenerated	62, 63
			10 pigs	Long defect in the bile duct healed with neo tissue resembling native in 4 months	

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5. Clinical Trials

Very few resorbable materials have been studied in large animal models. Among them, only PDO has been used in large-scale clinical trials globally. The reason is its superior flexibility and elasticity combined with a favorable degradation time of 6-8 months. Pilot studies in patients with benign strictures and postcholecystectomy bile leaks using self-expanding braided PDO stents placed endoscopically over two years of follow-up revealed good clinical feasibility and safety without any adverse events except for mild cholangitis[31]. The same PDO stents had shown good outcomes when placed percutaneously in about one hundred and seven patients with benign biliary stenosis with some cases of cholangitis and mild haemobilia.[64] In another non-randomized study involving 159 patients for treatment of biliary strictures, PDO stents were successfully placed percutaneously. However, it was observed that recurrence of stricture still could not be completely avoided, and a substantial fraction of patients (32.6%) required new percutaneous drainage with or without implantation of a new stent. Hence, it can be clearly seen that even resorbable stents are not completely efficient at avoiding restructuring of the bile duct. Larger trials involving more patients and more detailed follow up will be required to fully comprehend the mechanism behind the reappearance of blockage.

A single-center, prospective pilot study was carried out in patients using a novel resorbable Archimedes stent (Amg International GmbH, Winsen, Germany) which has three different sets of polymers with varying degradation profiles. They include a blend of PDO with polyethylene glycol (PEG) of fast degradation rate, medium degradation by PDO alone with a radiopaque marker of barium sulfate ($BaSO_4$), and slow degrading ter-copolymer of poly (lactide-co-caprolactone-co-trimethylene carbonate) PLCLMC with $BaSO_4$. The unique helicoidal designed stent had a very good technical success in placement, loadability, and

pushability. Also, the safety profile was excellent, with none of the patients required to be readmitted or needing additional interventions. However, it should be noted that the follow-up time in this study was six weeks, which may be short for some clinical usages. The fact that no adverse events, including cholangitis, were reported could again be attributed to the relatively shorter degradation time, which inhibited stricture recurrence and sludge attachment[65].

The clinical trials so far look promising, but there are still are major concerns about the long-term placement of stents over six months, such as insufficient radial expansion force and build-up of stent fragments during degradation leading to duct obstruction and AEs, including cholangitis that need to be resolved for large scale clinical usage.

Table 5: List of resorbable polymers studied in clinical trials of biliary stents

Sl no	Polymer	Commercial Name	No. of patients	Follow up time	Indications	Reference
1	PDO	ELLA-CS	13	1-12 months	• Endoscopic insertion successful • Mild cholangitis during 3 months • Long-term success rate>80%	23, 39,66,64
		ELLA-DV, ELLA-CS	159	12-60 months	• Technical and clinical success rate=100% • Recurrence of symptoms in 32% patients • Hemobilia as a potential complication	
		ELLA-CS	13	18-24 months	• Cholangitis and sump syndrome after 11 months • Re-drainage required in 2 patients • >80% patients	

					asymptomatic	
		ELLA-CS, ELLA-DV	107	6-49 months	• 98% technical success (stent migration in 2%) • 4%- mild hemobilia • 20%-stricture recurrence after 2 years • 15%-cholangitis	
2	Multiple; (varying degradation profiles) Fast: PDO+PEG Medium: PDO+$BaSO_4$ Slow: PLCLMC+$BaSO_4$	Archimedes stent; Amg International GmbH, Winsen, Germany	38	2 weeks-6 months	• Excellent safety profile • Stent migration as a mild complication • Complete degradation of all stents by 6 weeks • No cases of cholangitis	67

6. Manufacturing

We briefly discuss some of the typical manufacturing techniques and innovations used to fabricate biliary stents. Notably, there has been a progressive change from conventional methods to additive manufacturing for making biliary stents.

6.1 Conventional Processes

For most metallic stents, laser micro-cutting has been the most scalable production route. Usually, Nd: YAG lasers are used to make intricate patterns on metal tubing, after which they are deburred and polished. SEMSs are constrained in delivery devices and spring back to

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their preset diameters upon release. Coiling, braiding, and knitting are some of the other common techniques if the raw material is in the form of a wire to yield a wire-mesh kind of a stent design. The most common wire-based SEMS is that of WallFlex, a braided design. Cook is an example of knitted stents. For polymeric stents, extrusion, injection molding, and blow molding are commonly used.

6.2 Additive Manufacturing

Stents manufactured by the conventional methods are available in a very narrow size range and hence, lack customization. Additive manufacturing, or 3D printing, has taken the field of biomedicine by storm, finding use in the rapid production of personalized bone implants and scaffolds, etc. There are, however, few studies that have investigated making biliary stents via 3D printing, and there is still a lot of scope in this field. Extrusion printing is the most widely used technique and has been reported for making tubular crosslinked polyvinyl alcohol (PVA) materials coated with cholangiocyte-laden gels and PVA-coated PCL structures. A whole anatomical structure of a branched bile duct system (intra- and extrahepatic ducts) with very thin walls (around 60 μm) was designed with PVA dip-coated PCL to make it more flexible and hence easier to insert. There were no abnormal histological changes after three days of implanting the constructs in rabbits[68]. However, such thin-walled constructs might not be able to maintain stent patency for long durations, and hence, longer *in vivo* studies in large animal models are needed. There are also efforts to make anatomically realistic models focussing on intrahepatic as well as extrahepatic biliary tracts via another type of 3D printing, namely stereolithography (light-based printing). For instance, phantoms used for simulation of surgical interventions, and patient counselling, etc[69] along with biomimetic extrahepatic bile duct model (EHBD) was fabricated as a robust platform for *in vitro* testing of biliary stents to reduce dependence on expensive and time-consuming pre-clinical testing in large animal models [70].

Table 6: List of common manufacturing strategies for fabrication of different biliary stents

Sl. No.	Manufacturing technique	Advantages	Disadvantages	Highlights	Ref
1	Laser cutting	• Low shortening rate • Accurate positioning • Favorable removal • Lower risk of stent migration	• Absence of randomized studies to compare with other strategies	• Unresectable malaignant obstruction	71, 72
2	Braiding	• Good mechanical strength, stability • High shape recovery, flexibility • Suitable to make both SEMSs and polymeric stents	• Requires monofilaments of specific diameters • Multiple post-processing steps involved • Higher migration rate	• Properties largely depend on filament diameter, braiding angle, bobbins number, etc • Useful in making anti-reflux SEMSs	73-76
3	Molding	• Less expensive for scaling up • Can be extended to create nano features in the mold	• Can only yield closed walled hollow tubes • Not flexible with design	• Ideal for plastics • Various polymer blends can be shaped by injection molding	77-80
4	Additive Manufacturing	• Design flexibility • Complicated shapes can be realized • Customization according to patient needs	• Slow, more expensive • Limited library of materials • Not matured to prepare SEMSs	• Can be combined with drug eluting technology • More control over dimesnsions, etc	52, 81

6.3 4D printing

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The field of additive manufacturing and 3D printing in medicine has rapidly progressed, with the latest technology being 4D printing. Using such a technology, one could envision creating shape memory polymers that can be delivered using a catheter in a compressed state and then recover back to its initial expanded state when triggered with an appropriate stimulus such as light and magnetic field, etc. This can completely avoid the need for a surgical procedure as the stents can be deployed in a compressed form in a minimally invasive manner. This has been demonstrated in a study by Wei *et al*. where crosslinked PLA, which is intrinsically shape memory reinforced with magnetic nanoparticles (Fe_3O_4), was 3D printed into a vascular stent and stimulated with an alternating magnetic field for recovery of the compressed stent[82]. Using a similar concept, bioinspired tracheal stents were printed using PLA/ Fe_3O_4 composite, deformed, and deployed back into their confirmed shape using a magnetic field[83]. Such studies show the potential of advanced materials complemented with equally advanced manufacturing techniques in enabling high precision, customized, and deployable biliary stents.

6.4 Future Directions in Precision Medicine

In this new era of precision/ personalized medicine, quality of life and patient care form the basis of any medical treatment strategy. In view of this, biliary stent technology has also adapted from its early years where only plastic stents were in use without any customization to self-expanding metallic and resorbable stents with patient specificity. As discussed above, resorbable stents are poised to pave the way forward in terms of next-generation stents for improving quality of life. Advances in biomaterials allow the development of unique polymers and blends of desired physical characteristics-; for instance, a thinner stent may be more suitable for a bile leak as compared to a more rigid stent for a fibrous blockage. Stents can be produced in desired shapes and sizes very rapidly using 3D printing and prototyping, while the addition of post-deployment structural 4D properties may help position stents better

in unique anatomical situations. Resorbable polymers could also be leveraged to incorporate suitable drugs and other biomolecules of interest as controlled delivery platforms. While this has been extensively done with vascular stents [84], this remains largely unexplored for biliary stents. Most studies have focused on having a resorbable coating with the active drug moiety on the surfaces of metallic stents[41-43], which doesn't make the device degradable anymore. Hence, efforts are required to incorporate the drugs with their delivery platforms into the resorbable polymers, which would be both resorbable and exhibit a prolonged release profile. Advanced materials complemented with complimentary advanced manufacturing techniques truly have the potential of enabling high precision, customized, and deployable biliary stents.

7. Conclusions

The clinical trials of biodegradable stents, particularly the ones using PDO, have shown promising results and may present an attractive alternative in the treatment of hepatobiliary strictures or leaks. However, more rigorous trials are needed involving more patients with diverse clinical needs to gauge the efficacy of bioresorbable stents. Researchers should also focus on blending PDO with other polymers such as PEG and PCL, etc., to tune the degradation and mechanical properties. As a result, a library of biomaterials can be made available from polymers widely used in devices approved for clinical use. Another feature that is largely untapped is the design features, which play a crucial role in preventing restructuring. The Archimedes stent with helicoidal shape is one such example. There also needs to be an integration of drug-eluting features with absorbability to have a synergistic advantage. Also, development of drug-eluting anti-reflux valves for preventing sludge formation can be explored. Finally, 4D printing can be exploited to fabricate miniaturized stents, which could be deployed in non-surgical ways. In summary, the field of bioresorbable biliary stent technology is nascent but rapidly progressing towards making a mark in the

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markets. It is envisaged that future innovations in materials, design, and manufacturing can synergistically accelerate the process.

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