Challenges for the development of surface modified biodegradable polyester biomaterials: A chemistry perspective

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Challenges for the development of surface modified biodegradable polyester biomaterials: A chemistry perspective

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The design of current implants produced from biodegradable polyesters is based on strength and rate of degradation and tailored by the choice of polyester used. However, detailed knowledge about the degradation mechanism of surface modified materials with applications in biomaterials science and tissue engineering is currently lacking. This perspective aims to outline the need for a greater focus on analyzing the degradation of modified polyesters to ensure they can fulfil their intended function and that degradation products can effectively be cleared from the body. The status of the literature regarding surface modified polyesters is summarized to illustrate the main aspects investigated in recent studies and specifically the number of studies investigating the fate of the materials upon degradation. *Published by the AVS.* https://doi.org/10.1116/1.5045857

I. INTRODUCTION

Implantable medical devices (implants) are a cornerstone of modern medical practice, saving millions of lives every year. Biodegradable polyesters, such as those shown in Fig. 1, currently have medical applications for uses in, e.g., sutures, bone fixation devices, and stents.[1] While these materials are one group identified as promising candidates for use in the topical fields of biomaterials science and tissue engineering (TE),[1,2] these uses necessitate additional requirements beyond degradability. For applications in TE, the materials should be porous to allow ingress of tissue during the regenerative processes.[2] Furthermore, the surface of the material should encourage specific cell attachment to limit inflammatory reactions as well as bacterial colonization. The exact requirements for the material degradation rate, the morphology, and the surface chemistry will depend on the intended application. However, common to all of these is the use of surface modification processes that aim to change the hydrophobic nature of the polyesters to become hydrophilic, as well as in some cases to introduce specific moieties. This allows proteins from the implantation site to retain their native structure upon adsorption, thereby allowing favorable cellular response and tissue growth.[2] The surface properties may be altered as a result of fabricating composites or blends or they can be intentionally altered using postsurface modification processes. This perspective will focus on the introduction of functionality through postsurface modification. In some cases, the introduction of functional groups is the end goal, while in other cases, the functional groups are subsequently used to, e.g., link biological molecules or initiate controlled radical polymerization (CRP).[3] This perspective will highlight shortcomings in current work and give recommendations as to where future research efforts should be made in order to progress this important area of biomaterials science and TE.

II. STATUS OF THE FIELD

A review of the literature on the use of postsurface modification processes for the polyesters (shown in Fig. 1), published in the period January 1, 2017 to June 15, 2018, was done in order to ascertain the status of the field. A search using Web of Science resulted in 79 articles investigating surface modification specifically, and these articles are considered here. Full details of these studies are provided in the supplementary material.[13] This literature "snap shot" reveals that 2D and 3D substrates receive similar attention with 56% of studies performed on solid films/disks/capsules while 44% are on porous materials (e.g., electrospun fiber mats and scaffolds). There is a large array of methods used for surface modification, with the relative proportions of these different treatments summarized in Fig. 2(a). Many involve adsorption of either biological or synthetic macromolecules (e.g., proteins and polyelectrolytes), some make use of chemical treatment (e.g., hydrolysis and aminolysis), while others make use of high-energy radiation (e.g., plasma, UV, or gamma) either as the treatment process or in conjunction with grafting of graft-copolymers. Characterization of the surface modified materials falls into three areas, each evaluating a particular surface feature: surface chemistry, surface wettability, and surface morphology. The number of studies investigating each of these aspects is summarized in Fig. 2(b). The majority of studies (68 of 79) investigated the surface morphology using SEM, AFM, or TEM, while just over half the studies included evaluation of surface wettability using contact angle measurements and less than half included evaluation of surface chemistry by FTIR, XPS, or energy dispersive spectroscopy. A large number of studies involved *in vitro* and/or *in vivo* work (71 of the 79 articles considered) showing strong evidence that surface modification of polyester biomaterials enhances the biological response including tissue ingress into porous scaffolds as a result of changes to the surface properties.

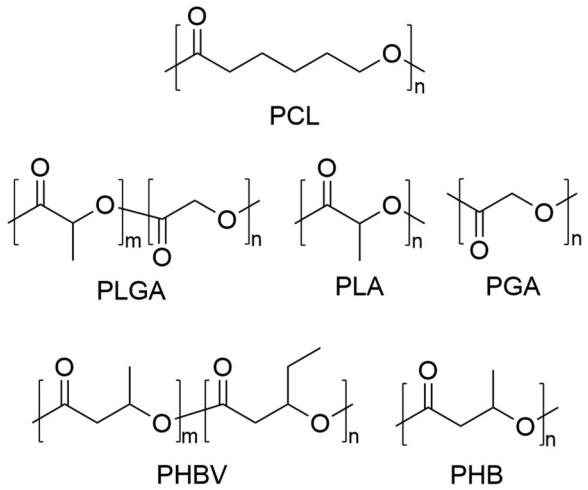

FIG. 1. Chemical structures of the biodegradable polyesters considered in this article.

While these studies provide support for the use of surface modified polyesters in biomaterials science and TE, most do not investigate or consider a set of crucial design parameters. First, the effect of the surface modification process on the bulk properties of the material is evaluated in only one-third of recent studies where the methods of chemical treatment or high-energy radiation are used. Second, insufficient attention is paid to the toxicity and renal clearance of the degradation products of surface modified biodegradable materials. Third, there is a limited number of degradation studies of surface modified materials [7 of the 79 articles evaluated; Fig. 2(c) indicates the type of degradation studies conducted]. Even many *in vitro* and *in vivo* studies do not evaluate the effect of degradation products. Evaluating how the specific morphological properties of surface modified biomaterials affect the rate of degradation of both the surface and the bulk as well as the likely *in vivo* fate of degradation products is crucially important. They are the ultimate critical properties and must be considered in the development of meaningful surface modification strategies if this field of biomaterials science is to move forward.

III. SAFETY OF DEGRADATION PRODUCTS

In a large number of recent studies, biological macromolecules are used in surface modification of biodegradable polyesters and as such this aspect of the construct is nontoxic. However, many studies have not considered the *in vivo* fate of the degradation products and currently, some chemical treatment processes make use of toxic chemicals. An example of this is aminolysis, which involves converting the ester moiety of a polyester into an amide and a hydroxyl group. When using a diamine, a free amine group is introduced allowing for a range of postmodification processes. The diamines most commonly used are ethylene diamine and 1,6-hexanediamine,[4] and these molecules also appear in recent studies (see supplementary material[13]). However, these molecules are toxic and when the surface modified polyester material degrades, these diamines will be regenerated. A relatively simple solution to this issue would be to use nontoxic diamines ensuring that nontoxic degradation products are produced when the material degrades.

Another issue is that many studies create surface layers composed of nondegradable polymers. Examples of this include adsorption of nondegradable polyelectrolytes or block-copolymers, plasma polymerization, and graft copolymerization. For the 15 studies that modified samples with

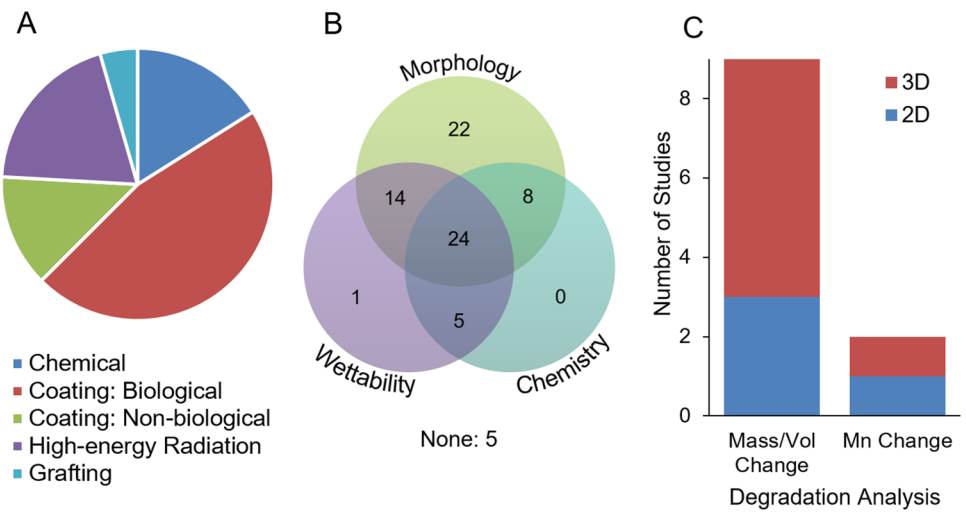

FIG. 2. Data presented are based on a literature search on Web of Science (using the search terms "surface modification" and "PCL or PLGA or PLA or poly(glycolic acid) or PHBV or polyhydroxybutyrate") between January 1, 2017 and June 15, 2018. This resulted in 323 articles published of which 79 relevant articles investigated surface modification specifically and these papers are included. (a) Proportions of each type of modification in the relevant literature. Some studies included two or three modification steps and these have each been included as separate entries. (b) Number of articles investigating different surface properties, where morphology tests include SEM, AFM, and TEM; wettability is tested by contact angle; and surface chemistry is determined through XPS, FTIR, or EDX. (c) Type of degradation studies described in the relevant literature for both 2D and 3D substrates based on seven studies. Full detail of the analysis of the literature is provided in the supplementary material (Ref. 13).

nonbiological coatings [Fig. 2(a)], 3 studies produced cross-linked films and only 2 studies analyzed the molecular weight of the coatings. None of the studies forming graft-copolymers analyzed the molecular weight of the grafted chains. The issue is that in materials with surface layers composed of nondegradable polymers, the entire polymer chain or cross-linked film will be dislodged as the polyester backbone degrades. Figure 3(a) illustrates the scenario of using, e.g., plasma polymerization to produce a cross-linked and nondegradable surface layer on a degradable material. Once the bulk material degrades, this cross-linked film will remain. Likewise, graft-copolymers produced by radical polymerization (using high-energy radiation) are covalently attached to the backbone of the degradable polymer so as the material degrades; the polymer chain with a polyester fragment will enter circulation. This scenario is illustrated in Fig. 3(b). To ensure renal filtration of these nondegradable polymers, discrete chains of a molecular weight less than 30 kg mol^{-1} are required.[5] Furthermore, linear polymer chains are preferable as branching leads to increases in blood circulation time.[5] This issue of combining a nondegradable polymer layer and a degradable polymer substrate can be addressed by careful selection of the surface modification strategies. For example, low molecular weight linear polyelectrolytes/block-copolymers could be used, and graft copolymerization could use CRP from the surface and thereby control the molecular weight of the graft-copolymer through the synthesis conditions applied.

IV. LIFETIME OF SURFACE MODIFIED POLYESTERS

A more difficult aspect to tackle is the effect of the surface modification on the degradation properties of the material. In order to appreciate the complexity of studying the degradation of surface modified polyesters, the current knowledge for homogeneous materials should be considered. Biodegradation of the polyesters proceeds by means of acid/base catalyzed hydrolysis and for, e.g., poly(lactic-co-glycolic acid) (PLGA) and poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV), this can also occur by enzymatic processes resulting in cleavage of the polymer chain.[1,6] *In vivo*, they resorb to form hydroxy acids which can readily be cleared from the body. Implant stability is strongly linked to polymer erosion, where the erosion process refers to the loss of mass from the degradable polymer material.[6] In cases where the diffusion of water into the polymer is faster than the degradation of polymer bonds, the polymer will undergo bulk erosion, whereas when the opposite is the case, it will undergo surface erosion. The erosion mechanism also depends on the thickness of the film or scaffold wall. Thus, for any specific polymer, a critical sample thickness, L_{crit}, describes the polymer matrix thickness above which a bulk eroding material becomes surface eroding.[6] This dimension can be expressed in terms of the diffusion coefficient of water, D, and the pseudo-first-order hydrolysis rate constant, λ', by the following equation: $L_{crit} = (D/\lambda')^{1/2}$.[6] This is an important aspect to consider since the diverse type of scaffolds investigated for applications in TE has very different dimensions as illustrated in Fig. 4.

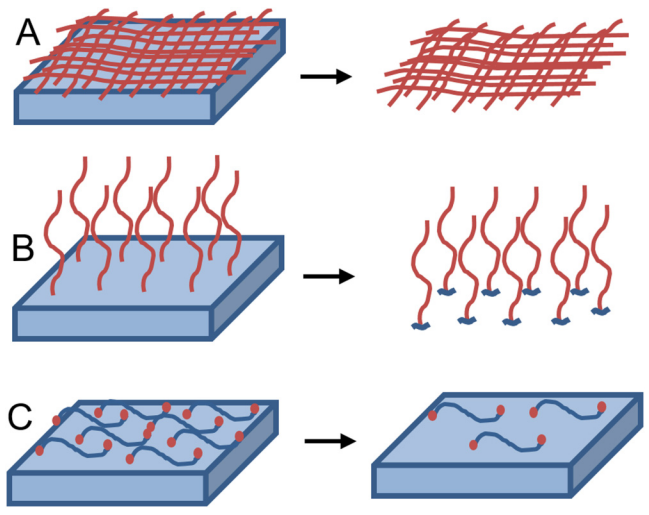

FIG. 3. Schematic illustrations of various scenarios that could occur during material degradation. (a) Illustrates how a cross-linked polymer film produced by, e.g., plasma polymerization on a biodegradable polymer will remain after the polymer construct degrades. (b) Illustrates how grafted chains produced by, e.g., high-energy radiation grafting will remain after the polymer construct degrades. (c) Illustrates how a portion of the surface functionalities introduced using, e.g., aminolysis or hydrolysis may be dislodged from the surface resulting in a reduced surface density of functional groups.

Importantly, the detailed knowledge of degradation mechanisms and lifetime predictions for polyester materials assume homogeneity,[6] but knowledge is lacking for heterogeneous materials such as surface modified materials. In order for a surface modified polyester material to be suitable for use as a biomaterial, it is essential that the rate of degradation of the surface layer can be tuned independently to that of the bulk. If the rate of degradation of the surface layer is too rapid, functionality can be reduced or lost before the construct has fulfilled its function. One apparent issue is that the increased hydrophilicity of the surface layer will affect diffusivity, causing the degradation mechanism to be altered compared with a homogeneous material; however, the extent of this cannot currently be predicted. A specific example may be useful to illustrate this. Hydrolysis and aminolysis are processes that inherently involve breaking of an ester bond resulting in reduced molecular weight of the polyester chains. This in combination with increased hydrophilicity of the surface layer and its contact to fluids would likely result in faster degradation than the bulk. Figure 3(c) illustrates a likely scenario for surface functionalities introduced using, e.g., aminolysis or hydrolysis where a portion may be dislodged from the surface resulting in a reduced surface density of functional groups. Indeed, it has been reported that within 3 days, the amine groups remaining were only 20% of the original amount for polycaprolactone (PCL) modified by 1,6-hexanediamine aminolysis.[7] In addition, the study using 1,6-hexanediamine aminolysis of PCL found the average molecular weight of the bulk to decrease significantly.[7] These key observations highlight that it is important to consider not only the altered degradation rate of the surface layer but also the bulk material lifetime. Recent literature investigating

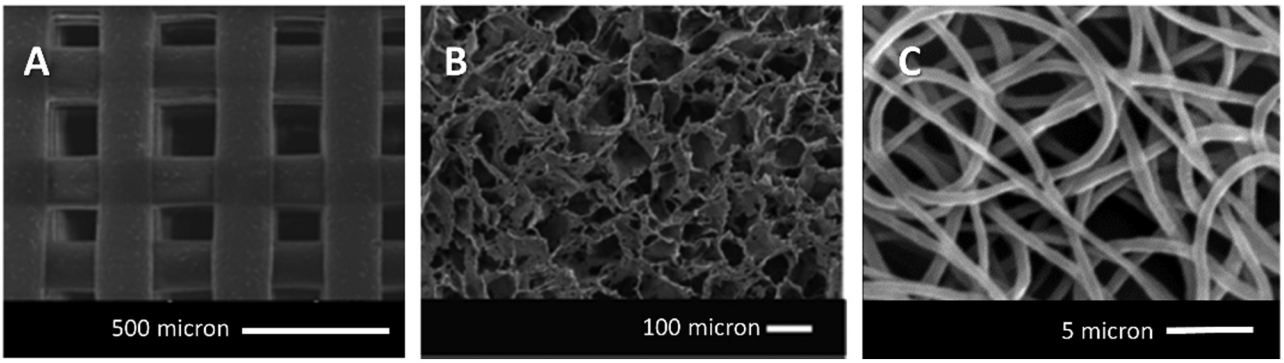

FIG. 4. TE polyester scaffolds prepared by (a) 3D printing, (b) thermally induced phase separation, (c) electrospinning. The approximate wall thickness is (a) 200, (b) 1–5, (c) 0.5–1 μm.

enzyme mediated bulk degradation by mass or volume change of aminolyzed and PEGylated PCL,[8] poly(propylene fumarate) coated PCL,[9] as well as degradation in buffer of PLGA with a ceramic coating,[10] a gelatin-modified poly(lactic acid) (PLA) material[11] and hydrolyzed PCL (Ref. 12) found an increased degradation rate of the modified material compared with the pure polyester. For one study,[8] it was found that the greater mass loss correlated with different initial molecular weights (as a result of the aminolysis process).

While it is promising to see that a few studies do investigate the effect of the surface modification on the bulk degradation properties, none of these studies investigated explicitly the degradation mechanism or the stability of the surface layer. Systematic studies of the effect of surface modification methods on the bulk degradation properties are required to develop models that can predict the lifetime of such heterogeneous materials. In addition, considering the surface functionalities introduced using various surface modification approaches is often used to link, e.g., biological cell signaling molecules; it is clear that investigations into the surface layer stability is of importance. Key questions to answer in this regard include "how quickly do surface layers erode?" and "how quickly are signalling molecules lost?". The added complexity arises when considering the large array of surface modification methods applied [Fig. 2(a)] to many different polyester substrates (Fig. 1) which are used to fabricate constructs of varying morphological features (e.g., for 3D materials; Fig. 4). However, without this knowledge, it is not possible to rationally design surface modified materials with applications in biomaterials science and TE. It would therefore be valuable to these fields if more attention were placed on such studies to determine best modification strategies for different applications.

V. SUMMARY AND FUTURE DIRECTIONS

Surface modification of biodegradable polyester materials is used extensively in biomaterials science and TE. Most studies focus on showing enhanced cell growth and have not ensured that the degradation products can be cleared from the body without accumulation of high molecular weight and/or toxic species. Furthermore, plasma polymerization and traditional grafting (gamma or UV radiation) generally produce very high molecular weight polymers or cross-linked films that cannot be cleared from the body. With the ultimate aim of using these materials for applications in biomaterials science and TE, the safety concerns must be addressed and it is recommended that more effort is placed on studies that consider and evaluate these aspects. In addition, only very few recent studies have investigated how the surface modification process affects the degradation of the constructs and none have explicitly looked at the surface layer stability. With only limited information of bulk degradation and surface layer stability, it is, at present, not simple to design a surface modified construct to have a certain rate of degradation. Addressing this knowledge gap is essential for the future development of sound surface modification strategies for surface modified materials with diverse applications in biomaterials science and TE.

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[13]See supplementary material at https://doi.org/10.1116/1.5045857 for a summary of the literature investigated including type of material used, type of surface modification and any degradation analysis included.

Alexandra L. Mutch is currently a first year PhD student at the University of Queensland. She graduated from the same university in 2017 with a Bachelor of Advanced Science with Honours in Chemistry. Her work focuses on tuning biomaterials to enhance bone regeneration.

Lisbeth Grøndahl received a Master's degree in Chemistry and a PhD in Chemistry from the University of Copenhagen (Denmark) in 1995. Her doctoral research was in the field of inorganic coordination chemistry evaluating the mechanisms of metal-mediated reactions and the extrusion of metal ions from cage complexes. During her Masters and PhD studies, she spent time at the Research School of Chemistry of the Australian National University (Australia). An important lesson that she learnt from her PhD supervisor was to look at all the available data and identify overall mechanisms, and she continues to apply this philosophy to her research. After completing her PhD, she held positions at the Department of Life Science and Chemistry, Roskilde University (Denmark), and a range of positions at the University of Queensland (Australia) and Queensland University of Technology (Australia) prior to joining the School of Chemistry and Molecular Biosciences, the University of Queensland, in 2002 as a lecturer. She was promoted to Senior Lecturer in 2006 and to Associate Professor in 2012. Since her doctoral research, she has branched out from her original core competencies and, while she enjoyed inorganic chemistry, she has pursued her interest in biology and now finds that working at the interface of chemistry and biology is incredibly stimulating and challenging—there is always a driving force to learn and apply new knowledge. She currently works in the interdisciplinary field of biomaterials science with a focus on the development of approaches to create functional polymeric biomaterials in the form of membranes, scaffolds, hydrogels, and nanoparticles. Her core research expertise includes surface modification of polymers and inorganic particles, controlled assembly of biopolymers and nanocomposites, as well as comprehensive characterization of surfaces, composites, and biopolymer assemblies. She finds that understanding the underpinning chemistry that enables the development of new materials with applications as biomaterials is an exciting and rapidly developing field to be part of. She enjoys the complexity and richness of the data that is generated with collaborators in engineering and biology, and how these data assist in the development of new materials.

Grøndahl's standing in her field was recognized internationally through the award of Fellow of Biomaterials Science and Engineering (FBSE) at the World Biomaterials Congress in 2016. She currently leads a research team of six PhD students, one Honours student, one research assistant, and a Postdoctoral Fellow. Since entering into the field of Biomaterials Science, she has graduated 16 PhD students as well as 3 Research Masters and 26 Honours students. She has more than 100 publications and is currently a member of the Editorial Advisory Boards of Biointerphases and Bioactive Materials. She was President for the Australasian Society for Biomaterials and Tissue Engineering (ASBTE) during 2012–2014 and Conference Chair for the 2015 meeting of the 5th International Symposium on Surfaces and Interfaces for Biomaterials held in conjunction with the 24th Annual Conference of the ASBTE. She is currently one of two Australasian representatives on the Committee for the International Union of Societies for Biomaterials Science and Engineering (IUSBSE).

She passes on the recommendation that success will come through balancing sustained productivity with taking risks. Many researchers work in areas of science that they are most comfortable with and this allows them to progress their research and achieve publication benchmarks. This work can be very innovative but typically does not encourage them to look for the bigger picture questions in science. However, her experience has found that tackling the big picture questions is often much more rewarding and builds cross-disciplinary perspectives and understanding. Therefore, we should all try to find a balance between publishing to meet performance expectations (so as to fulfil criteria for our employment and career progression) while looking more deeply into the broader questions that are really holding back progress in our own area of science.