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Polymer coatings for biomedical applications - a review

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Abstract

This review surveys some of the recent literature concerning the use of polymer coatings for a variety of biomedical applications. These have been grouped into six broad categories: orthopaedic materials, cardiovascular stents, antibacterial surfaces, drug delivery, tissue engineering and biosensors. These, to some extent overlapping, sections have been ordered such that the literature generally progresses from polymer coatings on metallic to non-metallic substrates. Polymer coatings can bestow a wide-range of functionalities due to their various properties, such as anti-wear and characteristics, mechanical strength, corrosion protection, electrical conductivity, biocompatibility and surface chemistry. The review period is from 2011 to the present (2013).

Keywords: polymer coatings, conducting polymers, orthopaedics, cardiovascular stents, antibacterial surfaces, drug delivery, tissue engineering, biosensors

List of abbreviations

Cat-PAsp-PPhe	catechol-poly(L-aspartic acid)-*b*-poly(L-phenylalanine)
hexylPVP	poly(vinyl-*N*-hexylpyridinium salts)
L-PPE:O	low-pressure plasma-polymerised ethylene film coatings rich in bonded oxygen groups
PAn	poly(aniline)
PAPBAOT	poly(3-aminophenyl boronic acid-*co*-3-octylthiophene)
PCL	poly(ε-caprolactone)
PDLA	poly(D-lactic acid)
PDLLA	poly(D,L-lactide)
PDMS	poly(dimethylsiloxane)
PEDOT	poly(3,4-ethylenedioxythiophene)
PEG	poly(ethylene glycol)
PEGDA	poly(ethylene glycol diacrylate)
PEI	poly(ethyleneimine)
PET	poly(ethylene terephthalate)
PGA	poly(glycolic acid)

PHA	poly(3-hydroxyalkanoate)
PHBV	poly(hydroxybutyrate) / poly(hydroxyvalerate)
PHBHV	poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)
P(HBHV-*b*-LA)	poly((3-hydroxybutyrate-*co*-3-hydroxyvalerate)-*b*-(lactic acid))
PHO	poly(3-hydroxyoctanoate)
PLA	poly(lactic acid)
PLGA	poly(DL-lactic-*co*-glycolic acid)
PLLA	poly(L-lactide)
PMAA	poly(methacrylic acid)
PMMA	poly(methyl methacrylate)
POSS-PCL	polyhedral oliogmeric silsequioxane poly(ε-caprolactone)
POSS-PCU	polyhedral oliogmeric silsequioxane poly(carbonate-urea) urethane
PPy	poly(pyrrole)
PSMA	poly(styrene)-*co*-poly(acrylic acid)
PTFE	poly(tetrafluoroethylene)
PVA	poly(vinyl alcohol)
polyNaSS	poly(sodium styrene sulfonate)
PU	poly(urethane)
SIBS	poly(styrene-block-isobutylene-block-styrene)
UHMWPE	ultra-high molecular weight poly(ethylene)

Introduction

Polymer coatings continue to be used in evermore increasingly diverse applications and sectors. From simple barrier coatings to elaborate nanotechnology-based composites, polymers offer a bastion of functionalities for their underlying hosts. In the field of biomedicine, such characteristics include wear-resistance, improved mechanical strength, corrosion protection, enhanced biocompatibility, electrical conductivity and tailored surface chemistry; switchable smart materials are even possible in at least the latter two cases. This paper reviews some of the recent literature, from 2011 to 2013, describing the use of polymer coatings for biomedical applications. The cited publications have been arranged into six main themes that seem to dominate; these include orthopaedic materials,[1-18] cardiovascular stents,[19-40] antibacterial surfaces,[41-54] drug delivery,[55-70] tissue engineering[71-83] and biosensors.[84-101] There is considerable crossover between these areas and certainly this review, as with others published in Transactions,[102-104] is by no means exhaustive; rather, it represents an overview to whet the appetite, particularly for those readers considering how their existing skills and technologies could be extended into new sectors. With this in mind, the sections have been arranged to broadly span from polymer coatings on metallic to non-metallic surfaces.

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Applications

Orthopaedic materials

There has been much recent media attention on the ban of UK hospitals to perform metal-to-metal hip resurfacing due to corrosion and high levels of wear debris (metallosis).[105] The use of ceramics or poly(ethylene) for the acetabular cup, which may also involve total hip placement (THR), usually offers an effective solution. Research into novel metallic and non-metallic coatings for orthopaedic materials, for a variety of applications, continues to be an area of interest. Magnesium and its alloys are attractive materials for potential temporary implantable devices due to their low density, great fracture toughness, and matched elastic modulii and compressive yield strengths relative to bone.[1,2] The corrosion products are also non-toxic, although of course, a reduction in the corrosion rate of pure Mg is required. Luo *et al.* electropolymerised Mg with the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) from an ionic liquid electrolyte.[2] The coating was found to reduce the corrosion rate and an anti-inflammatory drug, dexamethasone, incorporated into the electrolyte during electropolymerisation, was released upon subsequent electrical stimulation.

Xu and Yamamoto reported that uniform, nonporous amorphous poly(L-lactide) (PLLA) coatings had better adhesion strength to Mg compared with semi-crystalline poly(ε-caprolactone) (PCL) layers – polymers investigated to reduce the corrosion rate of Mg and increase its cytocompatibility.[3] Both polymers enabled good cell (SaOS-2) attachment and growth. Abdal-hay *et al.* investigated the effect of a spray-coating of hydroxyapatite (HA)-doped poly(lactic acid) (PLA) on the corrosion behaviour and bioactivity of AZ31 Mg alloy.[4] Lower corrosion rates were reported following a 15-day *in vitro* test and cytocompatibility studies revealed increased cell growth. Kunjukunju *et al.* reported the fabrication of multi-layered coatings of alginate and poly(L-lysine), using a layer-by-layer (LbL) technique, on alkaline and F^- pre-treated AZ31 Mg alloys for the controlled delivery of growth factors and other biomolecules.[5] The materials were further functionalised with FN to improve cell bioactivity, which was found to be the case. Electrospinning and dip-coating techniques were used by Abdal-hay *et al.* to coat PLA onto Mg alloy AM50; Ca-P and/or Ca-P-Mg layers lowered the corrosion rate and the surfaces promoted cell attachment (Fig. 1).[6] Ivanou *et al.* found that sealing the anodic layers on ZE41 Mg alloy with an epoxy-silane coating markedly improved the corrosion resistance of the alloy in 0.6 M NaCl.[7]

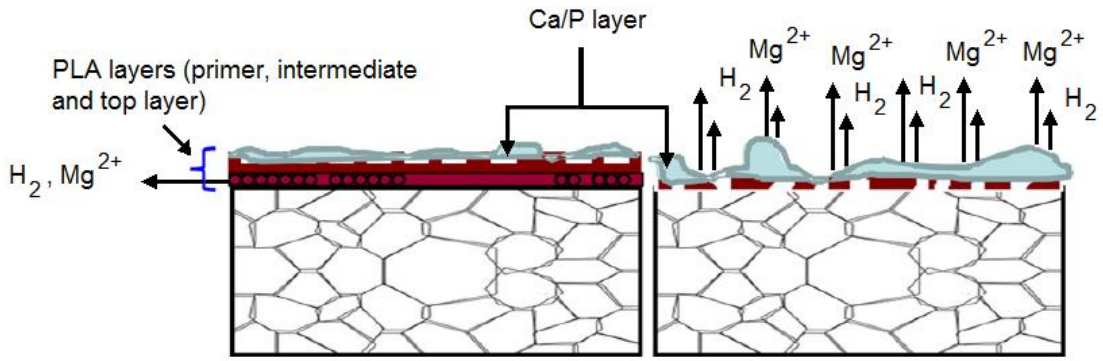

Figure 1. Schematic diagram illustrating the degradation mechanism and formation of a Ca/P layer on treated Mg alloy (AM50) surfaces upon immersion in simulation body fluid; porous coated film (left) and membrane coated film (right). Adapted from [6] and used with permission.

Titanium and its alloys are commonly used as orthopaedic implants; however, bacterial infection and poor osseointegration have been identified as the main reason for orthopaedic implant failures. Gulati *et al.* produced a Ti implant with drug-eluting properties to locally deliver drug molecules to address these undesirable characteristics (Fig. 2).[8] Ti surfaces were modified with titania nanotube (TNT) arrays that have incorporate the drug indomethacin with two biodegradable and antibacterial polymers, chitosan and PLGA. Drug delivery to the bone was demonstrated over an extended period, with liable kinetics and good biocompatibility. Incorporation and release of antibiotics in combination with growth factors is important for the prevention of infections and to stimulate bone healing. With this in mind, Strobel *et al.* incorporated three drugs (gentamicin for burst release, insulin-like growth factor I (IGF-I) for a burst release followed by a sustained release, and bone morphogenetic

protein-2 (BMP-2), to promote osteogenesis, for slow sustained release) into a poly(D,L-lactide) (PDLLA) coating on Ti.[9] Sequential release of the three drugs was successfully demonstrated. Son *et al.* used biodegradable nanoparticle carriers for the release of drug molecules from Ti surfaces.[10] Resorbable blast media (RBM)-treated Ti surface was prepared by blasting Ti with resorbable HA particles. Human serum albumin (HSA) nanoparticles loaded with vancomycin, pre-coated with positively charged poly(ethyleneimine) (PEI) molecules and then immobilised *via* electrical interaction on the Ti disc surfaces. Lee *et al.* also functionalised a Ti surface to release BMP-2 using Ti-adhesive nanoparticles self-assembled with catechol-poly(L-aspartic acid)-*b*-poly(L-phenylalanine) (Cat-PAsp-PPhe) (Fig. 3).[11] Controlled release of BMP-2 for 40 days and increased cell attachment were observed.

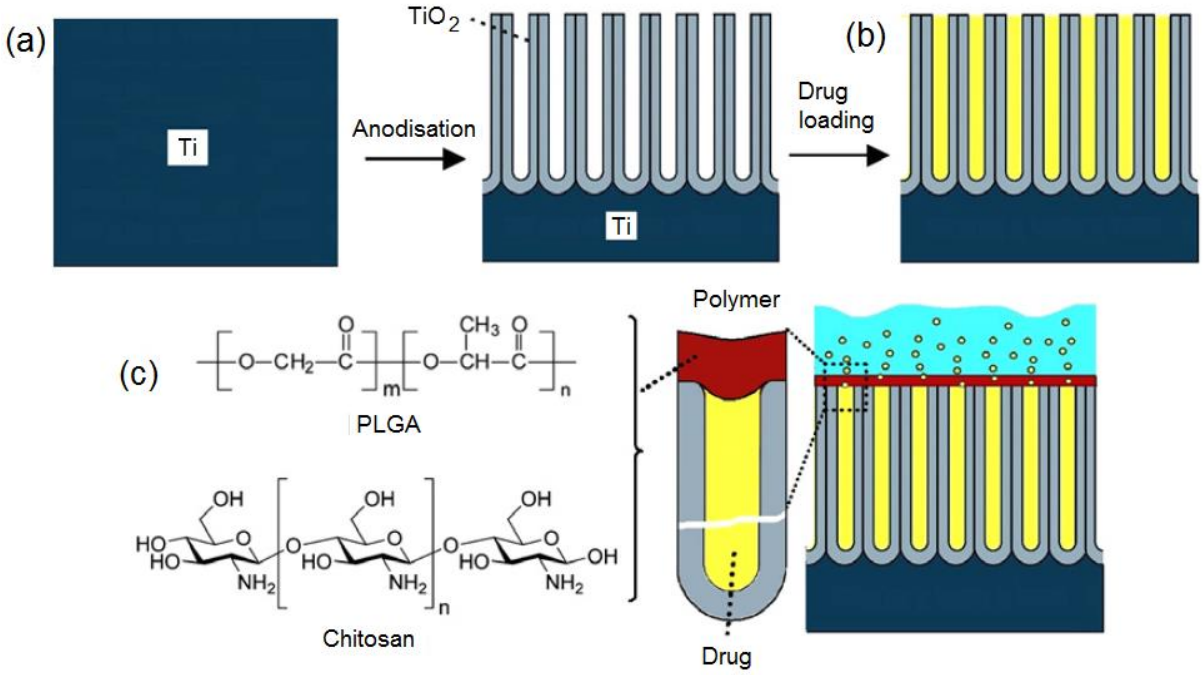

Figure 2. Scheme of titania nanotube (TNT/Ti) implants modified with polymer film: (a) bare TNT layer formed on Ti substrate by electrochemical anodisation; (b) loading of drug inside TNT structures; (c) chitosan or PLGA polymer film coated on TNT by dip coating (thin and thick) with the aim of controlling drug release and improving antibacterial properties and bone integration. The scheme shows diffusion of drug molecules through the polymer matrix. Adapted from [8] and used with permission.

Chebbi & Stokes produced flame-sprayed, biocompatible, biogradable (poly(hydroxybutyrate) / poly(hydroxyvalerate) (PHBV) 98:2) and non-biodegradable (poly(methyl methacrylate) (PMMA)) as single coatings on Ti and as top coatings on plasma sprayed HA.[12] Spraying parameters were investigated using a Design of Experiments approach and good cell proliferation was reported. Oughlis *et al.* found that a polymer of sodium styrene sulfonate (polyNaSS) could be used as a scaffold on Ti to increase cell (human mesenchymal stem cells, hMSCs) spreading and differentiation;[13] polyNaSS therefore has potential in bone tissue engineering. Hieda *et al.* examined differences in adhesion between a biomedical β-type Ti alloy, Ti-29Nb-13Ta-4.6Zr (TNTZ), and poly(urethane) (PU), caused by the addition of different silane layers.[14] A ten-fold increase in shear bonding strength was found, with 3-methacryloxypropyltrimethoxysilane (γ-MPTS) being particularly notable for its water resistance when exposed for 30 days.

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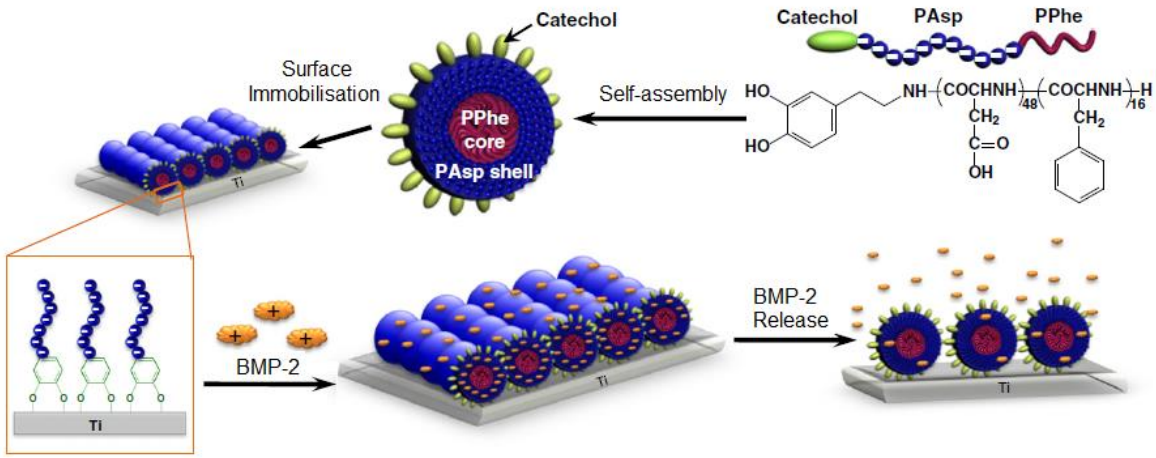

Figure 3. Schematic illustration showing formation of Ti-adhesive nanoparticles, immobilisation on Ti substrates and subsequent loading and release of BMP-2. Adapted from [11] and used with permission.

Atomic force microscopy (AFM) and field emission scanning electron microscopy (FE-SEM) was used by Liao *et al.* to assess the morphology of Ti coated with nanostructured poly(pyrrole) (PPy) – a conducting polymer.[106,107] The roughness of the deposit, for improved osteoblast adhesion, could be controlled by varying the duration of the electropolymerisation reaction. Mindroiu *et al.* electrodeposited PPy on Ti6Al7Nb using different electrolytes with the aim of producing materials of improved biocompatibility and antimicrobial activity.[16] Synthesis conditions were found to be correlated with biological properties. Using a dip-coating method, a thin film of ultra-high molecular weight poly(ethylene) (UHMWPE) was applied to Ti6Al4V by Panjwani *et al.*[17] High wear durability and adequate cytotoxicity test results (ISO 10993-5) were achieved. Further improved wear performance was found using an overcoat of perfluoropolyether (PFPE).

Madhan Kumar & Rajendran coated 316-stainless steel with a PPy/TiO_2 nanocomposite using cyclic voltammetry.[18] Biocompatibility tests in simulated body fluid (SBF) proved successful and the corrosion rate of the underlying substrate was reduced.

Cardiovascular stents

Bare-metal stents (BMS), introduced in 1994 for the treatment of coronary artery disease (CAD), have suffered problems associated with stent thrombosis and restenosis – recurrence of the vessel narrowing (stenosis).[19]

First generation drug eluting stents (DES; DES-1) used sirolimus and paclitaxel (PTX) (immunosuppressants) on stainless steel, which generally reduced restenosis.[20,21] However, some of these led to other clinical issues, such as late stage thrombosis, thought to be caused by cracking, flaking and delamination.[22] Strut dimensions, geometry and positioning relative to vessel walls also play a key role in thrombogenicity.[23]

Second generation DES (DES-2) used everolimus and zotarolimus on CoCr to lower rates of thrombosis.[19] Permanent polymer DES, such as the everolimus-eluting stent (EES) and sirolimus-eluting stent (SES), continue to be used and developed.[22] Byrne *et al.* compared the clinical outcomes of EES and SES after three years and found them to be similar.[21] Youssefian and Rahbar used simulation studies and AFM force measurements to investigate the poor adhesion between stainless steel 316 and parylene C (a chemical vapour-deposited, chlorine substituted poly(*p*-xylylene)) with and without a silane adhesion layer.[24] The AFM results correlated well with the modelling studies, although silanisation did not improve adhesion characteristics. The biocompatibility of poly(styrene-block-isobutylene-block-styrene) (SIBS), the most common DES coating used in China, on Co-Cr was improved by Zhu *et al.* by increasing the sulfonic acid content.[25]

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More recent strategies have been to produce carrier-free systems,[26] such as rapamycin (RM) crystals grown directly on a CoCr stent,[22] or biodegradable (bioabsorbable) DES on CoCr or Ni-Ti.[19] The latter approach allows for slow degradation of the coating to inactive and soluble forms without causing the problems associated with the early durable polymers.[21,22] For example, PLA, PDLLA and poly(DL-lactic-*co*-glycolic acid) (PLGA) undergo ester hydrolysis to yield lactic and glycolic acids that can be cleared without causing inflammatory responses.[27] Moore *et al.* used a PLA-poly(ethylene glycol) (PEG) biocompatible block-*co*-polymer to coat carbon nanotubes (CNTs) to reduce their short-term and long-term toxicity and prevent their aggregation; the polymer also aided sustained drug release of PTX and reduced *in vitro* inflammation.[28]

Bege *et al.* studied a reproducible, spray-coating process for stainless steel stents costing with the biocompatible and thermoelastic polymer poly(ethylene carbonate) containing PTX (Fig. 4).[20] Abluminal (outer) surfaces were more thickly coated than luminal (inner) ones and diffusion-controlled release occurred within two months. The polymer coatings were investigated as biodegradable DES by Bian *et al.* and were compared to those produced using PLGA.[29] The stability and release profiles (PTX and sirolimus) were found to be superior to the PLGA coatings. Karagkiozaki and co-workers found PEDOT coatings were cytocompatible and promoted human serum albumin adsorption and cell adhesion.[30]

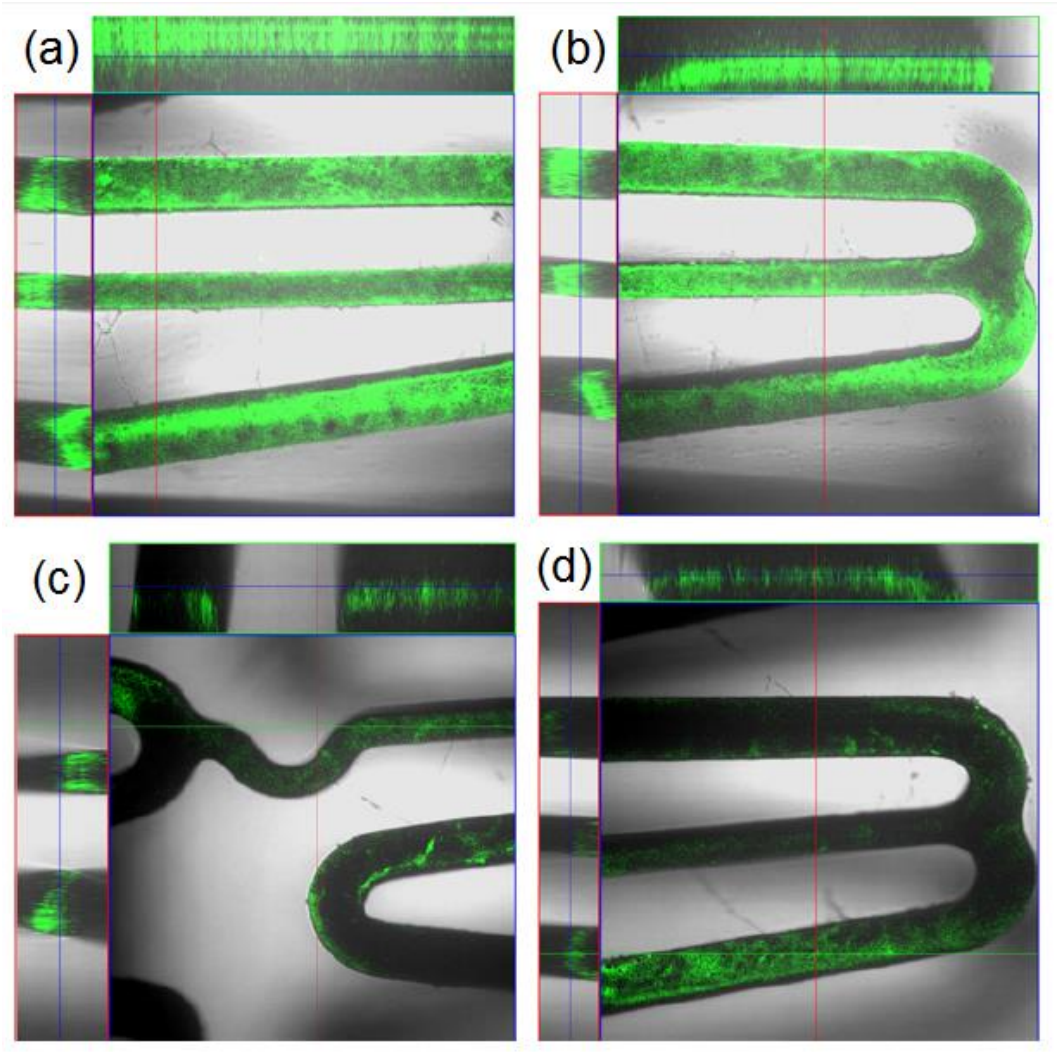

Figure 4. Homogeneity of the polymer film on stents. CLSM images of spray-coated PEC stents with incorporated coumarin-6 as fluorescent maker (10×). Z-stack images of the coated stents were performed; (a and b) abluminal (outside) and (c and d) luminal (inside) stent side. Green: Coumarin-6 in the PEC layer. Adapted from [20] and used with permission.

Variation in solvent and spray parameters upon DES surface morphologies was investigated by Shanshan *et al.*[31] PLGA coating thickness, on stainless steel, could be controlled by flow rate, roughness by nozzle power, and polymer distribution on internal and external surfaces by rotation speed. The addition of PEG was also found to increase drug (sirolimus) release rates. Jian *et al.* produced an aspirin/stainless steel 316L DES with a silica/PEG matrix to aid flexibility.[32] L-3,4-dihydroxyphenylalanine was used as a bio-adhesive and the drug was slowly released from the coating. Sirolimus release from stainless steel BMS stents sprayed with degradable poly(3-hydroxyalkanoate)s (PHAs), *i.e.*, natural poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBHV), poly(3-hydroxyoctanoate) (PHO), functional polyesters containing carboxylic groups and the diblock copolymer poly((3-hydroxybutyrate-*co*-3-hydroxyvalerate)-*b*-(lactic acid)) P(HBHV-*b*-LA), were investigated by Vergnol *et al.*[33] The bilayer systems offered many options for controlled release, including a burst effect.

Anti-vascular endothelial-cadherin (VE-cadherin) antibodies were attached to silanised and PEG-grafted stainless steel using a dip-coating by Kang and co-workers.[34] These antibodies are specifically expressed on the surfaces of endothelial progenitor cells (EPCs) and are important in cell proliferation and signalling. Non-specific biofouling was reduced and re-endothelialisation was achieved within three days. Shen *et al.* sprayed a heparin-immobilised copolymer of L-lactide (LA) and 5-methyl-benzyloxycarbonate-1,3-dioxan-2-one (MBC) (9:1) in tetrahydrofuran (THF) on to BMS.[35] The films were fully degraded in 16 weeks *in vitro* and *in vivo*, with only mild inflammation being exhibited.

Tan *et al.* speculates on a new generation of stents that use nanocomposite biodegradable polymers, such as polyhedral oliogmeric silsequioxane poly(carbonate-urea) urethane (POSS-PCU) and POSS PCL, with endothelial progenitor cell (EPC)-specific antibodies to promote cell growth and nitric oxide (NO)-eluting polymers for thrombosis prevention and maintaining healthy endothelial surfaces (Fig. 5).[36,37] LbL coating technologies could also be used for multiple drug delivery. In a letter to the Lancet, Waksman & Maluenda concluded that although biodegradable polymer technology is appealing, it still remains to be confirmed whether this strategy will replace durable polymers for DES.[38] The field has been recently reviewed in depth.[19,39,40]

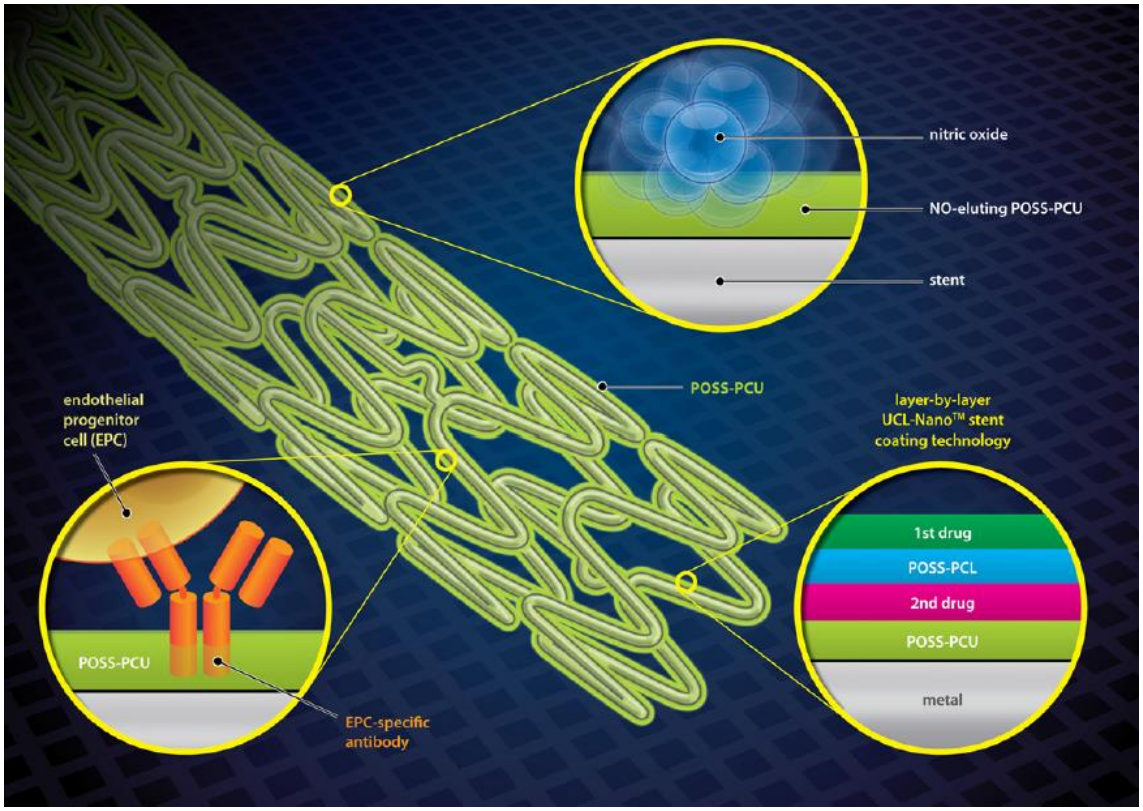

Figure 5. A three-pronged approach for the next generation of coronary stents: (i) nanocomposite polymer coatings, such as POSS-PCU with EPC-specific antibody attachment for enhanced endothelialisation; (ii) NO-eluting polymers for thrombosis prevention and promoting healthy endothelial surfaces; and (iii) LbL coatings (*e.g.*, POSS-PCU and POSS-PCL) for multiple drug release [36,37]. Used with permission.

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Antimicrobial surfaces

Antimicrobial surfaces, prepared by chemical and physical approaches, have been recently reviewed by Hasan *et al*.[41] With regard to polymer coatings, the review makes the distinction between structural polymers grafted with antibacterial polymers, *e.g.*, poly(vinyl-*N*-hexylpyridinium salts) (hexyl PVP), and those incorporating (entrapping) antimicrobial compounds, *e.g.*, antibiotics, Ag^+ and F^-. Substrates generally appear to be metallic implants, although other materials have been coated. Interestingly, the authors note that greater importance needs to be paid to surface topography (nanotopography) for the fabrication of new generation antimicrobial biomaterials.

Simple antimicrobial PU coatings, reported by Bakhshi *et al.*, were prepared by coupling quaternary ammonium salts bearing reactive hydroxyl groups on to the backbone of soyabean oil, conversion to polyols and subsequently reacting with diisocyanate monomers.[42] The coatings showed good mechanical properties and adhesion strength and were found to reduce bacterial activity by up to 95%, suggesting their promise as implant coating materials.

Cristescu *et al.* used matrix assisted pulsed laser evaporation (MAPLE) to deposit thin films of poly(1,3-*bis*-(*p*-carboxyphenoxy propane)-*co*-sebacic anhydride) 20:80 containing gentamycin on Si(100) and quartz substrates.[43] Controlled drug delivery was demonstrated and films were shown to be effective against *E. coli* and *S. aureus* populations, suggesting their potential for use with catheters and implants.

Electrosynthesised hydrogels on to Ti surfaces from aqueous solutions containing 2-hydroxyethyl methacrylate (HEMA), poly(ethylene glycol diacrylate) (PEGDA) and acrylic acid (AA) were reported by Di Giglio *et al*.[44] Polymers were loaded with ciprofloxacin (CIP), either during or after the polymerisation step, and *in vitro* inhibition against methicillin-resistant *S. aureus* (MRSA) was evaluated. The same drug was incorporated into a deposited low-pressure plasma-polymerised ethylene film coatings rich in bonded oxygen groups (L-PPE:O) on poly(ethylene terephthalate) (PET) by Jose Garcia-Fernandez *et al*.[45] Sustained release of CIP was monitored over several hours and inhibition of *S. aureus* was observed, suggesting the coating would be attractive for medical devices.

The use and fabrication of polymer coatings for controlled release of the new generation, broad-spectrum biocide, nanosilver, has been reviewed by Guo *et al.* and Knetsch & Koole.[46,47] Composite polymer coatings were found to offer improved biocompatibility. Pishbin *et al.* used the natural polysaccharide, chitosan, together with Bioglass® particles (9.8 μm) and Ag nanoparticles (AgNP) to produce a composite orthopaedic coating following a one-step electrophoretic deposition process.[48] Release of Ag^+ (< 2.5 ppm) was effective against *S. aureus* for up to 10 days. Osteoblast cell proliferation was supported, but maintaining an AgNP content below 342 μg was important to ensure no cytotoxic effects. Liu *et al.* investigated AgNP/PLGA-coated stainless steel alloy (SNPSA) for potential use as an antimicrobial implant material.[49] The material was found to reduce microbial populations and also promoted osteoblast proliferation.

Gao *et al.* grafted hydrophilic poly(acrylamide) brushes coupled to a series of antimicrobial peptides (AMPs) to produce infection-resistant implant coatings.[50] Biofilm resistance, *in vitro* and *in vivo*, was demonstrated and toxicity to osteoblasts and platelet adhesion were not observed. Williams and co-workers incorporated into poly(dimethylsiloxane) (PDMS) a novel antimicrobial agent cationic steroid antimicrobial-13 (CSA13), a convenient synthetic analogue to naturally occurring AMPs.[51] The coating system was tested against MRSA with an *in vitro* flow-through cell design.

To minimise the risk of post-implantation infection, Guillaume *et al.* coated poly(propylene) meshes with dual drug-release degradable polymers (PCL/PLA) containing ofloxacin and rifampicin (Fig. 6).[52] Sustained release of the antibiotics for 72 h was observed and surfaces were more rapidly invaded by fibroblasts than the uncoated substrate.

Ding *et al.* coated silicone rubber, a commonly used a catheter material, with a range of PEG/cationic poly(carbonate) block copolymers *via* a poly(dopamine) coating with the aim of reducing intravascular catheter infections (CAIs).[53] Polymers with a more hydrophobic component were found to kill methicillin-susceptible *S. aureus* (MSSA) and MRSA; blood protein adsorption and platelet adhesion was not observed.

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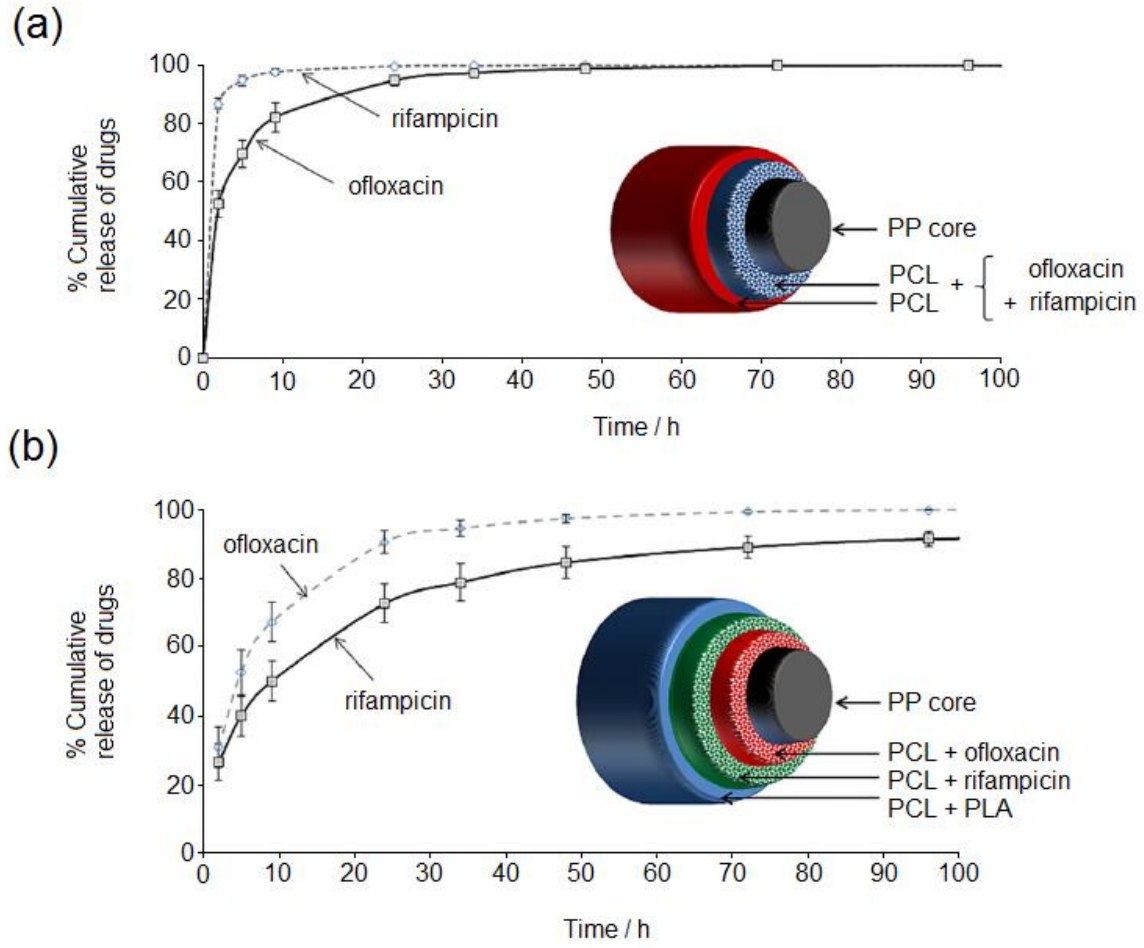

Figure 6. Drug release profiles from ofloxacin + rifampicin-coated meshes prepared using different coating strategies: (a) bilayer coating based on a first coating consisting of ofloxacin (1 mg) and rifampicin (1 mg) dispersed in PCL (10 mg) and a second coating consisting of PCL (10 mg; per 9 cm^2 mesh) followed by rapid heating; (b) tri-layer coating based on a first coating consisting of ofloxacin (1 mg) dispersed in PCL (5 mg), a second coating consisting of rifampicin (1 mg) dispersed in PCL (5 mg), and a third coating consisting of PCL–PLA (10 mg; per 9 cm^2 mesh) followed by rapid heating. Adapted from [52] and used with permission.

Antimicrobial polymer coatings were also prepared by Han *et al.* by dip-coating glass slides into a solution of dodecyl quaternary ammonium, methoxyethyl and catechol groups with subsequently drying and heating.[54] The functional groups respectively allowed biocide, hydrophilic/hydrophrobic balance and immobilisation to take place. Surfaces were resistant to *E. coli, S. aureus and Acinetobacter baumannii* for up to 96 h.

Drug delivery

Drug delivery systems display diverse pharmacokinetic profiles with variations in size, shape, chemical composition and surface characteristics, and are classified according to whether they are purely organic, organic-inorganic or purely inorganic. The main goals in drug delivery are to improve the drugs' bioavailability, decrease their therapeutic dose to reduce possible side effects and so increase safety, to enable targeted drug delivery and to approach personalised medicine for the long term future.[55] Therefore, new formulations are being studied to achieve a greater pharmacological response, and to deliver and control the release of drug molecules; these are being tested with several types of polymers with a variety of physicochemical properties. However, synthetic polymers may cause toxicity problems due to their degradation *in vivo*, and natural polymers usually face reproducibility problems due to the difficulty in controlling monomer purity. Polymeric matrices,

both synthetic and natural, have been used continuously as drug delivery vehicles. Natural polymers, such as dextrans, chitosan, sodium alginate, lignin and cellulose derivatives, are particularly interesting due to their higher biodegradability and biocompatibility compared with many synthetic polymers.[56] Goh *et al.*, in a review paper in 2012, emphasised the role of alginates in microencapsulation and therapeutic applications.[57] These materials provide good drug delivery matrices, where the release could be controlled by changing various factors such as cation type, porosity and composition of alginate, pH and drug molecular mass. Moreover, the good mechanical properties of alginates make them a valuable product for the treatment of wound healing and tissue repair.

Microneedles are being increasingly used in drug delivery.[58] These have the potential to overcome many of the disadvantages associated with traditional hypodermic needle. In addition, coated microneedle patches have demonstrated potential for effective, minimally invasive, drug and vaccine delivery. Processing parameters such as concentration of coating material, liquid input rate, duration of spraying, atomisation air pressure, gun-to-surface distance and air cap setting are very important.[59] McGrath *et al.* spray-coated microneedle patches using a conventional film coating process, and investigated two film-coating materials, hydroxypropylmethylcellulose (HPMC) and carboxymethylcellulose (CMC); these could be potentially drug loaded for intradermal drug and vaccine delivery.[59]

In addition to cardiovascular applications described above, stents have been used for treating other diseases. Moon *et al.*, for example, deposited a layer of acetylated polysaccharides on a poly(tetrafluoroethylene) (PTFE) coated self-expandable non-vascular metallic stent (EMS).[60] Gemcitabine, for astrointestinal cancer and cancer-related stenosis, was incorporated in the acetylated layer and sustained release was observed over 30 days; tumour regression was also noted.

Craig *et al.* tethered the active component of *cis*-platin, *cis*-$\{Pt(NH_3)\}^{2+}$, to gold nanoparticles (AuNP) *via* PEG linkers to produce drug delivery vehicles for this anticancer agent.[61] Improved formulation reproducibility, drug loading, stability and cytotoxicity were achieved.

Aznar-Cervantes *et al.* coated electrospun silk fibroin meshes with chemically polymerised PPy.[62] Chemical attachment was confirmed and the meshes offered improved mechanical resistance; drug (anion) storage and delivery could be controlled electrochemically. Antischistosomiasis drugs (praziquantel and trichlorfon) were also incorporated into PPy coatings on Pt, indium-tin oxide glass and reticulated vitreous carbon (RVC) by Li *et al.*[63] Electrochemical release of trichlorfon was demonstrated. Tsai and co-workers incorporated indomethacine, used to alleviate chronic pain, into PVA on conductive poly(aniline) PAn;[64] controlled, electro-stimulated release of the drug reduced problems associated with gastric irritation.

Tang *et al.* investigated effect of pH on drug delivery by using a pH-responsive polymer shell (chitosan / poly(methacrylic acid) (CS-PMAA)) for coating mesoporous silica nanoparticles (MSN), and then combined them with the drug molecule doxorubicin hydrochloride (DOX) to investigate drug storage and release behaviour.[65] The results demonstrated that DOX could be effectively loaded into the composite microspheres. Tarafder *et al.* examined lovastatin release behaviour from a PCL coating on β-tricalcium phosphate (β-TCP) to investigate the effects of pH, concentration and drug–polymer interactions.[66] They found that the hydrophilic–hydrophobic and hydrophobic–hydrophobic interactions between lovastatin and PCL could be a key factor on controlling the diffusion dominated release kinetics over dissolution and degradation processes.

Casting, printing, electrospinning and melt extrusion have been used increasingly for the preparation of implants (biodegradable and non-biodegradable) for the treatment of diseases such as cancer and epilepsy; these materials combine hydrophobic drug molecules with polymers for the successful release/targeting of drugs.[67] Polymers may also be functionalised appropriately to aid the coupling of bio-inert layers on implants, which are biologically inactive. Phosphoryl choline, commonly used in contact lenses, is such an example. Laga *et al.* reviews the many uses of hydrophilic polymer coatings for medicinal applications, including those for gene delivery.[68]

The field of polymer coatings for colon delivery have been reviewed by Maroni *et al.*[69] These are mainly in the form of functional coatings applied to solid dosage forms that are protected from gastric and small intestinal fluid exposure. Release mechanisms are mainly based on pH changes, time-dependent break-up, microbial enzymatic activity.

The sensitivity of controlled release dosage forms to the presence of ethanol in the gastro intestinal tract is also critical, which is for instance the case for most opioid drugs. Therefore, Rosiaux *et al.* prepared controlled release film coatings that are ethanol-resistant, by using blends of ethyl cellulose with medium or high viscosity guar gums.[70] The release of theophylline from pellets coated with the aqueous ethyl cellulose dispersion Aquacoat® ECD 30 was unaffected in the presence of ethanol (40%) in the release medium.

Polymeric coatings have been also used on cochlear implants.[71] Chikar *et al.* combined an arginine-glycine-aspartic acid (RGD)-functionalised alginate hydrogel with a PEDOT conducting polymer to produce a non-cytotoxic coating with low electrode impedance.[71] The hydrogel was soaked in brain-derived neurotrophic factor (BDNF), important for auditory nerve survival and cochlea development and maintenance.

Tissue engineering

The fabrication of polymer coatings plays a critical role in tissue engineering applications, since biocompatibility and elasticity are important parameters in this field.[72] Biomaterials used for tissue engineering applications include thermoplastic rubbers, physically (such as PUs, PHA-based polymers, PCL copolymers with glycolide or lactide) and chemically cross-linked elastomers (such as poly(polyol sebacate), poly(diol citrate), silicone elastomers), elastic proteins (such as collagen, elastin, fibrin, titin, resilin, gluten), and elastomer-based ceramic-filled composites.[72] Natural polymers such as starch, gelatin, alginate, cellulose and chitin represent attractive candidates for tissue culture application.[73] One disadvantage of natural polymers comparable to synthetic polymers is that are not bio-based. Croisier & Jérôme, however, prepared a bio-based polymer using chitosan for use in 3D-scaffolds as gels and sponges, and in 2D-scaffolds as films and fibres, which could be very attractive for tissue engineering.[73] The use of chitosan-based polymers for use as cartilage scaffolds for such applications has been reviewed by Iwasaki *et al.*[74] Lamprou and co-workers used gelatine and gelatine/elastin (different ratios) for the preparation of tubular nanocomposite gels and investigated them on rat smooth muscle cells (SMCs) for their use in tissue engineering of vascular grafts.[75] They found that gels were stable with mechanical behaviour (microstructure and stiffness) similar to natural arteries.

Tissue scaffolds that provide 3-D geometry and mechanical structure are mandatory for vascular tissue engineering applications, since most current synthetic scaffolds are not suitable. Dubey & Mequanint investigated fibronectin (FN) conjugation onto highly porous 3-D poly(carbonate) urethane scaffolds through grafted poly(acrylic acid) spacers on the urethane backbone.[76] These showed improved cell attachment and infiltration depth compared with scaffolds without FN conjugation. Tsai *et al.* found proliferation of chondrocytes (cartilage cells) on poly(dopamine)-coated 3-D porous scaffolds of polymers such as PCL, PLGA, PU and biodegradable polymers.[77]

The development of clinically relevant scaffold-based for bone tissue engineering (BTE) therapy is an important area that is of increasingly interest due to challenges relating to osseointegration of bioresorbable scaffolds and bone infection management.[78] BTE scaffold materials comprise of ceramics, composites and biodegradable (synthetic and natural) polymers; some regulatory approved polymers include poly(glycolic acid) (PGA) and poly(lactide)s (such as PLLA and poly(D-lactic acid) (PDLA)).[78] Synthetic degradable polymers, such as PLLA, PGA, PLGA, PCL, and PU, have also been approved for clinical use polymer scaffolds.[77] The biodegradable synthetic polymers, such as PLLA, are often coated with collagen to prepare porous sponge surfaces for tissue engineering.[79] Mathews *et al.* has investigated the effect of chitosan, collagen type 1 and hyaluronic acid on coating tissue culture plates for BTE application to evaluate their effect on osteogenic differentiation of human bone marrow derived mesenchymal stem cells (hMSCs).[80] Modification improved osteoblast differentiation, mineralisation and osteoconductivity.

Polymer coatings are also showing promise for neural prostheses, where the main challenge has been the development of highly stable and reliable microelectrode arrays (MEAs). For such applications, multiwall carbon nanotube (MWCNT)-doped PEDOT composite films have been electropolymerised onto Pt microelectrodes.[81] Graphene has been also investigated for neural prostheses.[82]

Ameringer *et al.* produced brush-type copolymers of PEG methyl ether methacrylates and poly((meth)acrylates) bearing spacer groups onto amine-functionalised poly(styrene) cell culture surfaces, followed by covalent immobilisation of cyclic peptides.[83] The aim was to control biointerfacial interactions with HeLa cells whilst reducing non-specific interactions for improved biomedical devices; the effectiveness of the system was demonstrated.

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Nandivada and co-workers developed the first polymer coating, poly[2-(methylacryloyloxy) ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide] (PMEDSAH) applied to poly(styrene) dishes, that sustains long-term growth of human embryonic stem (hES) cells in different culture media.[84]

Biosensors

Nambiar & Yeow reviewed the use of conducting polymers as sensors for clinical applications.[85] The attraction of these materials is in their flexibility, biocompatibility and ease of deposition. An enzyme-free glucose sensor was produced by Ciftci *et al.* using the conducting polymer poly(3-aminophenyl boronic acid-*co*-3-octylthiophene) (PAPBAOT) on a glassy carbon electrode (Fig. 7).[86] The biosensor showed no response to ascorbic acid, dopamine or uric acid and a glucose detection limit of 0.5 mm was exhibited. Mazeiko *et al.* immobilised glucose oxidase (GOx; for the detection of glucose), with and without AuNPs, in a Pan layer on carbon rod electrodes.[87] The catalytic properties of the enzyme were maintained in this novel nanocomposite that shows promise for amperometric biosensors as well as for other nanotechnological applications.

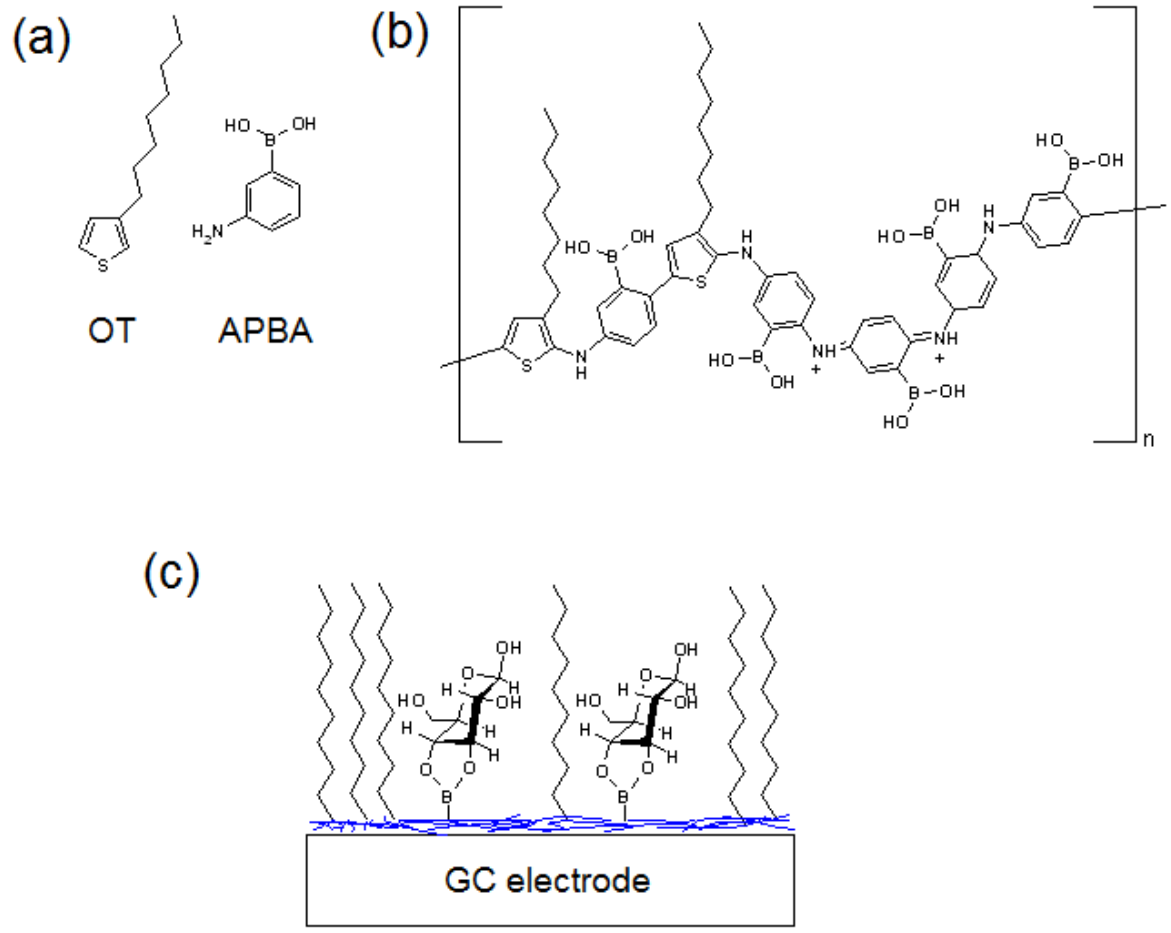

Figure 7. (a) Chemical structures of octylthiophene (OT) and 3-aminophenylboronic acid (APBA); (b) possible structure of PAPBAOT copolymer; and (c) schematic illustration of the interaction of PAPBAOT with glucose. Adapted from [86] and used with permission.

Kiilerich-Pedersen *et al.* produced an inexpensive, label-free, all-polymer electrochemical biosensor (conducting polymer PEDOT:OTs) for the detection of acute viral disease in human cell culture.[88] Changes in impedance correlated with AFM and scanning ion conductance microscopy observations. A disposable enzyme biosensor was reported by Serafín *et al.*, where the same polymer was deposited on AuNP-modified screen-printed carbon electrodes from an ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate) ($BMIMPF_6$) containing alcohol dehydrogenase (ADH) or Tyrosinase.[89] The use of this electrolyte offers great potential for incorporating enzymes into many of the conducting polymers hitherto only accessible *via* organic solvents.

ElKaoutit *et al.* used a matrix of Nafion (perfluorosufonic acid polymer) and glutaraldehyde to entrap horseradish peroxidase onto PPy.[90] The enzyme was incorporated in its native state and hence peroxide sensing was permitted in the absence of a mediator. A PPy and poly(thiophene) solid phase microextraction (SPME) fibre coatings for the rapid determination of the antibiotic amoxicillin in small volumes of human plasma was produced by Buszewski *et al*.[91]

Osmium-modified redox polymers were incorporated as mediators into GOx electrodes by Conghaile and co-workers.[92] The complexes were coupled to epoxy-functionalised polymers of various compositions on graphite and they showed promise for use in glucose oxidising biosensors. Wang *et al.* used PLGA microspheres dispersed in a poly(vinyl alcohol) (PVA) hydrogel as a drug releasing layer for use with implantable GOx biosensors to reduce local inflammation.[93] Feasibility of the study was demonstrated. PLGA was also used to produce nitric oxide reducing layer (for anti-platelet/anti-inflammation) for use with intravenous amperometric needle-type GOx/lactate electrodes.[94] Release of NO for more than one week and a reduction in thrombus formation were observed.

PU coatings have also been reported by a number of authors. Popescu *et al.* reported a method for producing HA-functionalised PU nanostructured films on $Si/SiO_2/Ti/Au$.[95] HA and PU, respectively, combine biocompatibility and mechanical properties and the hybrid offers promise for the construction of impedance biosensors for bone disease diagnosis and therapy. The effects of the electrospinning conditions of PU coatings on GOx biosensors have been investigated by Wang *et al*.[96] Control of the fibro-porous structure and thickness of the electrospun coatings was found to have little effect on electrode sensitivity.

Chang *et al.* used a biocompatible polymer poly(*p*-xylylene) (parylene) to coat CNTs grown on a poly(imide) substrate.[97] The insulating coating permitted this flexible biosensor to be suitable for human serum albumin detection (3×10^{-11} mg/ml) *in vivo*. Stable glutamate dehydrogenase (GDH) biosensors crosslinked with PEI were produced by Garcia-Galan *et al*.[98] Biotechnological uses for this enzyme have been unreported to date, owing to their poor stability. Varma described a method for fabricating thin-film, disposable reflectance biosensors based on polymers, *e.g.*, poly(carbonate), that are orders of magnitude cheaper than their semiconductor counterparts.[99]

Lv *et al.* reviewed the literature for the preparation of polymers imprinted with various proteins that exhibit antibody-like specificity.[100] Various applications are presented, although these materials still present many challenges. A polymer coating for detection of specific monoclonal antibody 10B2 (MAb 10B2) against bacterium *Acidovorax avenae subsp. citrulli* (*Aac*) was reported by Puttharugsa *et al*.[101] This was produced by immobilising a monolayer of *Aac* antigen on 95:5 poly(styrene)-*co*-poly(acrylic acid) (95PSMA). The polymer proved successful in antibody screening experiments.

Concluding remarks

Polymer coatings are extensively used for biomedical applications and continue to show great promise. They bestow a vast range of functionality to their underlying metallic and non-metallic hosts, such as improved wear-resistance, mechanical strength, corrosion protection, biocompatibility, electrical conductivity and tailored surface chemistry. There are numerous application areas, with many of these being concentrated in the areas of orthopaedics, cardiovascular stents, antibacterial surfaces, drug delivery, tissue engineering and biosensors.

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