Chapter 5 Biodegradable medical implants

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Every year millions of patients can improve their quality of life through surgical procedures that involve implanted medical devices. U.S. Food and Drug Administration (FDA) defined medical implants as devices or tissues that are placed inside or on the surface of the body, replacing missing body parts, delivering medications, monitoring body function and providing support to organs and tissues. The general medical implants include orthopaedics, pacemakers, cardiovascular stents, defibrillators, neural prosthetics or drug delivery system [1].

Over the years, metals, polymers and ceramics have found their applications in various medical implants. Metals are widely used in load-bearing implants, ranging from plates, screws for bone fracture fixation to joint prostheses for hips, knees, shoulders, ankles and so on. The most commonly employed metals are 316L stainless steels, cobalt-chromium alloys, titanium alloys and magnesium alloys [3,4]. Polymers have been used in facial prostheses, kidney and liver parts, heart components, dentures, and hip, knee joints, for instance, ultrahigh molecular weight polyethylene (UHMWPE) for load carrying devices [4], polymethylmethacrylate (PMMA) as bone cement [3], polyethylene terephthalate (PET) for vascular grafts and heart valves [5]. Ceramics are used to replace or fix hard connective tissue, such as bone and teeth due to high strength, toughness and surface finish [6].

Lately, biodegradable materials have been utilized in medical applications and have attracted a lot of attention. The development of fully biodegradable medical implants have started from biodegradable sutures first approved in 1960s [6]. Basically, biodegradable implants provide a temporary support and degrade away after service. The degradable nature of biodegradable medical implants allows for excretion of the materials from the body, enabling the injured site to restore its function over time after having benefited from the implants [6]. There are 4 types of degradation mechanisms that are responsible for implants degradation and these are hydrolysis, oxidation, enzymatic and physical degradation [7]. Polyhydroxy acids are the main materials for biodegradable devices due to their good biocompatibility. These materials include polylactide (PLA), polyglycolide (PGA), and copolymers based on lactide, glycolide, trimethylene carbonate (TMC) and caprolactone [6].

Biodegradable implants offer many advantages over traditional permanent implants, especially metallic implants, which are related to stress shielding, corrosion, ion leaching, inflammation and implants removal. Currently, there is a shift in use of the permanent metallic implants for temporary therapeutic applications to biodegradable implants. This chapter mainly discusses the advance of biodegradable implants used in orthopaedic, cardiovascular and wound closure systems.

5.1 Biodegradable sutures

Sutures are widely used in wound closure and have been used for centuries. Collagen, cotton, silk, linen, poly (propylene) (PP), poly (ethylene glycol terephthalate) (PET), poly (butylene glycol terephthalate) (PBT), nylons, polyamide (PA) etc. have been used as sutures materials. However, since the successful introduction of two synthetic absorbable suture: Dexon® and Vicryl® in early 1970s, a new chapter of suture materials has been opened [8]. Biodegradable sutures can break down in tissue after the wound is closed firmly in a given period of time, are extensively used currently for healing internal wounds to avoid secondary removal surgery [9]. Originally biodegradable sutures were made of the intestines of sheep, the so called catgut, but with numerous advantages over catgut sutures, including ease of handling, low cost, low tissue reaction, synthetic biodegradable polymers, such as poly (lactic-co-glycolic-acid) (PLGA), Poly (glycolic acid) (PGA), polylactic acid (PLA), polyglyconate (PG), and

poly (L-lactide-co-ε-caprolactone) (PLA-ε-CL), are currently the main materials for biodegradable sutures [10]. The common commercial biodegradable sutures and their polymeric materials are listed in **Table 5.1**.

Table 5.1 Common commercial biodegradable sutures [11,12]

Suture name	Material	Manufacture
Dexon®	Polyglycolide (PGA)	Davis & Geck Corp
Vicryl®	poly(lactic-co-glycolic-acid) (PLGA)	Ethicon
Maxon®	Polyglyconate	Davis & Geck Corp
Monocryl®	Polyglycolide co-ε-caprolactone	Ethicon
Biosyn®	Polydioxinone co-trimethylene carbonate-co-glycolide	Formerly US Surgicals
Bio-Anchor	Poly L-lactic acid (PLLA)	Mitek
Vicryl Rapide™ (Polyglactin 910)	Glycolide/PLLA	Ethicon
Bio-PushLock	PLLA	Arthrex
Polysorb	PLLA/PGA	Covidien-Medtronic
Vicryl Plus	Glycolide/PLLA with Triclosan	Ethicon

Biodegradable sutures are defined by the loss of their strength within 60 days after placement [12]. In most cases, a period of 3 weeks is well enough for a wound to close, and biodegradable sutures are able to keep tissue from separating for this period and degrade away afterwards. Vircryl, made of PLGA, remains 65% of its tensile strength at 2 weeks and 40% at 3 weeks. Complete absorption occurs between 60 and 90 days by hydrolysis [13]. Dexon, made of PGA, remains 89% of its tensile strength at 7 days, 63% at 14 days and 17% at 21 days [14]. Compared with Dexon, Vicryl showed slower loss of function and higher knot-breaking strength, but lesser irreversible elongation [15].

When a wound requires a period shorter than 3 weeks to heal, fast degrading sutures can be used. Vicryl Rapide, made from the same material as Vicryl but partially hydrolysed in buffer solution and sterilized with gamma radiation, hence the degradation process is rapid and 50% of tensile strength is retained at 5 days, and by the 2 weeks the tensile strength is 0%. Monocryl, made of Polyglycolide co-ε-caprolactone, remains 25 to 40% of its tensile strength at 2 weeks and 0% at 21 days [13]. Compared to Vicryl Rapide, Monocryl can result in significantly smaller and less reactive scars, and a lower tendency to hypertrophic scar formation [16].

In some particular cases, a much longer healing period than 3 weeks is required. PDS, made of polydioxanone, remains 74% of its tensile strength after 2 weeks, 50% after 4 week and 25% after 6 weeks. PDS is stiff and difficult to handle, it is a low reactivity suture that maintains it integrity in the presence of bacterial infection. Maxon, made of polygliconate,

remains its tensile strength up to 92 days, and absorption is complete in 6 to 7 months [13]. PLA sutures have more prolonged tensile strength retention (TSR) than that of Maxon and they have been suggested as an alternative in the repair of the Achilles tendon [17]. SR-PLA sutures exhibited the most prolonged strength retention and could be applied to the closure of wounds that need prolonged support, such as bone repair [18]. Recently, a drawn PLLA suture with helical structure was investigated in rat patellar ligament and reported to generate a piezoelectric charge under cyclically applied tensile stress. A significantly higher ossification was observed around the implanted helical PLLA suture in the rat keen joint compared to untwisted PLLA suture, which suggested helical PLLA fibre may be useful for surgical suture or artificial ligament connecting to the bone [19].

Antibacterial sutures are a recent development in the wound closure area. Surgical site infections (SSI) are the challenging complications, anti-microbial coated sutures can effectively defend against various bacterial pathogens [20]. Vircryl Plus is made from 90% glycolide and 10% L- lactide, and produced by Ethicon. This suture contains Irgacare MP (troclosan), a broad-spectrum antibacterial agent. Since the first triclosan-resistances were reported recently, an alternative chlorhexidine was coated on sutures by Obermeier et al. and they demonstrated the high antimicrobial efficacy against *S.aureus* in vitro [20].

Fibre mat covering wound is another recent development in the closure system, which is very promising when it comes to complex shape of wound. Biodegradable polymeric fibres can be fabricated into mat with various shapes used in medical treatment. Behrens et al. reported the use of solution blow spinning to generate PLGA nanofibers on the wound surface in situ, utilizing a commercial airbrush and compressed CO_2 [21]. The PLGA fibres airbrushed onto the incision of the wound can take the shape of the area and promote healing [22]. Zhang et al. developed multilayered PLA electrospun nanofibres with cisplatin loaded. They reported that by covering the surgical site with this PLA mat following resection of subcutaneous liver cancer in mice, retarded tumor recurrence, prolonged survival time of mice and less systemic toxicity were observed compared with other treatment groups [23]. Similiarly, Zhang et al. implanted PLA nanofiborous mats loaded with 5-fluorouracil and oxaliplatin into mice with colorectal cancer, and they found suppressed tumor growth rate and prolonged survival time of mice in comparison to drug-free control group [24].

In summary, biodegradable sutures have replaced traditional non-biodegradable sutures in most cases, where biodegradable sutures can keep the wound tissue closed for a short period and break down in tissue afterwards, limiting the site infection and avoiding secondary suture removal. Non-biodegradable sutures are still used in the cases that require a suture to stay a long time, for instance, heart and blood vessels with rhythmic movement, and other organs, such as bladder, containing fluids which speed up the degradation process of biodegradable sutures. However, with the recent development, such as reinforced PLA sutures used in bone repairing, the usage of biodegradable sutures will be widen.

5.2 Bone fixation devices

Bone fracture occurs as a completely detached or partially attached fragment, without fixation human cartilage can only repair these defects imperfectly [25]. Therefore, it is customary to use fixation devices such as plates, screws, pins, nails and rods to hold the bone together to allow regrowth and healing. Such devices are traditionally constructed of metals, which are reported to cause medical complications [26].

Stress shielding is one of the major complications related to metal fixation devices [27]. It occurs when two or more components with different moduli form one mechanical system. The component with the higher modulus bears the majority of the load and protects the other component from stress. Such is the case with rigid metallic fixation devices, which at first may favour primary bone healing with sufficient mechanical support. However, at the later stage of the healing stress shield occurs and the bone recovers with insufficient strength,

which leads to osteoporosis [28]. Thus, the bone may have a tendency to fracture again when the metal plates are removed [29]. In addition, metallic bone fixation devices have also been reported to interfere with skeletal growth, particularly for the paediatrics, and MRI investigations [32,33]. Moreover, metallic ion leaching to adjacent tissue is problematic. For instance, titanium as a common metal used for bone fixation has been reported to be found in the lymph nodes, liver, spleen, bone marrow, and in the brain [34,35]. Finally, implant removal for functional improvement and pain relief, which accounts for 15% of all operations in the orthopaedic and trauma unit in Scandinavian, is expensive and challenging [34].

On the other hand, fully biodegradable bone fixation devices appears to be a great alternative for patients. The major benefits of fully biodegradable bone fixation devices include redundancy of implant removal, minimal risk of implant related complications and early functional rehabilitation [35]. Fully biodegradable bone fixation devices are often made of biodegradable polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), copolymers of polyglycolide polylactide (PLGA), polydioxaone (PDS), polysulphose (PS), and polycarbonate (PC) [36]. PLA is a relatively strong biodegradable polymer and has been intensively used in medical applications. With L- and D- enantiomeric forms of lactic acid, PLA appears as PLLA with only L-isomer, PDLA with only D-isomer, PDLLA with half L-isomer and half D-isomer, and PLA with majority of L-isomer and a small amount of D-isomer [37]. The common used biodegradable bone fixation devices and their materials are listed in **Table 5.2**.

Table 5.2 Common used biodegradable bone fixation devices [38, 40–42]

Devices	Material	Applications
SmartPins, Smart Screws, SmartTack	SR-PLLA	Fracture fixation
BioScrew	PLLA	Interference screws
Clearfix Meniscal screw and Dart	PLLA	Meniscus repair
Resorb X	PDLLA	Neurosurgery, carniofacial surgery
LactoSorb®	PLLA/PGA	Malar fracture
Biosteon Wedge Interference screws	HA/PLLA	ACL reconstruction
Sysorb® screws	PDLLA	ACL reconstruction
ProToeTM EndoSorbTM	PLGA	Hammertoe Correction
Inion Plates, rods, screws, meshes	PLA, PGA, TMC	Bone fracture
Matry® screws	SR-PLA	ACL/PCL graft fixation
Fixsorb®	PLLA/HA	Fracture fixation
Smartscrew ACL	PLLA	ACL repair

Biodegradable bone fixation devices outweighs traditional rigid metallic devices in terms of the redundancy of implant removal, which is especially beneficial in spine repairing. Implant loosening of permanent implants is a clinically serious complication requiring subsequent surgical removal of these implants [43,44]. Removal of permanent implants in spine due to instability or dislocation may leave a deficit leading to instability of spine [45,46]. Therefore,

biodegradable fixation devices, which provide mechanical support and degrade with the pace of healing process, offer an ideal option for spine fixation. Several spinal biodegradable implants include a myriad of posterior lumbar interbody fusion devices, anterior spinal plates and a variety of screws and meshes [45].

Furthermore, biodegradable bone fixation devices are found to be superior to traditional metallic devices in terms of biocompatibility and functional recovery. Research has been conducted to compare tissue reaction to titanium and biodegradable screws with postoperative irradiation on rats. It was found that the intensity of inflammation around the titanium screws was more evident than that around the biodegradable screws, which indicated that biodegradable screws could be safer reconstructive devices than titanium screws in patients undergoing radiotherapy [46]. Several studies showed that the infection rate and plate removal rate of biodegradable plates are significantly lower than that of titanium plates [49,50]. A follow-up study of 10 patients with maxillofacial fractures, who had implanted with biodegradable Ioion CPS, reported that favourable healing was observed and no local tissue immune reaction was found [49]. In addition, Ioion CPS biodegradable fixation system was clinically evaluated on 8 patients with mandibular body fractures, and sufficient mechanical strength and stable fixation were observed [50]. Ioion CPS was reported as reliable fixation devices with only minor infections in a clinical assessment on 19 patients with unilateral fracture of the mandibular angle [51]. Biodegradable fixation devices have adequate shear resistance, but less load resistance and stiffness compared to titanium, which helps to avoid stress shielding and promotes healing [52]. The use of biodegradable fixation devices is a promising technology and favourable healing can be achieved in patients of all ages, as well as mandible fractures in early childhood [55,56].

The average Young's modulus of trabecular bone and cortical bone was measured to be 10.4 GPa and 18.6 GPa respectively [55], and the tensile strength of bones was reported to be in a range of 50-150 MPa [58, 59]. Biodegradable polymers do not have the comparable mechanical strength, and they are not suitable to be used in many orthopaedic applications [58]. For instance, the tensile yield strength of PGA and PCL has been reported to be 57 and 19-21 MPa respectively [59]. PLA is one of the strongest biodegradable polymers with tensile modulus of 3-4 GPa, tensile strength of 50-70 MPa and elongation at break of 2-10% depending on molecular weight, crystallinity and processing methods [60,62]. Therefore, biodegradable polymers reinforced with various fillers have been intensively studied. Hydroxyapatite nanorod-reinforced PLLA composites were found to have a Young's modulus of 1.3 GPa and a compressive strength of 110.3 MPa [61]. OSTEOTRANS MX (Takiron Co, Ltd, Osaka, Japan), made from unsintered hydroxyapatite/PLLA composite, has clinically proved beneficial in maxillofacial fracture treatment, shown in **Figure 5.1**. Basalt fibre reinforced PLA composites were developed and have a Young's modulus of 8.31 GPa and a tensile strength of 123.5 MPa with 40%wt loading of basalt fibre [62]. Self-reinforced PLA was found to have a Young's modulus of 3.3 GPa and a tensile strength of 48 MPa [27]. Phosphate glass fibres reinforced PLA was reported to have a flexural strength of 110-180 MPa and a modulus of 11-18 GPa, which might be benefit for high loading applications [63]. Polyvinyl alcohol (PVA)-hydroxyapatite composite reinforced with catgut fibres was found to have adequate mechanical strength for facial skeleton fixation with a tensile strength of 39.88 ± 1.33 MPa after a degradation period of 60 days when compared with the mechanical strength of the masseter muscle in the molars region (14.28 MPa) [57]. Reinforcing fillers can improve mechanical properties of biodegradable polymers. The adhesion between polymer matrix and fillers determines the final mechanical properties of the composites. A desirable interfacial affinity between polymer matrix and fillers can optimize the enhancement of mechanical properties of composites [64].

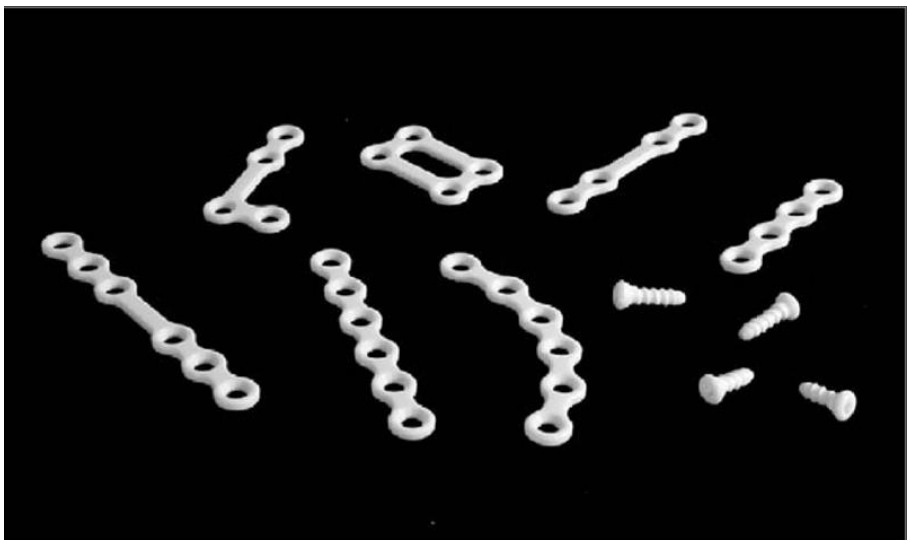

Figure 5.1 OSTEOTRANS MX (Takiron Co, Ltd, Osaka, Japan) composed of a forged unsintered hydroxyapatite/poly-L-lactide composite. Reproduced with permission from S. Sukegawa, T. Kanno, N. Katase, A. Shibata, Y. Takahashi and Y. Furuki, *The Journal of craniofacial surgery*, 2016, 27, 1391 Copyright © 2016, by Mutaz B. Habal, MD [66]

The ideal biodegradable bone fixation devices not only provide physical support, but also degrade away at the pace of healing process. Degradation Bone plates and screws made from PDLLA have long degradation period, which is around 2 years, and those devices made from self-reinforced PLLA take up to 5-6 years to be resorbed completely, while those made from PGA can be resorbed in 3 months and suitable for short term bone fixation [59]. The degradation of these implants has been postulated to be the cause of marked foreign-body reactions, synovitis, and even activation of the complement cascade [65]. The foreign-body reactions of PLA based implants has been reported. PDLLA plates were reported with marked local foreign body reaction as early as 3 months after implantation. However, PLA plates, screws and rods were reported to cause significantly less local soft tissue reactions compared to PGA devices [66–68]. The rapid degradation of PGA is the cause for the soft tissue reactions [65]. By changing the copolymer ratios of PGA and PLA, the degradation rate can be optimized [65], PLGA plates were not report with foreign body reaction [69].

In addition, biodegradable polymeric composites are reported to promote bone healing, and the implants made from these materials are very promising. Poly (D, L-lactide-*co*-trimethylene carbonate) (PLMC) and nano-hydroxyapatitie composite has found to enhance the alkaline phosphatase secretion as well as mineral deposition in bone formation, and is currently under investigation in the feasibility of bone screw hole healing [70]. Zhang et al. developed PLA/demineralized bone matrix (DBM) composite and found that PLA combined with DBM promoted better bone healing than PLA alone in radius of rabbits models [71].

In summary, the benefits of biodegradable fixation devices outweigh traditional bone fixation devices because 1) Biodegradable plates, rods and screws do not interfere with imaging and allow a clear view of fracture site on radiographs [50,78]. 2) Biodegradable plates are easier to handle than metallic plates, and bending instruments such as pliers are not needed placing biodegradable plates against bone surface [47]. 3) No need for removal operation and reduce costs [72]. 4) Biodegradable bone fixation devices promote better bone healing than traditional plates and screws[48,56,75–77].

However, the problems related to biodegradable plates and screws are also reported. 1) Biodegradable screws require a drill hole that must be tapped, and this increases operative time [76]. 2) Its more difficult or technique sensitive to place biodegradable screws than metallic screws [77]. Biodegradable screws require slower drilling rates into the bone [76]. As high drilling speed might cause friction heat, which can cause difficulties to place the screws [78]. 3) Polymer debris causing inflammatory foreign body reactions has been reported [79].

5.3 Fully Biodegradable Stents

The percutaneous coronary intervention (PCI) is the standard procedure for treating coronary heart disease (CHD). PCI started with plain old balloon angioplasty, but it has a very high rate of restenosis, recoil and constrictive remodelling. Therefore, it has been replaced by bare metallic stenting [80]. Bare metallic stents (BMS) were revolutionary inventions, but due to the major problem of in-stent restenosis, drug eluting stents (DES) have taken their place [83,84]. DES with coated antiproliferative drugs can effectively reduce the rate of in-stent restenosis, but late stent restenosis has being a recent cause for concern [83]. The lumen size after DES is implanted remains fixed over the long term with an ongoing annual accumulation of events of 1-2% [86,87]. Neointimal tissue growth results in restenosis requiring an additional intervention in about 2-5% of DES cases [86]. Fully biodegradable coronary stents, which provide transient vessel support with drug delivery capability, and degrade away after service providing temporary support without the long-term limitation of metallic stents, appear to be an ideal option to treat CHD [87].

The efforts to create biodegradable stents started approximately 20 years ago. However, the common types of fully biodegradable materials, including polyglycolic acid/polylactic acid copolymer (PGLA), polycaprolactone (PCL), polyhydroxy-butyrate/-valerate copolymer (PHBV), polyorthoester (POE), polyethyleneoxide/polybutylene terephthalate (PEO/PBTP) and low molecular weight poly-L-lactic acid (PLLA 80kD), all resulted in intense inflammation leading to neointimal hyperplasia and/or thrombus formation. This technology failed to develop due to inflammation, restenosis and growing interest in DES [90,91]. The capability in producing high molecular weight PLA and biodegradable metal such as magnesium brought fully biodegradable stents back. Currently, 28 companies are developing fully biodegradable stents. The most commonly used biodegradable material is PLLA (24 products), due to its relatively high strength, excellent biodegradability and good biocompatibility [90]. It has a long history in stents industry as polymer coating and drug carrier for DES which helps to streamline regularity approval [91]. The other materials being used are tyrosine polycarbonate, salicylic acid polymer, magnesium and iron [87]. Several fully biodegradable polymeric stents that are currently manufactured are presented in **Table 5.3** and **Figure 5.2**.

Table 5.3 Fully biodegradable polymeric coronary stents [92–95]

Stents	Manufacture	Material
Absorb BVS	Abbott	PLLA
Igaki-Tamai	Kyoto Medical	PLLA
DESolve Nx	Elixir	PLLA
ReZolve	Reva	Tyrosine polycarbonate
MeRes100	Meril life sciences	PLLA
IDEAL	Bioabsorbable Therapeutics Inc.	Poly (Anhydride Ester) Salicylic Acid.

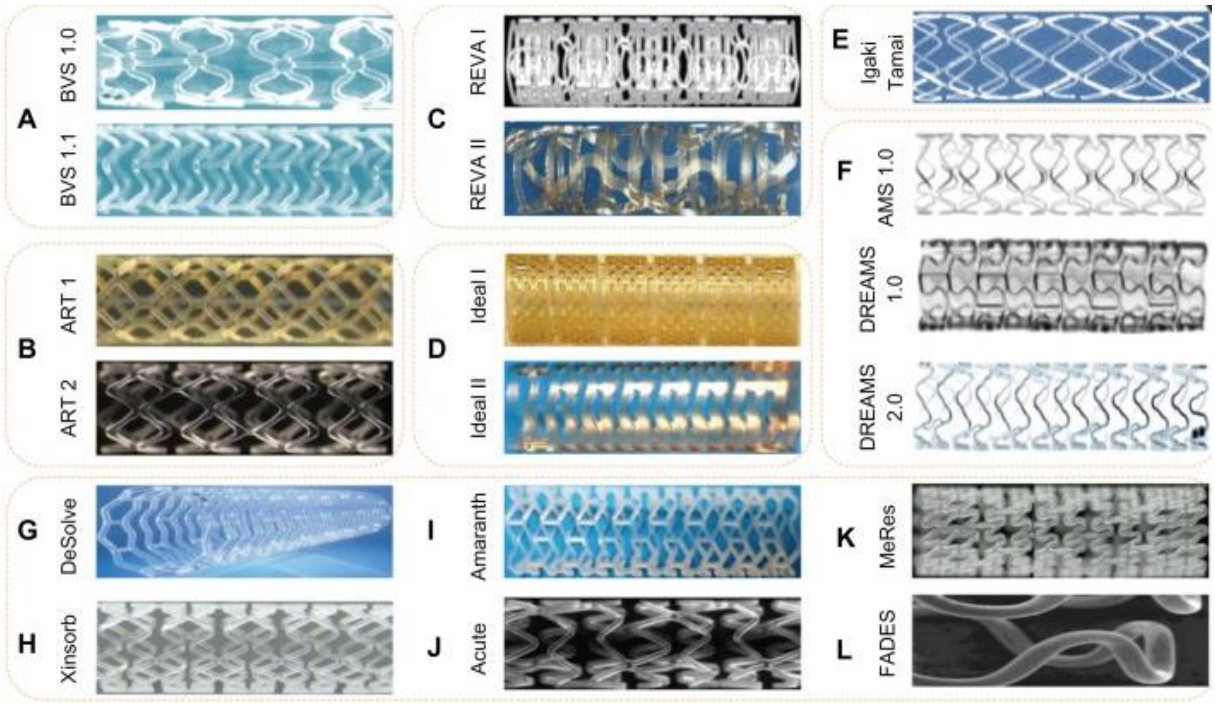

Figure 5.2 Currently available fully biodegradable stents. (**A**) Abbott Vascular 1.0, 1.1; (**B**) ART 1, 2; (**C**) REVA Medical I, II; (**D**) IDEAL scaffold I, II; (**E**) Igaki-Tamai scaffold; (**F**) magnesium absorbable stents; (**G**) DeSolve™; (**H**) Xinsorb; (**I**) Amaranth; (**J**) Acute; (**K**) MeRes; and (**L**) FADES. Rproduced with permission from Y. Zhang, C. V Bourantas, V. Farooq, T. Muramatsu, R. Diletti, Y. Onuma, H.M. Garcia-Garcia and P.W. Serruys, *Medical devices (Auckland, N.Z.)*, 2013, 6, 37 Copyright © 2013, Dove Medical Press Ltd. [96]

The Igaki-Tamai stent is the pioneering fully biodegradable stent made from PLLA and it is currently used in peripheral arteries. Data from 50 patients over 10 years showed that some acute stent recoil occurred. However, this stabilized fastly and the performance at six months follow up was satisfactory with initial hyperplasia comparable to bare metal stents. Furthermore, a four year follow up showed the stents degraded completely with no further hyperplasia development [97]. The Igaki-Tmai stent has a zig-zag helical coils with straight bridges design and 24% stent-to-artery coverage ratio, the strut thickness is 170 μm [98]. This stent is self-expandable stent, and requires heat of 70°C to expand. The full deployment takes 20 to 30 minutes, and due to the complicated delivery methods requiring heat for self-expansion, Igaki-Tmai is not currently used in coronary arteries [94].

Biodegradable vascular scaffold (BVS) everolimus-eluting PLLA coronary stents are manufactured by Abbott. It is a balloon-expandable stent with a zig-zag hoops design, the strut thickness is 158 μm, crossing file is 1.4 mm, and stent-to artery coverage is 25% [98]. Zero stent thrombosis was published from a clinical trial of 130 patients [93]. The FDA approved the Absorb BVS, making it the first commercially available biodegradable coronary stent [99].

However, a very recent feedback of Absorb BVS from cardiologists conducted by cardiovascular research foundation (CRF) revealed that the Absorb BVS are very promising but still in infancy with cost being one of the main issues. Absorb BVS costs approximately 10 times than a normal metallic DES, and the potential advantages of Absorb BVS would not be expected until 2, 3, or even 5 years. What's more, when dealing with Absorb BVS, use of online quantitative angiography, intravascular ultrasound (IVUS), or optimal coherence tomography (OCT) is strongly recommended to correctly measure and confirm vessel sizing, which adds up the procedure cost of Absorb BVS [99].

Another major issue is increased risk of scaffold thrombosis due to thicker strut of biodegradable polymeric stents compared to that of metallic stents. For instance, Absorb BVS has a strut thickness of 158 μm [98], while Synergy which is made from Platinum Chromium

Alloy has a strut thickness of 74μm. Biodegradable polymers are weak, so the stents made from biodegradablde polymers have to be bulky to withstand the pressure from the vessel wall. The strut thickness directly links to stent performance and restenosis rate. Sorin Brener, MD (New York Methodist Hospital, Brooklyn, NY), called Absorb BVS clunky and reminded him of the Cypher first-generation DES. This safety concern was observed in the pivotal ABSORB III trial, which found the rate of definite/probable device thrombosis was numerically higher with Absorb, although the difference was not statistically significant compared with DES Xience (1.5% vs 0.7%; p = 0.13). In addition, physicians have found that they have to dilate the vessel more when implanting biodegradable stents because they don't have the radial strength, while with DES even if the lesion is not fully open, good results are still achievable [99]. Reducing the strut thickness of the stents made from biodegradable polymers might be achieved by reinforcing the biodegradable polymers. Halloysite nanotube (HNTs) reinforced PLA composites were found to have a Young's modulus of 2 GPa and a tensile strength of 62.69 ± 4.25 MPa with 5%wt loading of HNTs. For further improvement in mechanical strength, surface treatment of HNTs is under investigation [100].

Furthermore, the traditional method of laser machining, which has been used for metallic stents manufacturing, has also used to fabricate biodegradable stents, such as Absorb BVS, but the problems of the heat affected zone and solidification of molten material on cut edges have been reported [101]. The improvement in manufacturing biodegradable polymeric stents has been investigated. Femtosecond laser was reported by Heublein et al. to fabricate biodegradable stents but high cost was an issue [102]. Excimer laser was reported by Barenghi et al. to fabricate biodegradable polypropylene fumarate stent [103]. Stepak et al. utilized CO_2 laser and claimed that elements cut with CO2 Laser have better mechanical properties than those fabricated with excimer laser.[101] Apart from laser machining other fabrication methods include rapid prototyping [104], weft-knitting [105] and braiding technology [106].

In summary, fully biodegradable polymeric stents are very promising, but they are early-stage technologies. Currently, only the Absorb and Elixir scaffolds succeeded in acquiring a CE mark, and other scaffolds are undergoing clinical trials [87]. The advantages of fully biodegradable stents include: 1) No requirement for removal surgery due to the degradation nature of fully biodegradable stents. 2) Improve recovery of the blood vessels compared to DES and BMS, since fully biodegradable stents don't persist long term and trigger late stage thrombosis. 3) Reduce the bleeding complications as there is no requirement for long-term dual antiplatelet therapy. 4) Improve the treatment of complex multi-vessel disease that frequently results in the use of multiple long DES. Previously implanted biodegradable stents won't be an issue when revascularisation is required in complex cases [107]. 5) Polymeric stents allow the use of non-invasive imaging techniques such as CT and MRI for follow-up, while metallic stents can cause a blooming effect making interpretation difficult [108]. Challenges still remain: 1) Fully biodegradable stents are very expensive compared to traditional metallic stents. 2) The clinical trial experience of fully biodegradable stents is limited, long term follow-up is required. 3) Fully biodegradable polymeric stents have lower radial strength and rigidity compared to metallic stents, which contributes to a high rate of recoil [109]. 4) The strut of fully biodegradable polymeric stents is much thicker than that of metallic stents, which directly links to stent performance and restenosis rate [110]. 5) The polymers that have been used to develop biodegradable stents, e.g. PLLA, PLGA and PLLA-based polyester block copolymer, exhibit a brittle fracture mechanism at physiological conditions (37°C), in which there is little or no plastic deformation prior to failure. Thus these polymeric struts can crack or fracture during crimping, delivery and deployment [109]. 6) Some polymeric stents, e.g. BVS, have a c.a. 2 years degradation period, which might be too long [111]. For the first 6 months the stents are required to keep the vessel open while the vessel is healing and remodelling, after 6 months the stents are required not to interfere with

luminal enlargement of blood vessels, which often takes place between 6 months and 5 years after angioplasty [92].

5.4 Biodegradable anti-adhesive tissue barriers

Tissue adhesion following surgery is one of the most common challenges in clinical practice, particularly abdominal and bowel surgeries. Abdominal adhesions are not only the leading cause of small bowel obstruction, but also cause at least 20% of infertility and about 40% of chronic abdominal and pelvic pain. The Adhesion formation typically occurs as a result of the formation of a fibrin clot, which transforms into scar tissue connecting different tissues that are normally separated in response to trauma, infection, dehydration, ischemia, haemorrhage and foreign bodies [115,116]. Surgical intervention is frequently required in order to eliminate the adhesions.

Multiple strategies to reduce the adhesion include fibrinolytic agents, anti-inflammatory drugs and anti-adhesive barriers [114]. Recently, tissue adhesion barriers that cover tightly onto the damaged surface can physically isolate wounds, thus effectively prevent the formation of tissue adhesion and become a hot topic in both research and industrial fields. In the initial stages of developing tissue adhesion barriers, non-biodegradable polymers were used, such as polyethylene (PE), expanded Polytetrafluoroethylene (PTFE). However, with the development in biodegradable barriers, the traditional barriers, which require secondary removal surgery, have been gradually replaced. Ideal biodegradable tissue anti-adhesive barriers should have good biocompatibility, biodegradability, immunological inertness, and no interference in wound healing [113].

Currently, biodegradable polymers have been extensively used in anti-adhesive barriers, including poly (vinyl alcohol) (PVA), PLA, poly (lactic acid)-polyethylene glycol (PLA-PEG), Poly (lactic acid)-poly(oxyethylene-co-oxypropylene) (PLA-Pluronic F68), D,L-Polylactide-ε-caprolactone-trimethylenecarbonate (PCT copolymer), Hyaluronic acid, Collagen, Gelatin, silk, HA/carboxymethylcellulose (CMC), cellulose etc. [113]. PLA film has anti-adhesive properties due to low permeability against serum proteins as we as cells. PLLA nanosheet was report not only can effectively seal a surgical incision without scarring, but also significantly reduce adhesion by inhibiting the permeation of oozing blood cells and the infiltration of fibroblastic cells [115]. PLLA nanosheets were found to reduce tissue adhesion that accompanies liver injury [116]. Bilateral PLA/alginate membranes were developed with a smooth PLA side keeping the affected tissues glidingly separated and a mucoadhesive side made of alginate keeping the barrier resident on the site of injury [117]. PLA nanosheet was found better in reducing postoperative intestinal adhesion treatment compared to Seprafilm®, which is made of HA and CMC, because PLA nanosheet did not affect bacterial propagation in the peritoneal cavity, while Seprafilm® showed bacterial propagation, leading to increase mortality [118]. PLA pericardial membrane was found to be promising for cardiac surgery [119]. Compared to PLA film, Poly (vinyl alcohol-g-lactic acid) PVA-G-PLA film was found with improved hydrophilicity and flexibility and demonstrated good anti-tissue adhesion behaviour and suitable degradability [120]. Biodegradable PLGA electrospun membrane was fabricated and found useful for anti-adhesion of Achilles tendon [121].

Chitosan was found to have the anti-adhesive ability and used as coating on polypropylene mesh [122]. Chitosan-PLGA-PEO nanofiber mats were manufactured via electrospinning and reported positively in craniofacial surgery [123]. Similar results were reported with chitosan/PLGA nanofibrous sheets [124]. Injectable chitosan/dextran-based hydrogel was developed as an adhesion prevention postsurgical aid, and claimed to have an appropriate biocompatibility with mild inflammatory response observed [125]. PCL-gelatin hybrid membrane was developed via electrospinning and revealed to possess a good biocompatibility and degradation behaviour with anti-adhesion function observed in rabbit model [126].

PEG/PCL nanofibrous membrane was found to prevent cell penetration better than PCL membrane and Seprafilm [127].

A novel hydrogel of poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG) has been developed by Yang et al. who reported that PEG-PCL-PEG hydrogel can be easily adhered to the damaged peritoneal surfaces and degraded away within 14 days along with the healing of peritoneal wounds. This hydrogel is found to be effective to prevent post-surgical abdominal adhesion in mouse and rat models, shown in **Figure 5.3** [128].

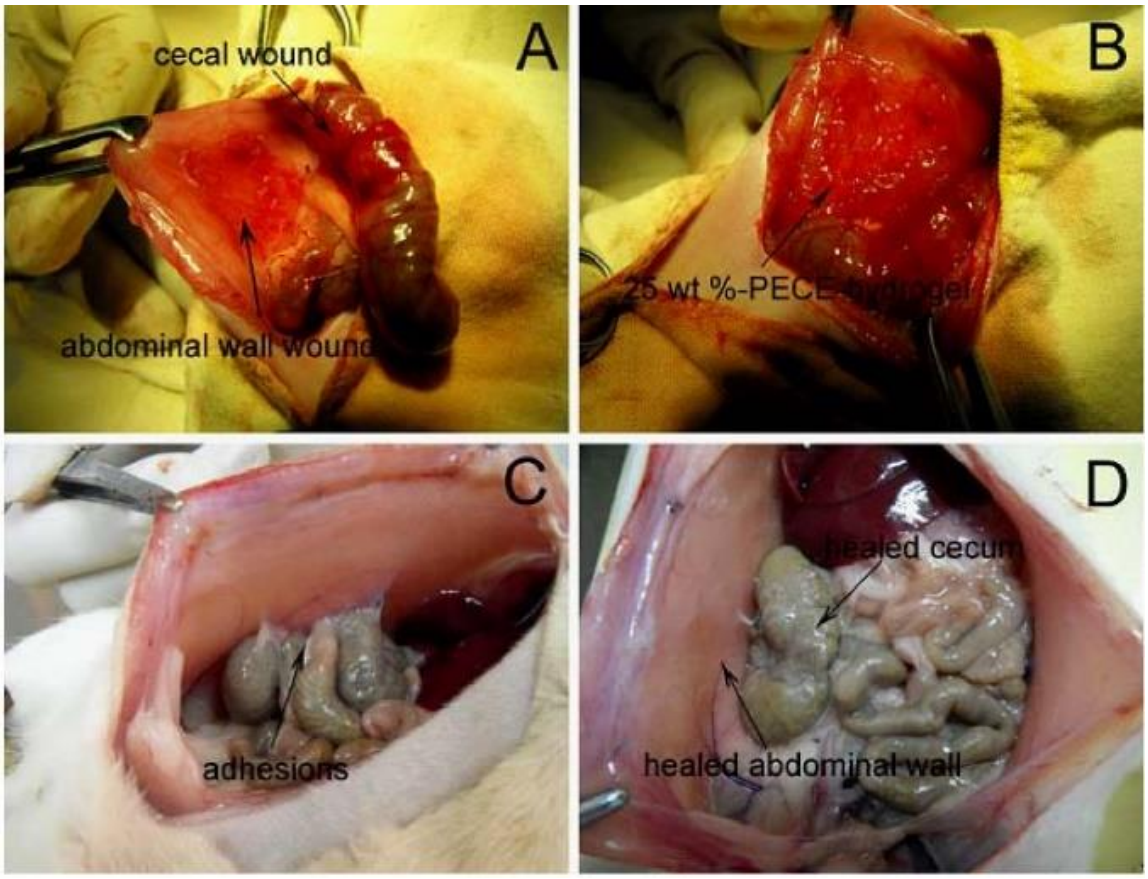

Figure 5.3 Prevention of abdominal adhesions in a rat abrasion model**.** A) The establishment of rat model of abdominal sidewall defect-cecum abrasion. B) PECE hydrogel applied on the injured abdominal wall and cecum. C) Adhesion was observed in a saline-treated rat. D) No apparent adhesion was observed in a PECE gel-treated rat, with healed abdominal wall and cecum. Reproduced with permission from B. Yang, C. Gong, Z. Qian, X. Zhao, Z. Li, X. Qi, S. Zhou, Q. Zhong, F. Luo and Y. Wei, *BMC Biotechnology*, 2010, 10, 65 Copyright © 2010, BioMed Central Ltd. [128]

There are various kinds of commercially available anti-adhesive barriers, including Seprafilm (HA/CMC), SurgiWrap (PLA), Oxiplex (PEG/CMC), Surgical, REPEL-CV (PLA/PEG), Incert (cross-linked HA), Interceed (Oxidized regenerated cellulose), Adept, Intercoat, Spraygel and Guardix gel. [116,117]. Most focus on the mechanical barrier by creating an inert barrier to cellular adhesion. However, some challenges have been reported. The difficulty in handling sheet barriers in an operating room remains a problem. The need for fixation using sutures can lead to additional tissue adhesion [129]. Barriers made from crosslinked polymer were reported to lose tissue adhesiveness because of the decrement of specific functional groups in interacting with tissues after the cross-linking procedure [113]. Despite of the limitation of biodegradable tissue barriers, the anti-adhesion approach utilizing biodegradable polymers is still promising.

5.6 Tissue engineering

The definition of 'tissue engineering' was first defined at a national science foundation workshop in 1988 and was further finely defined to a broad scientific community in 1993 by Langer and Vacanti [133,134]. Tissue engineering is a multidisciplinary field that aims on the replacement of damaged tissue or organs. It does this by exploiting the natural physiological nature of an in vivo environment to temporarily replace damaged tissue. It utilises cells and growth factors and implantable medical devices to aid in a patient's recovery. In doing so, it focuses on the development, application and knowledge of a variety of scientific fields such as chemistry, physics, engineering and life science [132]. This collaboration has led to immense research and a rapid expansion in biomedical research due to its vast potential in repair or replacement of tissue and organs [133]. Over the recent years materials science in conjunction with biotechnology has prioritised several worldwide medical problems such as the development of artificial bone, organ implants, drug delivery and the development of scaffolds for bone, cartilage, vascular and nerve tissue engineering [134]. The major aim of tissue engineering is to construct scaffolds that are capable of recreating an in vivo environment with the incorporation of biophysical, biomechanical and biochemical cues to aid in the cellular proliferation, differentiation and function [131]. In order for a scaffold to replace the mechanical function of a living tissue it must meet complex functional demands (pore shape, size and interconnectivity) to temporally generate an optimal environment for the generation process. For example Ghorbanie et al., constructed Hydroxyapatite (HA)-gelatin scaffolds loaded with PLGA via freeze casting for bone regeneration. Ghorbanie studies suggests by controlling the freeze rate the porosity of the scaffold can be controlled, however lower freeze gradients compromised mechanical features of the scaffold. Ghorbanie also explains increased concentration of HA can have beneficial mechanical properties to the scaffold [135].

Two methodologies are used in medical science for the regeneration of damage tissue or organ failure, such as transplants and implants. Transplants use donor tissue or organs (e.g., vascular or nerve) or cadavers (e.g., lyophilized and frozen bone) to aid in the regeneration process. However, transplants have disadvantages such as ethical concerns and the requirement of immunosuppressive drugs to prevent rejection of the transplant. Implant device are designed to act at the recipient tissue interface in an organism interacting with tissue, in addition, it does not present as many issues in comparison to transplants due to the use of biomaterials [136]. Bone and peripheral nerve repairing via biomaterials are discussed in this section.

5.6.1 Bone tissue engineering

Traditionally, bone grafts including autograft and allograft have been used to restore damaged bone. However, both have limitations. Currently, it is a hot topic that synthetic bone scaffolds used as bone graft substitute due to their high mechanical strength and the ability to enhance tissue growth [137]. Major advances in bone grafts are achieved through growth factors, drugs and genes embedded within the bone scaffolds. The ideal bone scaffolds should be three – dimensional and contain a highly porous network of interconnected pores to promote cell growth, adhesion, proliferation and differentiation by facilitating the flow and transport of nutrients and metabolic waste. In addition, they should have good biocompatibility and biodegradability to assure they are nontoxic, non-allergenic and do not induce any adverse reaction in the body. The formation of new tissues should also match the degradation rate of the implanted materials to prevent further damage. Finally, good mechanical properties are also the essential requirements of an ideal scaffold in bone tissue engineering [138–140].

Numerous biomaterials, such as metal, ceramics, polymers and composites, have been used in bone scaffolds. Metallic scaffolds are limited in use due to ion release, limited bioactivity and

biodegradation. Bioactive ceramics include calcium phosphates (CaP) and bioactive glasses, such as hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), and the mixture of HA and β-TCP [141, 145, 146]. Polymers used in bone scaffolds include collagen, alginate, chitosan, fibrin, polycaprolactone (PCL), polyethylene glycol (PEG), poly(propylene fumarate) (PPF), PLA, PGA and their co-polymers [143]. The common biodegradable polymers used in bone scaffold and their composites are discussed in this section.

Natural polymers can be used in bone tissue engineering due to their excellent biocompatibility, and they include agarose, collagen and chitosan [144]. Agarose, a type of polysaccharide, is extracted from seaweeds [144], and exhibits high turbidity and strong elasticity. It was found that agarose conferred toughness, ductility and a rubbery consistency for strains of up to 60% when incorporated into biphasic calcium phosphate and biphasic calcium phosphate–agarose scaffolds which may be suitable for use in bone regeneration [145].

Collagen is a fibrous protein that is a major component in connective tissues, which has been widely used for tissue regeneration applications [144]. It is the most common protein in the body and provides strength and structural stability to tissues in the body including skin, blood vessels, tendon, cartilage and bone [146]. As a material for scaffolds in tissue engineering, collagen provides excellent biological characteristics as it improves cell attachment, growth and proliferation. As a result of this collagen scaffolds have been used for many years in a number of *in vitro* and *in vivo* studies in skin regeneration, cartilage repair and many other tissues. While collagen possesses these advantageous characteristics it lacks the mechanical properties required for bone tissue engineering. Various approaches have been carried out to help strengthen the collagen scaffold including crosslinking methods yet the stiffness of crosslinked collagen scaffolds still remains an order of magnitude lower than bone [147].

Chitosan is one of the most abundant natural polymers next to cellulose, and it has received a lot of interest in the field of bone tissue engineering due to its favourable antimicrobial properties and its degradation rate of 2-8 weeks depending on the level of crosslinking which closely resembles normal bone repair rates [152,153].

However, scarcity in bulk quantity and difficulties in the processability of natural polymers limit their use in tissue engineering. In addition, the degradation rate of natural polymer materials is dependent on the patient, because the degradation of natural polymer materials is dependent upon enzymes which vary from patient to patient. On the other hand, synthetic polymers exhibit predictable and reproducible physical, chemical and degradation properties that can be modified to meet the specific requirements of bone tissue recovery [146]. Synthetic polymers used in scaffold preparation include PGA, PLA and PCL [150].

PGA is the simplest linear aliphatic polyester which has a high crystalline structure, high melting point and low solubility in organic solvents. The degradation products of PGA are naturally resorbed by the body which makes it a desirable biomaterial. As PGA degrades rapidly, between 4 to 12 months, this characteristic can make it difficult to process and handle. However, it is often extruded as thin polymer strands approximately 13μm in diameter and moulded into non-woven mesh discs to produce a scaffold structure. This structure provides a high porosity environment for cells to grow and proliferate. However, PGA can lack sufficient mechanical integrity. On the contrary PLA-PGA co-polymers have higher mechanical properties after going through two self-reinforcing techniques; sintering and fibrillation. These methods induce highly orientated polymer morphology and consequently make this copolymer material more attractive for use in clinical applications. PLA-PGA co-polymers are fabricated as non-woven mesh for use in engineering cartilage scaffolds and in order to produce proper construction, the interconnectivity, porosity, pore size and void space can be adjusted during the fabrication process [144].

PLA degrades slower than PGA due to its hydrophobic characteristic which limits the water absorption of thin films and slows the back bone hydrolysis rate. Based on available data to

date, it can take anywhere from 12 months to over two years for this material to degrade [144]. Although many researchers have tried to investigate porous PLA scaffolds for the usage in orthopaedic applications, PLA is primarily used as a non-woven mesh for tissue engineering applications. It is reported that *in vitro* cell culture experiments depicted good osteoblast attachment and proliferation following the fabrication process of continuous and uniform composite electrospun microfibers made of PLLA incorporated with HA nanopowder. It was also found that after 7 days of culturing, there was an enhanced expression of alkaline phosphatase (ALP) [151].
Polycaprolactone (PCL) is another type of synthetic polymer which due to its biocompatibility, degradation (up to 24 months) and mechanical strength makes it a suitable and compatible material for orthopaedic applications. Due to its degradation rate it is always used to co-polymerise with other materials to have desired degradation properties. Honda *et al*. carried out a study using poly (L-lactic-epsilon-caprolactone) as a biodegradable sponge and implanted it into mice. After four weeks of the study, it was found that there was a formation of cartilage-like structures within the polymer construct [152].
While these synthetic materials have shown much success as they can be fabricated with a tailored architecture and their degradation characteristics may be ontrolled by varying the polymer itself or the composition of the individual polymer [146], they have their disadvantages such as the risk of rejection due to reduced bioactivity. In addition to this, concerns exist about the degradation process of PLLA and PGA as they degrade by hydrolysis. As a result of this, carbon dioxide is formed and therefore lowers the pH which can result in cell and bone tissue necrosis.

Generally, a single type of scaffold material does not satisfy the current requirements for an extracellular scaffold. Therefore, two or more materials are used in the composition of bone scaffold. Today, bone scaffolds are usually made of composite of polymers and bioactive ceramics with the aim to increase the mechanical scaffold stability and to improve tissue interaction [153–156].

CaP-polymer scaffolds take advantages of both CaPs and polymers to meet mechanical and physiological requirements of the host tissue. Polymers in CaP scaffolds increase toughness and compressive strength similar to bone, while CaP can improve the bioactivity of the composites [137]. PLGA/β–TCP scaffold was reported to improve alkaline phosphatase activity, and has a great capacity to induce osteogenic differentiation [157]. PCL/β-TCP scaffolds were manufactured via a 3D printer and found to have good biocompatibility and suitable mechanical strength, and PCL/β-TCP scaffolds degrades faster than pure PCL due to the addition of β-TCP [158]. PGA/β-TCP scaffolds were developed using the solvent casting and particulate leaching method, and the PGA/β-TCP scaffolds exhibited a strong ability for osteogenesis, mineralization and biodegradation for bone replacement [159]. Poly (propylene fumarate)-co-polycaprolactone (PPF-co-PCL)/HA scaffolds were found to be able to induce maturation of pre-osteoblasts and have the potential for use in bone tissue engineering [160]. PDLLA/ β-TCP scaffolds were manufactured by selective laser melting, and revealed good osteoinductive properties promoting complete bone healing [161]. PLA/HA scaffolds were fabricated by 3D printing, and revealed to have good osteogenic capability and biodegradation activity [162]. Similarly, HA/ poly(ester-urethane) (PU) scaffolds [163] and HA/PCL [164] scaffolds proved beneficial for use in bone repair.

Biodegradable polymer based bone scaffolds have demonstrated excellent new bone formation. However, some challenges still remain: 1) Biodegradable polymeric scaffolds show rapid strength degradation in vivo even with high initial strength [137]. 2) Degradation of PLA, PGA creates a local acidic environment that can cause adverse tissue responses [169, 170].

Scaffolds made from polyesters causes poor wetting, lack of cellular attachment and interaction due to hydrophobicity.

5.6.2 Peripheral nerve repair

There is a long history relating to peripheral nerve injuries, Herophilus in 300 BC first traced the nerve to the spinal cord via meticulous dissection. Rhazes in 900 AD was the first to discover nerve repair. Cruikshank demonstrated healing and recovery of the distal end of a neuron. In the early 1900s, Cajal introduced the concept of axon regeneration guided by chemotropic substances [167]. Peripheral nerve injuries presents issues both clinically and socioeconomically by affecting the patient's quality of life. These injuries can have devastating results to the sensory and motor impairments on patients, affecting 1 in 1000 patients [168]. Unlike the central nerve system, the Peripheral nerve system (PNS) has the ability to regenerate damaged tissues; however this intrinsic ability to repair itself relates to various factors such as age, mechanism of injury and most importantly the proximity of the injury to the nerve cell body [169]. Sunderland classifications categorises the severity of the injuries. Neurapraxia (grade 1) related to radical nerve compression resulting to a block in fibre conduction; axonotemesis (grade 2) axon transection with intact endoneurium; neurotmesis grade 3,4 and 5 [170].

Following traumatic injury the PNS, pathophysiological events occur in the injured nerve, leading to Wallerian degeneration in the distal end of the nerve, followed by axon degeneration. Macrophages and monocytes migrates into nerve stumps, resulting the removal of the myelin and axon debris. In addition, Schwann cell proliferate to form bands of Bunger and produce neurotrophic factors and extracellular material to aid in the axon regeneration. For short gaps, the preferred methodology employs the use of end-end suturing, however when the gap is large suturing cannot be performed because the transected nerve stumps cannot reconnect without exerting tension. Defects greater than 3cm in length are treated by nerve autografts which are the gold standard. Unfortunately nerve autografts inherit complications including neuroma, secondary surgery, donor site morbidity, nerve site mismatch and limited amount of donor tissue [171]. Alternative approaches utilise allogenic grafts which is isolated form cadavers and are of limited supply and immunological rejection. Fortunately the concept of nerve tubes has evolved in order to implement strategies to improve the regeneration process of the defective nerves. However, in the 1960's the first nerve scaffolds was constructed from non-degradable polymers such as silicone, acrylic and polyethylene. Despite limited nerve recovery the non-degradable polymers required a second surgery to remove scaffold they also became detrimental to the patient inducing neural toxicity and constrict nerve remodelling [172]. Modern strategies concerns on the utilisation of bioresorbable polymers, several have been approved by the FDA. Basing the design on natural, synthetic or a combination of both polymeric material such as collagen type 1 (Neuragen, Neuroflex, Neuro-Matrix, NeuraWrap, Neuromed), porcine small intestine submucosa (Surgis Nerve cuff), poly (glycolic acid) (Nerotube) and poly($_{D,L}$-lactide,co-ε-caprolactone) (Neurolac) [174,177]. Various materials with regeneration capacity was listed in **Table 5.4**. Surgical procedures has already being performed, for example, Ashley et al., used collagen Neurogen scaffolds to bridge the brachial plexus in 5 patients, Ashley and co-workers concluded the used of collagen tubes were simple and effective [174]. Hung and co-workers used a 4x20mm bioresorbable Nerotube for the recovery of the median nerve in a 53 year old women [175]. Additionally Donoghoe and co-worked also utilised bioresorbable Nerotube to bridge the median nerve of a 43 and 61 year old patient [172,180]. These nerve bridging devices are 3D tubular constructs that provide improved mechanical stability, flexibility and guidance properties that allow repair of the peripheral nerve, where direct repair by neurorrhaphy is not possible [177].

Table 5.4 Biomaterials regeneration capacity in-vivo

Material	Species	Fabrication method	Size of defect	Regrowth rate	Reference
PHB	Cat	Sheets	Superficial radial nerve	12 months	[178]

Silk	Wistar rat	Solvent casting	8mm sciatic nerve	4 weeks	[179]
Chitosan	Rat	Extrusion	10mm sciatic nerve	13 weeks	[180]
PLA	Rat	Melt-blow process	7mm facial nerve	13 weeks	[181]
PLLA	Rat	Extrusion	10mm sciatic nerve	16 weeks	[182]
PLLA/PCL	Rat	Coaxial electrospinning	10mm sciatic nerve	12 weeks	[183]

While these devices do have potential and share similar efficacy compared to autografts surgery, however they are limited to nerve gaps exceeding 20mm, due to the simplicity of the design. Current approaches is developing nerve tubes by incorporating physical, biological, chemical cues or filling nerve tubes with collage and laminin gel, Schwann cells and growth factors. For example Luo and co-workers constructed nerve conduits from cellulose hollow tubes comprising of Schwann cells and Pyrrolquinoline quinone (Pq) which is an antioxtant that stimulates nerve growth factors [182, 183]. Luo et al applied the nerve guiding conduit onto the sciatic nerve of a rat. Luo and research team demonstrated that conduit comprising of both NGF and Pq repairs and reconstructed nerve structure and function [186]. In addition Xu and research team fabricated PLGA with Nectin-like molecule 1 (NECL1) which is a member of the immunoglobulin superfamily and is responsible for cellular adhesion and communication, in addition it is also known to be responsible for the cellular adhesion on axons and Schwann cells. Xu and co-workers fabricated PLGA film with pre-coated NECL1 to mimic the physiological environment of the natural axons in vivo. Xu et al., showed PLGA/NCEL1 conduits improved both Schwann cell aggregation and recovery of the nerve in comparison to PLGA [185]. Schmidit and co-workers utilised PLGA films and electrically conductive polypyrrole (PP) to enhance neurite length in vivo on PC-12 cells. Schmidit and team showed increase in neurite length in compassion to polystyrene controls [187]. Catrina et al. engineered collagen and silk fibroin scaffolds loaded with neurotrophic factors and glial cell line-derived neurotrophic factors (GDNF) to induce axonal repair and regeneration. Theses scaffolds were constructed to provide sustained release to achieve discrete kinetics of both neurotrophic factors and GDNF [188].

Constructing a conduit possessing intraluminal cues is only one of several strategies that must be considered in order to generate a conduit that will be more efficient to make it permissive for axon growth. Semipermeable materials via inclusion of pores are an essential characteristic incorporated within the conduit not only does it promote cell attachment and axon regeneration it also aids in the diffusion of nutrients and wasted products. It has been found that pore size also plays a vital role most notably in natural materials such as collagen [194,195]. Other modification is using Laminin and Fibronectin material for coating to induce nerve regeneration, cell attachment and migration. Also the microarchitecture has been modified by incorporating filaments, sponges and multichannel nerve tube structures [191]. This modification is designed to induce regeneration of nerves across lesions, directing the sprouting of axons from the proximal nerve end and concentration growth factors. The desired effect of these NGC is to increase the recovery speed and length of axon regeneration. It has been previously mentioned that various approaches can be incorporated into nerve conduits to improve in nerve regeneration among them include porosity, coatings, microfabrication, intraluminal cues and fibres. Introducing fibre bundles into the conduit significantly improves the longitudinally cellular migration of neurons and Schwann cells. Chwalek et al. analysed the impact of fibre profiling on cellular growth in vitro on PLA fibres. Chwalek and research team concluded both neuron outgrowth and morphological design of PLA fibres dictate nerve

regeneration [192]. The aim of constructing synthetic scaffolds is to stimulate native nerve morphology and accelerate nerve repair on damaged nerve. Numerous strategies and abundance of literature have been explored however these improvements are limited to simple round geometries. This could be attributed to limitation inherited with current materials processing techniques. Fortunately there is ongoing research of utilising fibre photonic apparatuses; Koppes et al., employed the use of thermal drawing processing (TDP) to produce a variety of cylindrical and rectangular core neural scaffolds. Taking advantage of TDP's fine control over microscale features. Koppes and team concluded that the ability to direct integration of micro grooved topography of the scaffold allowed for improved Schwann cell migration [193]. In addition 3D printing technology was found to be a promising method to produce complex biomedical devices in particular PLA 3D printing has being used for the improvement of implants, scaffolds and drug delivery systems, unfortunately complex tissue such as bone, cartilage and nerves prove to be challenging due to technological limitations [194]. Artificial PLA conduits has been extensively explored in peripheral nerve regeneration due to their flexibility, mechanical characteristics and lack of antigenicity. In vivo studies has already been investigated, however Tyler et al., discuses gap lengths exceeding 10mm in the sciatic nerve model has been a consistent failure. This problem emphasises the importance in optimising the inner architecture of the conduit in order to induce nerve regeneration. Cai et al., has utilised preamble PLA conduits induces axonal migration in a maturation rat model [195]. Similar strategies has also being employed on spinal cord injuries, Oudega and co-workers used a resorbable PLA_{50}, PLA $_{100/10}$ and PDLA tubular scaffolds with implanted Schwann cells into a transected rat thoracic spinal cord for up to 4 months. Oudega demonstrated increased axonal regeneration [201,202]. In addition Goulart et al., transected the left sciatic nerve of a C57BL/6 mouse. They demonstrated that PLA conduit not only can be fabricated in a controlled environment and suitable substrate for cell survival but also induced axonal growth [198]. Studies performed by Lu et al., utilised a PLA conduit fabricated by microbraiding which improved the polymers mechanical strength as a result in-vivo studies demonstrated improved regeneration at 8 weeks post operation. In addition, PLA was used to bridge a 20mm nerve gap defect the conduits contain a macrospores exterior and interconnected microspores on the interior to provide sufficient outflow then inflow rate. This conduit was fabricated via immersion precipitation and had an 80% functional recovery after 18 months [187,204,205]. Another important parameter to take into consideration is the swelling and degradation of a nerve tube. Essential if there is a rapid degradation this may attribute to swelling and too slow may lead to compression or chronic foreign body reaction. To avoid this the swelling and degradation properties may be optimised via tube dimension and copolymer ration. The ideal nerve tube should remain intact until axons fully regenerate across the nerve gap [196,206, 207].

Summary

Biodegradable implants can provide support, deliver medicine and degrade away after service, offering a promising alternative for patients. However, there are still some challenges. Cost is one of the major issue. Not only the expensive material and manufacture cost, but also the additional medical procedures. It is important to bring down the price in order to spread the use of biodegradable implants. Another reported problem related to biodegradable implants is complications due to delayed or incomplete degradation process. Ideally, biodegradable implants should degrade at rates that satisfy the conditions of healing and load-carrying ability. However, incomplete degraded device parts have been reported to remain with the body and cause inflammatory response interfering the recovery of the injured site. Complex degradation mechanism of polymer composites, which often has been adopted by biodegradable implants, requires a thorough study. Moreover, mechanical strength of biodegradable implants, especially polymeric implants, needs to be improved. So far the use of biodegradable polymeric implants is limited in minimally loaded situations, due to the weakness of biodegradable polymers. Reinforced biodegradable polymers makes it possible for high load

applications such as long bone fixation. Finally, the fabrication methods need improvement to suit biodegradable polymers.

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