

Factors Controlling Degradation of Biologically Relevant Synthetic Polymers in Solution and Solid State

Jordan Brito¹, Alexander K. Andrianov^{2}, and Svetlana A. Sukhishvili^{1*}*

¹Department of Materials Science & Engineering, Texas A&M University, College Station, TX 77843, USA

²Institute for Bioscience and Biotechnology Research, University of Maryland, Rockville, MD 20850, USA

KEYWORDS: biodegradation, biomaterials, autocatalysis, degradable polymers, hydrolysis, controlled release

Abstract

The field of biodegradable synthetic polymers, which is central for regenerative engineering and drug delivery applications, encompasses a multitude of hydrolytically sensitive macromolecular structures and diverse processing approaches. The ideal degradation behavior for a specific life science application must comply with a set of requirements, which include a clinically relevant kinetic profile, adequate biocompatibility, benign degradation products, and controlled structural evolution. Although significant advances have been made in tailoring materials characteristics to satisfy these requirements, the impacts of autocatalytic reactions and microenvironments are often overlooked resulting in uncontrollable and unpredictable outcomes. Therefore, roles of surface *versus* bulk erosion, *in situ* microenvironment, and autocatalytic mechanisms should be understood to enable rational design of degradable systems. In an attempt to individually evaluate the physical state and form factors influencing autocatalytic hydrolysis of degradable polymers, this Review

follows a hierarchical analysis that starts with hydrolytic degradation of water-soluble polymers before building up to 2D-like materials, such as ultrathin coatings and capsules, and then to solid-state degradation. We argue that chemical reactivity largely governs solution degradation while diffusivity and geometry control the degradation of bulk materials, with thin ‘2D’ materials remaining largely unexplored. Following this classification, this Review explores techniques to analyze degradation *in vitro* and *in vivo* and summarizes recent advances toward understanding degradation behavior for traditional and innovative polymer systems. Finally, we highlight challenges encountered in analytical methodology and standardization of results and provide perspective on the future trends in the development of biodegradable polymers.

Table of Contents

1. Introduction.....	4
2. Factors governing polymer degradation: solution vs. solid state.....	6
2.1. Water-soluble synthetic polymers – degradation in solution.....	7
2.1.1. Molecular engineering aspects.....	11
2.1.2. Solution conditions and intra-/intermolecular interactions.....	12
2.2. Hydrophobic synthetic polymers – degradation in solid state	15
2.2.1. Hydrolytic degradation of monolayers	16
2.2.2. Hydrolytic degradation in bulk geometry	17
2.2.3. Morphology and microstructure	21
2.2.4. Surface hydrophobicity	24
2.2.5. Microtacticity and crystallinity	25
3. Methods for evaluating degradation behavior	27
3.1. <i>In vitro</i>	28
3.2. <i>In vivo</i>	30
4. Recent advances toward control of degradation behavior	31
4.1. Designer polymers	31
4.2. Polymer blends and composites.....	34
4.3. Architectural modifications	37
5. Conclusions and perspectives	38
6. List of acronyms and variables	40
7. References	44

1. Introduction

Biodegradable polymers have been of significant interest both in research and in enhancing human health and well-being. With the unprecedented effects of the COVID-19 pandemic on public health perception and plastic waste generation,^{1,2,3} the opportunities for biomedical and commercial growth of biodegradable polymers are stimulated. However, challenges in control over the degradation behavior of current materials pose barriers to their development. Specifically, in the cases of commercially available polyesters poly(lactic-*co*-glycolic acid) (PLGA) and poly(ϵ -caprolactone) (PCL), the autocatalytic hydrolysis from generation of acidic byproducts unpredictably amplifies degradation of bulk polymeric materials. To better appreciate the diverse factors affecting degradation of biomaterials, this Review focuses on the fundamental structure-property relationships that govern autocatalytic degradation behavior on the molecular level, before analyzing the advances made in degradation modulation *via* morphological, processing, and physico-chemical strategies. Although oxidative and enzymatic biodegradation are important processes in the physiological breakdown of degradable polymers,⁴ these processes are not easily predictable due to varying concentrations and species (*e.g.*, of reactive oxygen species or enzymes) between microenvironments. Consequently, we focus this Review specifically on hydrolytic degradation of polymers intended for use in life sciences applications, with emphasis on the factors influencing autocatalysis, microenvironment, and form factor.

Traditional classification of biodegradable polymers is based on their biomedical functionality rather than their physical state/geometry, and it differentiates between resorbable materials with temporary structural/mechanical support functions and drug delivery vehicles with modulated release and targeting capabilities. The former category includes implantable biomaterials, such as scaffolds for organ regeneration and tissue engineering^{5,6} and bioresorbable cardiovascular

stents.^{7,8} The latter category involves parenterally administered formulations (*e.g.*, nano-/microspheres, *in situ* gels, prodrugs, vaccine adjuvants), coatings, and matrices for controlled release. These categories are not exclusive, as many structural biomaterials benefit from controlled delivery of drugs. Additionally, coatings of biodegradable polymers have also been used to facilitate growth of a biocompatible interface between a permanent implant and the surrounding biological tissue.^{9,10}

Although natural polymers, such as chitosan, alginic or hyaluronic acids, continue to be popular choices, their limited diversity, batch inconsistencies, risk of an immune response, and weak mechanical strength limit their applicability.¹¹ Yet, the classification between natural and synthetic polymers is not always clearcut, as “natural” polymers have been synthesized for controlled degradation, such as synthetic polypeptides, and chemical modifications have been used previously with natural polymers to inhibit the enzymatic degradation of the polymer.^{12, 13} However, this Review will focus on the common families of synthetic polymers that can be tailored to control hydrolytic degradation behavior *via* structural manipulations. In this Review, we examine synthetic polymers that have been deemed “degradable”, *i.e.*, those that breakdown during or immediately after their application,¹⁴ including polyesters,¹⁵ polyamides,¹⁶ polyurethanes,¹⁷ polyanhydrides,¹⁸ polyorganophosphazenes,¹⁹ and polyorganophosphates,²⁰ among others.

Importantly, biomaterials must comply with federal regulations requiring their safety at all stages of degradation, effectiveness, and ability to be sterilized.⁴ A number of products and devices based on poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) have demonstrated excellent safety profiles and were approved by the U.S. Food and Drug Administration for pharmaceutical, surgical, and orthopedic applications.^{21,22,23} However, even these polymers can show rapid

accumulation of acidic byproducts, leading to potential foreign body reactions.^{24,25,26, 27,28,29} An in-depth understanding of degradation behavior of these polymers is critical for achieving precise timing for drug release and controlling changes in mechanical properties of these polymers during degradation.

There are multiple excellent reviews focusing on specific biodegradable polymers and their applications, such as drug delivery or tissue engineering, chemical degradation pathways, biological compatibility of degradation by-products, interactions with cells, and/or regulatory approval processes.^{30,31,32,33,34,35} While prior reviews provided detailed analysis of chemical aspects of either solution- or solid-state biodegradation, they often overlooked the morphological and physical state effects that distinguish degradation in solution from degradation in solid-state polymers. To close this gap, this Review offers a unified view of degradation by identifying the critical physico-chemical factors that govern the autocatalytic hydrolytic degradation of a polymer. Fundamental relationships between atomic-scale characteristics of macromolecules, their physical properties, and degradation behavior are reviewed with an objective to facilitate molecular engineering and morphological design and construction of complex degradable systems with precise control over degradation. Critical issues with evaluation techniques, mathematical models, and comparability of results are identified, leading to a proposed hierarchical multi-step approach to characterizing polymer degradation *in vitro*. Finally, recent innovative modifications of commercially available synthetic biodegradable polymers, with a focus on commercialized polyesters and clinical-stage polyphosphazenes, and novel macromolecular structures are evaluated critically against the unmet needs of life sciences applications.

2. Factors governing polymer degradation: solution vs. solid state

Factors that define the degradation behavior of a polymer span several scales and include the physical state of the polymer, its geometry, as well as molecular-level characteristics (**Fig. 1**). In solution, a polymer can undergo breakdown with maximized access of water and other environmental species to the polymer chains, and the degradation behavior is determined mainly by its molecular structure, chemical reactivity, intra-/intermolecular interactions, and environmental parameters (temperature, pH, ionic strength, concentration of enzymes, *etc.*). In contrast, the restricted penetration of species into and out of a solid-state matrix becomes increasingly important to the degradation rate and erosion mechanism of an insoluble material. For these reasons, this Review analyzes and, when possible, compares both polymer degradation in solution and in solid-state. This analysis also uniquely includes a discussion of interfacial effects on degradation that are significant to polymer blends, composites, and high surface-to-volume architectures.

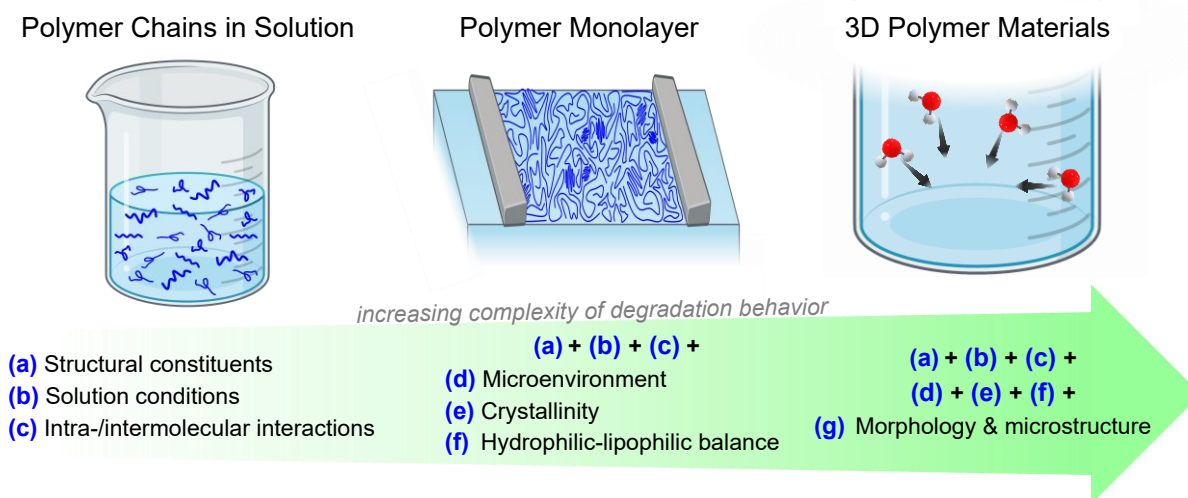


Figure 1. Relationships between the physical state of the polymer and physico-chemical parameters that govern the degradation behavior.

2.1. Water-soluble synthetic polymers – degradation in solution

Water-soluble synthetic polymers can improve pharmacokinetic and pharmacodynamic (PK/PD) profiles of therapeutic and preventive agents^{36,37} and are often employed for the delivery of small drugs, proteins, and nucleic acids in the form of prodrugs or PEGylated systems.^{38,39,40,41} Examples of PEGylated drug carrier systems are shown in **Fig. 2**, including polymersomes, micellar systems, and drug conjugates.⁴²

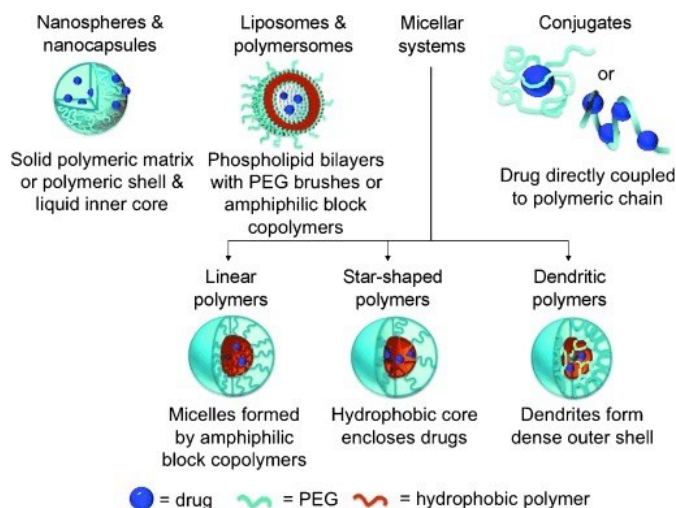


Figure 2. Drug-delivery systems utilizing water-soluble PEGs. Reproduced with permission from ref⁴². Copyright 2010 John Wiley and Sons.

The benefits of the use of synthetic polymers, such as an increase in the drug circulation time and supporting passive targeting of the drug, are often enhanced for high-molecular-weight polymers. However, because of the upper molecular weight limit of $\sim 30\text{--}50$ kg/mol for soluble polymers to be cleared from the body *via* glomerular filtration,⁴³ only low and moderate weight non-degradable polymers are usable, and high-molecular-weight polymers can be used only if they degrade into smaller biocompatible molecules for complete clearance from the body.⁴⁴⁻⁵¹ Although the covalent modification with non-biodegradable poly(ethylene glycol) (PEG) has been commercially successful in the development of long-circulating drugs (PEGylation technology), the polymer size restriction due to non-biodegradability, high cost, and even ‘anti-PEG

immunity^{42, 52-60} have stimulated research into alternative biodegradable and non-immunogenic water-soluble polymers.^{42, 60-62}

Among many synthetic water-soluble polymers, few exhibit degradability and biological functionalities suitable for biomedical applications. However, several groups of polymers with phosphorous- and amino acid-containing backbones show promising degradation characteristics (**Fig. 3**), such as biocompatible degradation products and versatile side-group chemistry. Another example of water-soluble macromolecules designed to degrade under acidic conditions and useful for endosomal or lysosomal degradation, include aconitic acid derived polymers.⁶³ While polyphosphazenes (PPZs)^{64,65} and polyphosphoesters (PPEs)^{66,67} degrade hydrolytically or enzymatically *via* main-chain cleavage and yield buffering phosphates, poly(amino acids), such as polyglutamates and poly(aspartic acid),^{68,69} degrade mainly enzymatically¹⁶ and thus are strongly influenced by the steric hindrance to the cleavable bond by neighboring groups.

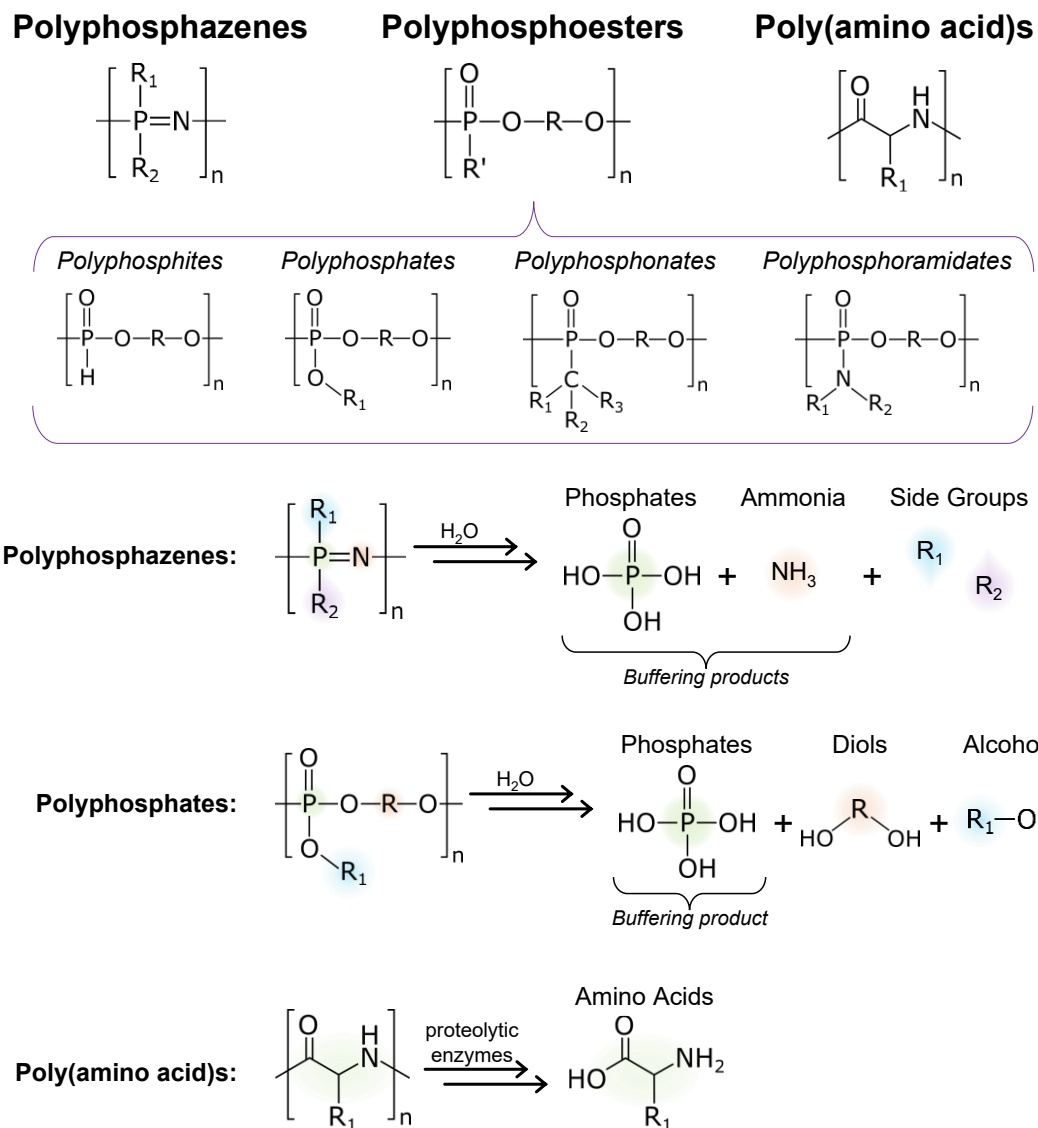


Figure 3. Prominent families of water-soluble biodegradable polymers and their simplified complete degradation products.

Studies with molecularly dissolved polymers allow isolation of the effect of chemical composition on polymer chain degradation without considering other physical factors that affect reactions in solid state, such as surface wetting, surface-to-volume ratio, or limitations of solvent and product diffusion. The autocatalytic effects are minimal on water-soluble polymers because

they are largely surrounded by an aqueous environment, and the degradation rate of water-soluble polymers is primarily governed by overall hydrolytic sensitivity of the molecule.

2.1.1. Molecular engineering aspects

Degradation rate of water-soluble polymers can primarily be controlled by molecular engineering of the polymer backbone and side groups. In the case of PPEs (**Fig. 3**), some structural modification of the backbone is possible via modulation of spacer groups (R).⁷⁰ In contrast, modulation of the hydrolytic sensitivity of PPZs is usually achieved through the side groups (R₁ and R₂). Multiple PPZ derivatives with diverse side groups such as carboxylic acid, pyrrolidone, or ethylene oxide (including PEG) units were synthesized that are both water-soluble and hydrolytically degradable.⁷¹⁻⁷⁷ Importantly, the degradation pathway leads to the release of the side group, which can be selected to be biologically benign, and ammonium phosphate.⁷⁸ Interestingly, the hydrolytic sensitivity of PPZs is strongly dependent on the nature of the side group. Thus, a commonly used approach to programming PPZ degradation rate includes synthesis of mixed substituent copolymers, in which the rate of degradation is determined by the relative ratio of hydrolytically labile and stable groups.^{79,80}

One successful example of using this approach includes modulation of the degradation rate of poly[di(carboxylatophenoxy)phosphazene] (PCPP) – an important clinical-stage macromolecule that has gained attention as a potent immunoadjuvant and vaccine delivery system.^{41, 81, 82} Introduction of more hydrolytically labile *N*-ethylpyrrolidone side groups to this polymer accelerated the release of side groups and the molecular weight degradation rate.⁷³ The same effect was achieved when highly hydrolytically sensitive residual chlorine atoms were intentionally left in a polymer structure or ethyl glycinato- side groups were introduced.^{72,82,83} Similarly, inclusion of glycine and valine spacers as side groups of hydrophilic graft PPZs had a

destabilizing effect, with up to half of the backbone degrading into phosphate groups after four weeks.⁷⁶

2.1.2. Solution conditions and intra-/intermolecular interactions

While the chemistry of a water-soluble degradable polymer may be customized for a desired degradation profile, the presence of external chemical groups, such as ionic species and macromolecules in proximity to the polymer, can significantly alter the degradation behavior. Many pharmaceutical formulations contain excipients, such as surfactants, macromolecular viscosity enhancers, and proteins. Although these materials are generally considered to be biologically inert, they nevertheless can potentially affect polymer degradation *via* intermolecular interactions. Moreover, the mechanism of polymer degradation frequently includes intramolecular reactions of neighboring groups.^{74,84} These hydrolytic pathways can be also greatly affected by excipients or sophisticated molecular engineering of the polymer itself, such as introduction of grafted PEG chains, which is commonly performed to improve the PK/PD profile of a polymer.

In solution, acid-promoted degradation with pronounced intramolecular catalysis was reported both for PPZs (**Fig. 4A and 4B**)⁷⁴ and aconitic acid-derived polymers.⁶³ However, the effect of other environmental factors, such as presence of surfactants or other pharmaceutical excipients, is frequently overlooked. Nevertheless, the influence of such factors, especially for polymers with profound effect of neighboring groups,^{74,84} can be significant. One example is the hydrolysis of polyphosphazene immunoadjuvant - PCPP, which is promoted by neighboring carboxylic acid functionalities. Hydrolytic breakdown of this polyelectrolyte is slowed in high ionic strength solutions, as these conditions effectively decrease the number of non-dissociated acidic groups that can participate in the intramolecular catalysis (**Fig. 4C**).⁷⁴ To the contrary, addition of hydrogen bonding excipients, such as non-ionic surfactants or PEGs, resulted in the

dramatic increase of the degradation rate (**Fig. 4D**) and was associated with the occurrence of intermolecular complexation in these formulations.⁷⁴ Interestingly, hydrolytic degradation of anionic and cationic PPZs was accelerated by increasing the content of methoxyethoxyethoxy- or grafted PEG chains.^{77,85} In particular, the degradation rate of mixed PCPP and poly[di(methoxyethoxyethoxy)phosphazene] (MEEP) copolymers was higher than that of their constituent homopolymers - PCPP and MEEP.⁸⁵ This accelerated hydrolysis can be potentially explained by similar interactions between ethylene oxide and carboxylic acid groups, but occurring within the same molecule.⁸⁵

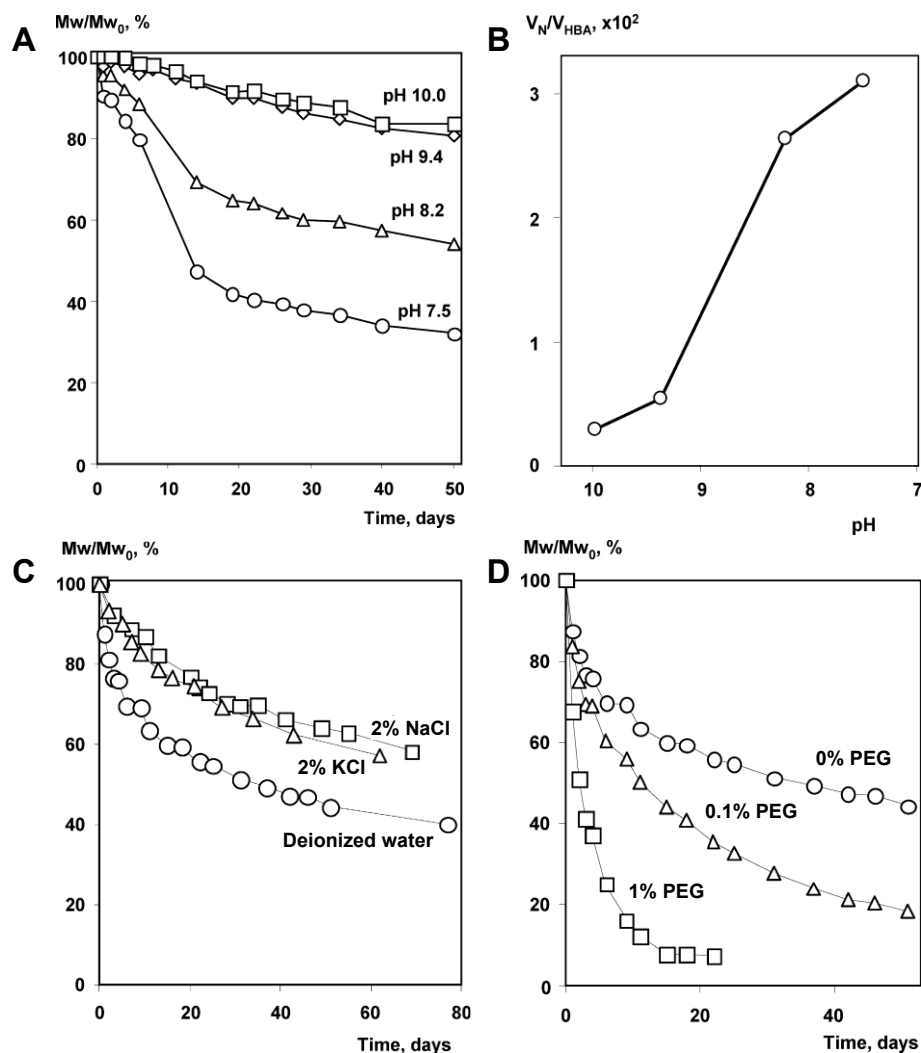


Figure 4. Environmental effects on degradation of PCPP: Effect of pH on the kinetics of PCPP molecular weight changes (A) and on the ratio of new chain formation to 4-hydroxybenzoic acid release (B); effect of the presence of ionic species (C) and PEG (D) on the kinetics of PCPP molecular weight changes. Adapted with permission from reference ⁷⁴. Copyright 2010 American Chemical Society.

The customizable side groups of polyphosphazene also allow for a unique comparison between macromolecules with the same backbone in different forms, such as in solution, ionically

cross-linked gels and nanoparticles, layer-by-layer assembled nanocoatings, and even in solid state. However, comparative solid state-solution degradation analysis is rarely conducted for PPZs with the same type of side groups. For example, important findings on the effect of the link between backbone and side groups (*e.g.*, phosphorus-nitrogen links appear to be more hydrolytically labile than phosphorus-oxygen), as well as the shielding effect of bulky side groups, were first established for hydrophobic polymers,^{78, 86-92} and still need to be validated for water-soluble polymers. Water-soluble mixed PPZ copolymers with a high content of hydrophobic fluorinated moieties and only a small fraction of ionic groups, which are capable of electrostatic self-assembly into nanocoatings or nanoparticles,⁹³⁻⁹⁹ open additional possibilities in bridging this gap.

2.2. Hydrophobic synthetic polymers – degradation in solid state

Although the degradation chemistry for hydrophobic polymers may follow similar reaction pathways as for water-soluble systems, the material erosion profiles may be dominated by other factors. Unlike water-soluble polymers, hydrophobic polymers, *i.e.*, those not soluble in water, pose a barrier to water diffusion, therefore limiting access of reactants to the reactive bonds. Common families of hydrophobic degradable polymers are shown in **Fig. 5**. One most common and well-studied family of degradable polymers includes ester linkages, whose rate of cleavage was demonstrated to depend on temperature and pH, with accelerated hydrolysis in both acidic and basic conditions and at elevated temperatures.^{100, 101} Hydrolysis of polyesters, along with that of polyanhydrides and polyorthoesters, produces acidic products that can accumulate and unpredictably autocatalyze hydrolysis when trapped in bulk 3D geometries. Furthermore, the end

groups of partially degraded groups of these families are often acidic which are believed to further catalyze the hydrolysis of surrounding labile groups.

To understand the effects of crystallinity, molecular weight, surface energy, and microenvironment on the hydrolytic behavior, each variable should be considered, as emphasized with the preceding water-soluble polymers. However, with hydrophobic polymers, the closest approximation can be made using high surface-to-volume ratios, such as Langmuir monolayers.

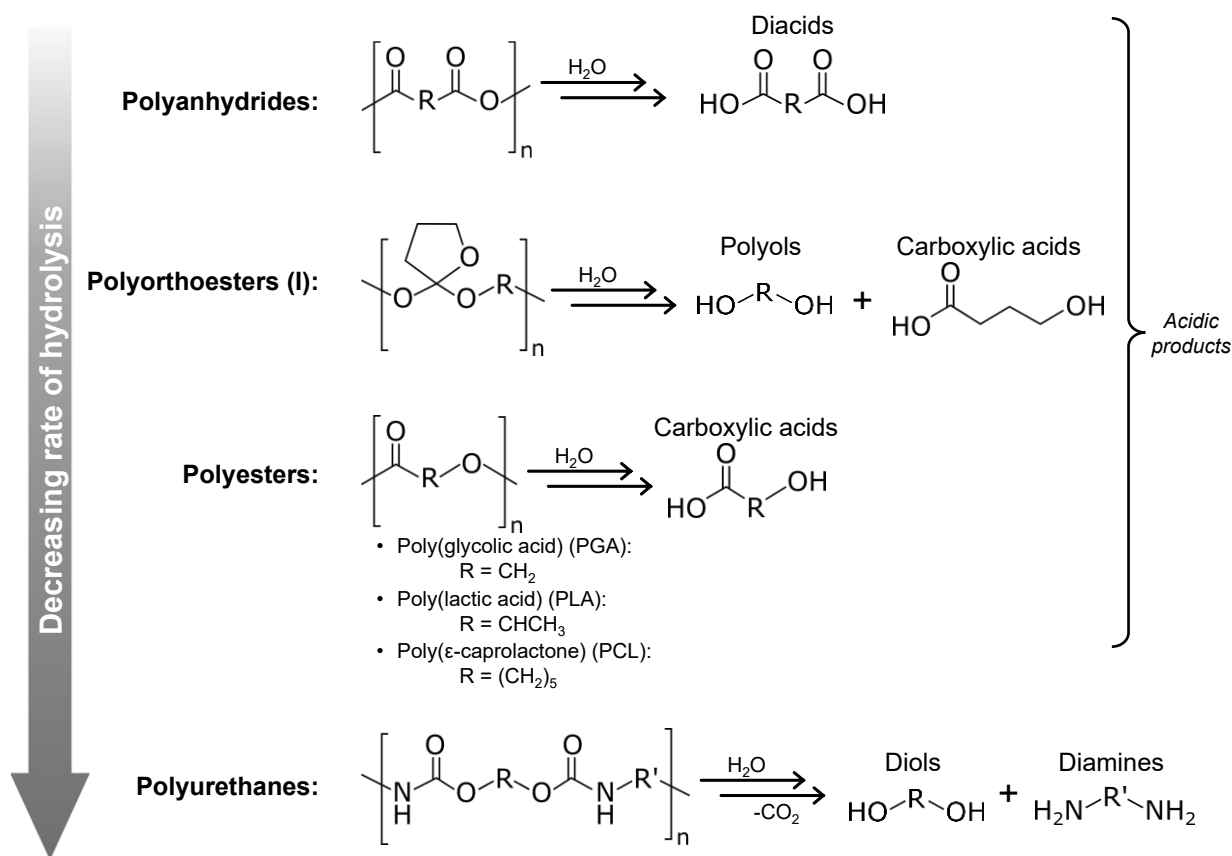


Figure 5. Prominent families of hydrophobic biodegradable polymers, listed in order of decreasing rate of hydrolysis, and their simplified degradation products.

2.2.1. Hydrolytic degradation of monolayers

By spreading a monolayer of sufficiently hydrophobic polymers atop an aqueous solution, researchers have been able to isolate the effects of molecular weight, crystallinity, and chemical modifications from the physical parameters of bulk polymer materials.¹⁰² For instance, the autocatalyzing nature of PLGA, along with other well-accepted theories, have been questioned based on the results of Langmuir monolayer degradation (LMD).^{103,104} The LMD technique offers crucial insight into the molecular reaction kinetics without the influence of water diffusivity, and allows use of enzymes, ionic species, and other water-soluble molecules in the aqueous trough to analyze the effect of solution conditions on the degradation. Using LMD studies, it was reported¹⁰³ that initial molecular weight of poly(D,L-lactic-*co*-glycolic acid) (PDLLGA) did not influence degradation rates, contrary to the commonly accepted theory that carboxyl chain ends autocatalyze hydrolysis. However, it is still important to note that the molecular weight plays a significant role in three-dimensional systems, as it can influence crystallinity, glass transition temperature, swelling, and other properties of polymers. Interestingly, authors also reported that acidic environments did not accelerate degradation of PDLLGA, although basic environments did.¹⁰³ These results challenge the common notion that polyesters autocatalyze degradation *via* local acidification by both chain ends and acidic byproducts. However, as a counterpoint, one could argue that the polar chain ends may orient away from the air interface, as they are hydrophilic in nature, so they do not represent the restricted environment in 3D materials and may not properly influence the surrounding hydrolytically labile groups. Further work into understanding this behavior could alter the approach to polyester stabilization.

2.2.2. Hydrolytic degradation in bulk geometry

Like monolayer degradation, the degradation of 3D solid-state polymer materials involves both degradation and solubilization of the polymer chains; however, in bulk materials, the

diffusion of solution into the material and the diffusion of solubilized hydrolysis products out of the material cause key differences in the degradation behavior. In bulk materials, factors such as crystallinity, swelling, and hydrophobicity largely influence the ability of species to diffuse in and out of the polymer material. These factors are intertwined with the chemical reactivity of the hydrolytically labile groups, as ranked in **Fig. 5**, which can dictate the mechanism of polymer erosion that the material will experience.

Polymer erosion is classified into surface erosion and bulk degradation based on the structural changes of a 3D degradable polymer. **Fig. 6** shows the changes in geometry and relative properties of materials undergoing surface erosion or bulk degradation. Surface erosion, which occurs when the rate of reaction exceeds the rate of reactant diffusion into the bulk, closely follows zero-order kinetics and proceeds at constant velocity.¹⁰⁵ In contrast, bulk degradation occurs when the rate of reactant diffusion exceeds the rate of reaction and proceeds at a nonuniform erosion velocity.¹⁴ These mechanisms can be evaluated by cross-sectional imaging or indirectly by monitoring the change in material properties with degradation.

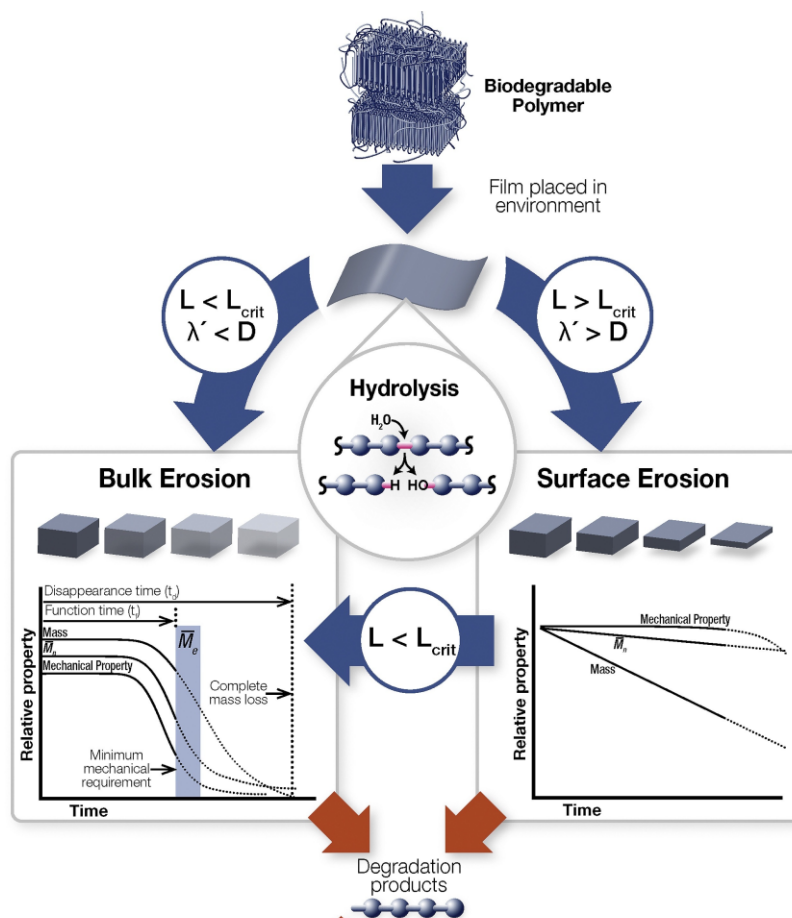


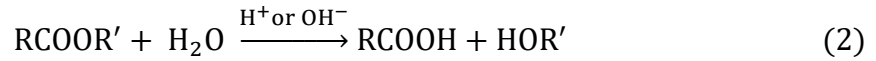
Figure 6. Schematic of hydrolytic degradation and accompanying erosion, where L is the thickness of a sample, L_{crit} is the critical thickness, λ' is the hydrolytic reaction rate constant, and D is the water diffusivity. Adapted with permission from reference ¹⁰⁶. Copyright 2017 Elsevier.

As implied in **Fig. 6**, the initial rate-limiting factors that govern the erosion mechanism of hydrolysis include the rate of water diffusion into the polymer and the rate of hydrolysis. In general, the ratio of these rates largely reflects the degradation mechanism. If water diffuses into the polymer much faster than the rate of hydrolysis, bulk degradation will dominate. Alternatively, if the rate of hydrolysis is much faster than the rate of water diffusion, surface erosion prevails. If the rates are similar, a combination of surface erosion and bulk degradation will occur. The evolution of properties and degradation behavior of surface-eroding materials is simpler to predict

than bulk-degrading materials. This predictability is preferred for drug-delivery applications;¹⁴ however, most commercial polyesters approved for biomaterials degrade heterogeneously *via* a combination of surface erosion and bulk degradation that has proven difficult to model.¹⁰⁷

As a simplistic representation, the rate of water diffusion into the polymer and the rate of hydrolysis are modeled separately below. First, the rate of diffusion of water is modeled using Fick's laws of diffusion (**Eq. 1**),¹⁰⁸ neglecting chemical reactions as a simplification for bulk degradation. Next, the rate of a generic hydrolysis reaction involving an ester group (**Eq. 2**)¹⁰⁹ is modeled using pseudo-first-order reaction kinetics (**Eq. 3**),¹¹⁰ neglecting diffusion control as in surface-eroding or water-soluble polymers. In these equations, specific attention is paid to the diffusivity and reaction rate constant, denoted as D and λ respectively, as these are factors that are affected by changes to the material.

$$\frac{\partial[\text{H}_2\text{O}]}{\partial t} = \nabla \cdot (D\nabla[\text{H}_2\text{O}]) \quad (1)$$



$$\frac{\partial[\text{RCOOR}']}{\partial t} = -\lambda[\text{RCOOR}'][\text{H}_2\text{O}] \quad (3)$$

By assuming a homogeneous polymer with a uniform degradation velocity, applying random walk theory to the diffusion rate, and applying Poisson kinetics to the reaction rate, a mechanistic model was developed¹⁰⁰ that defined an erosion number, ε , to predict the dominance of surface erosion or bulk degradation:

$$\varepsilon = \frac{\langle x \rangle^2 \lambda \pi}{4D_{\text{eff}} \left(\ln[\langle x \rangle] - \ln \left[\sqrt[3]{\overline{M}_n} / N_A (N - 1) \rho \right] \right)} \quad (4)$$

where D_{eff} is the effective diffusivity of water in the polymer, $\langle x \rangle$ is the mean distance traveled by water, $\overline{M}_n$ is the number average molecular weight, N is the degree of polymerization, and ρ is the polymer density. Essentially representing the ratio between the rates of reaction and diffusion, ε can be used to predict bulk degradation ($\varepsilon < 1$) or surface erosion ($\varepsilon > 1$).¹⁰⁰ The accuracy of ε is dependent on the values of λ and D_{eff} , which are influenced by the geometric, physical, and chemical properties of the polymer. In addition to the chemical properties reviewed for water-soluble polymers and physical properties reviewed for monolayers, the degradation mechanism can be predicted and controlled based on this model by accounting for the influence surface hydrophobicity, degree of crystallinity, and morphology and microstructure of the polymer.

Relating to D_{eff} , the rate of water diffusion into a polymer is associated with the geometry, wettability, and crystallinity of the polymer. Although useful as a prediction, **Eq. 4** has obvious limitations because of the assumption of a homogeneous matrix and uniform degradation velocity. In reality, the properties of bulk-degrading polymers are highly dynamic and evolve over time, such as the changes in morphology and microstructure, increases in crystallinity, and gradual reorientation of hydrophilic groups to the solid-liquid interface.

2.2.3. Morphology and microstructure

For $\varepsilon = 1$, **Eq. 4** can be used to predict a critical thickness L_{crit} (e.g., $L_{\text{crit}} = 2\langle x \rangle$ for slab geometry) that governs a transition between erosion mechanisms, where a thickness $L > L_{\text{crit}}$ implies surface erosion and $L < L_{\text{crit}}$ implies bulk degradation.¹⁰⁰ However, this prediction may be limited when considering the assumptions of a homogeneous polymer with constant

degradation velocity made in **Eq. 4**. For example, bulk-degrading systems that produce autocatalytic products are not well-characterized by this approach because of their localized accelerated hydrolysis rates, leading to microstructural changes and differential degradation rates. Additionally, as the surface morphology and chemistry changes, physical properties like wettability vary.^{111,112}

Importantly, following the initial stage of water diffusion in bulk-degrading systems, catalytic byproducts can accumulate within the bulk as the hydrolysis progresses and cause accelerated autocatalytic degradation in thicker geometries. In early work,¹¹³ a counterintuitive result was observed for PLGA: 2 mm thick plates were shown to degrade faster than 0.3 mm films, and 0.5-1.0 mm diameter beads were shown to degrade faster than 0.125-0.250 mm microspheres. At the time, the difference in degradation rate was thought to by no means be caused by pH changes of the aqueous media;¹¹³ however, later studies have theorized that degradation rate is increased by formation of acidic microenvironments within larger-sized materials.^{114,115,116} Although the thicker material was not expected to degrade faster than the thinner material, this observation is thought to be a result of the slower diffusion of byproducts out of thicker materials *versus* thinner materials. In contrast to the LMD results, the spatial restriction of acidic byproducts and chain ends in 3D materials may autocatalyze the hydrolysis of surrounding reactive groups, highlighting the importance of strategic buffering or diverting of acidic products for controlled degradation. Acid-catalyzed hydrolysis has been also established for hydrophobic polyphosphazenes⁷⁸ and was confirmed for multiple derivatives,^{73,76,80,117,118} highlighting their potential to develop pH-triggered delivery systems capable of responding to localized bacteria acidification⁹⁷ or other biorelevant pH gradients,¹¹⁹ as well as supporting intracellular delivery functionality.¹²⁰

The validity of L_{crit} is further complicated when considering that surface properties, such as wettability which influences the initial stage of water diffusion, can become dynamic with increased thickness. Large geometries can develop heterogeneous chemical microenvironments that alter physical properties, instilling a time dependence into diffusivity D and the reaction rate constant λ , complicating the application of **Eq. 4**. For example, surface segregation and restructuring in thick films of poly(D,L-lactic acid) (PDLLA) and PLGA has been detected by attenuated total reflectance – Fourier transform infrared (ATR-FTIR) spectroscopy and water contact angle (WCA) measurements.¹¹² An increase in intensity of surface methyl groups was detected for thicker PDLLA films using ATR-FTIR (**Fig. 7A**), indicating a reorientation of hydrophobic groups to the surface. The water droplet relaxation, indicated by the gradual decrease in WCA (**Fig. 7B**), was prominent for 15 μm PDLLA films, but not 1 μm PDLLA films. Increased segmental motion in thick films was hypothesized to enable reorientation of hydrophobic methyl groups to the bulk upon exposure to water.¹¹²

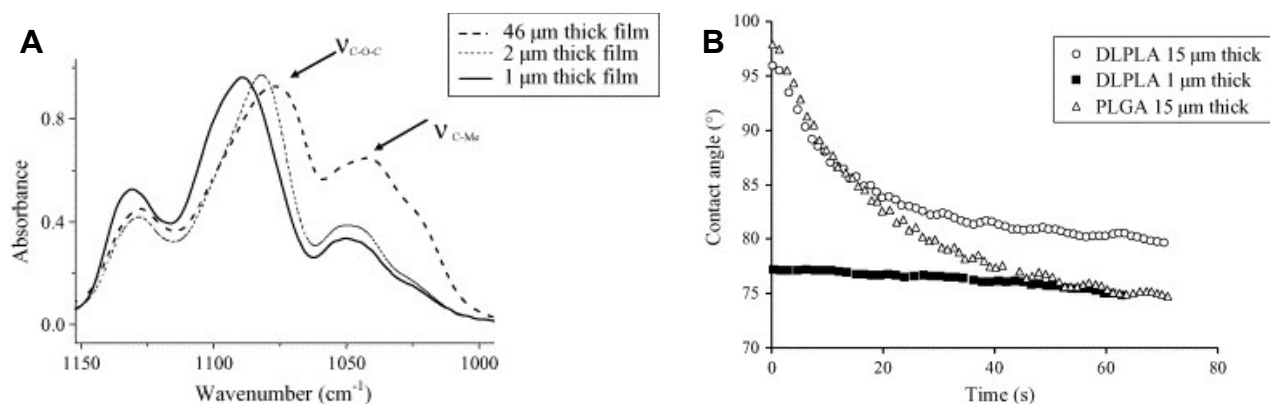


Figure 7. Evolution of surface characteristics of PLA and PLGA films: (A) ATR-FTIR spectra of PDLLA (denoted DLPLA in the Figure) films of varied thicknesses. (B) Temporal change in water contact angle on PDLLA films of varied thickness. Reproduced with permission from reference¹¹². Copyright 2006 Elsevier.

2.2.4. Surface hydrophobicity

Polymer materials with hydrophobic surfaces initially experience slower degradation than polymers with hydrophilic surfaces due to water exclusion. Importantly, varying either surface energy (through chemical modification) or surface roughness can display different effects on the degradation profile. As shown in **Fig. 8**, chemical modifications to PPZ side groups allowed tunable degradation rates while maintaining a similar degradation onset. The hydrophilic solid-state PPZs were shown to degrade faster than their more hydrophobic counterparts.⁸⁶ In addition to changes to the surface energy made by chemical substitution, surface roughness can also affect the degradation behavior; however, it typically affects just the onset of degradation rather than the degradation rate. For instance, increasing the hydrophobicity of a surface to superhydrophobic *via* incorporation of nanoparticles delayed the onset of degradation as compared to hydrophobic and hydrophilic surfaces, but the rate of degradation for each system appeared similar.¹²¹ Additionally, as degradation progresses, the surface can become more hydrophilic due to increasing polar chain ends.^{111,122} Together with surface restructuring¹¹² and the hydrophobicity of crystalline regions, the value of the diffusivity based on hydrophobicity may also be considered dynamic.

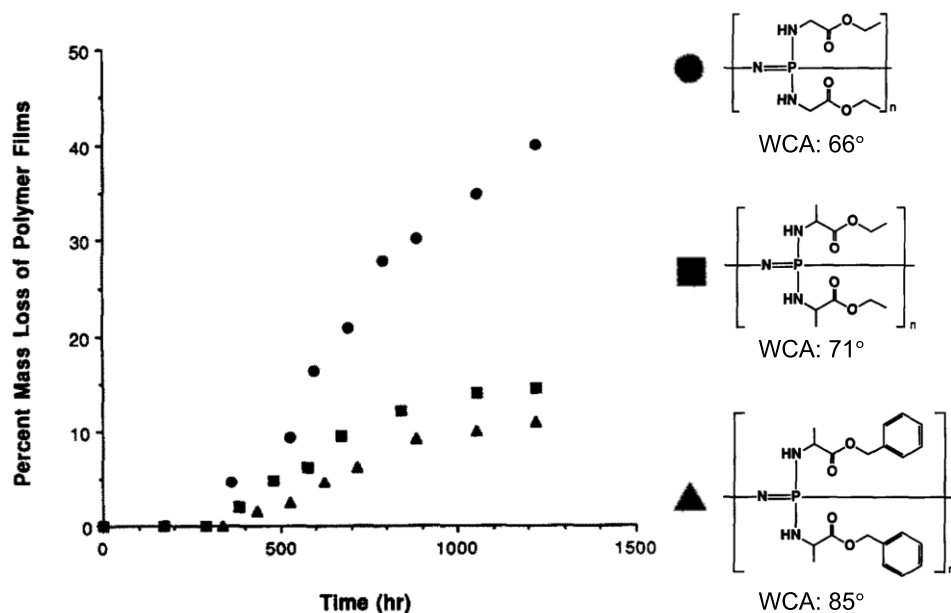


Figure 8. Mass loss evolution of PPZs (in legend on right) in borate buffer. Adapted with permission from reference ⁸⁶. Copyright 1994 Elsevier.

2.2.5. Microtacticity and crystallinity

In semi-crystalline polymers, crystalline regions can be considered barriers to water diffusion, reducing swelling and the rate of degradation compared to amorphous polymers. The disordered amorphous domains in semi-crystalline polymers degrade faster than the crystalline regions.^{123,124} To explain this behavior, the increased density of hydrophilic chain ends between crystalline regions was hypothesized to improve water diffusion (**Fig. 9A**).¹²⁴ However, as the amorphous regions become randomly cleaved, it is thought that the newly cleaved chains can form new crystalline regions, as demonstrated in **Fig. 9B**. These heterogeneities caused by crystalline regions impart a dynamic and spatially-dependent diffusivity, complicating the design of degradable systems. This is an occurrence of the synergy between competing diffusion and hydrolysis mechanisms.

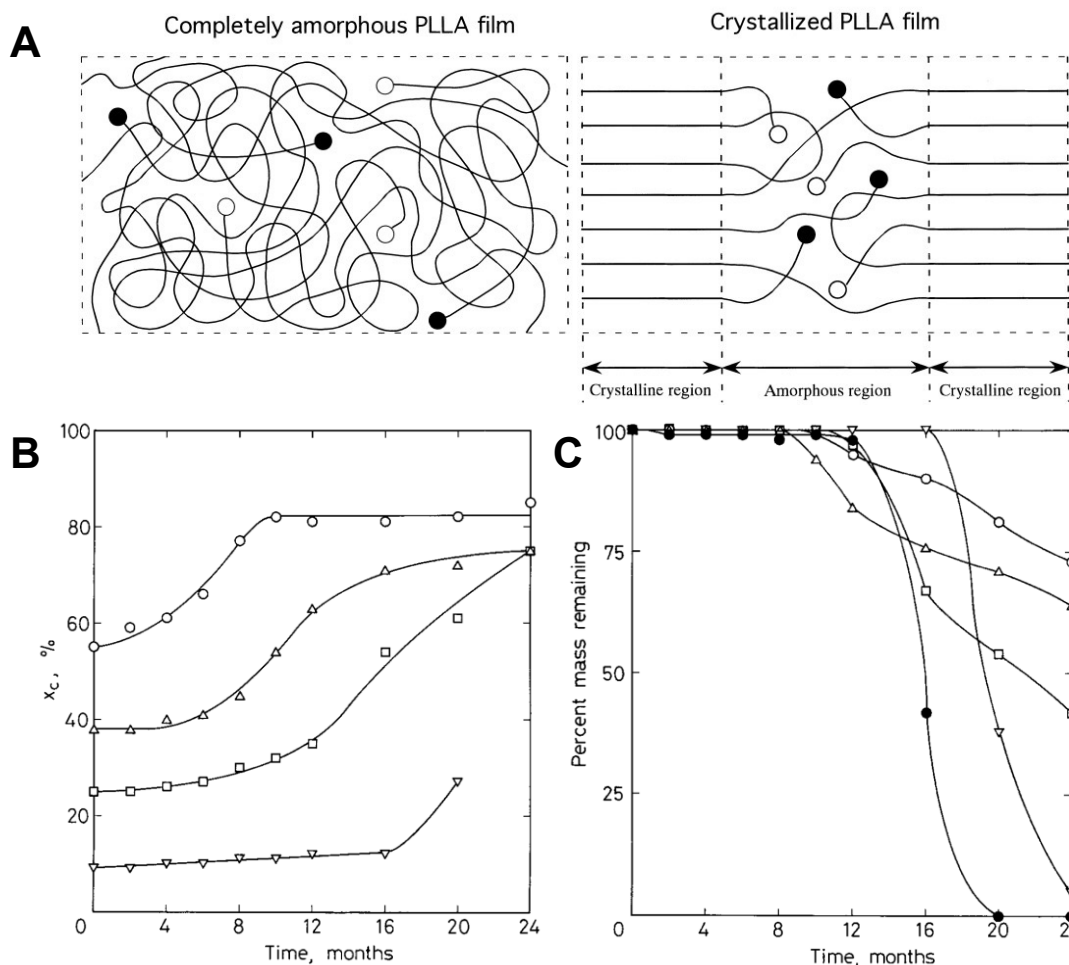


Figure 9. (A) Schematic demonstrating the increased density of chain ends between crystalline regions compared to fully amorphous PLLA. Reproduced with permission from reference ¹²⁴. Copyright 2000 John Wiley and Sons. Percent crystallinity (B) and mass remaining (C) during the degradation of amorphous (●) and semi-crystalline (initial x_c of ▽ = 9%; □ = 25%; △ = 38%; ○ = 55%) PLA in phosphate buffered solution. Reproduced with permission from reference ¹²⁵. Copyright 1997 John Wiley and Sons.

Degradation of semi-crystalline polymers proceeds by a less predictable mechanism than fully amorphous polymers. In amorphous polymers, the solubilization of the amorphous bulk occurs slowly assuming non-preferential chain scission. In contrast, degradation in semi-

crystalline polymers is limited to the amorphous regions between crystallites, causing more localized scission and rapid solubilization of the amorphous regions, followed by slow degradation of crystallites. Additionally, the initial morphology of crystalline regions affects the degradation speed and morphological progression.^{126,127} Importantly, both the preferential degradation of amorphous regions and formation of new crystallites from plasticized cleaved chains lead to a rapid loss of mechanical properties, which may limit the structural applications of semi-crystalline degradable polymers. These proposed mechanisms were supported for poly(butylene succinate), PLGA, and PLA systems.^{124, 126-128} For example, the higher weight loss of semi-crystalline PLA than amorphous is seen in the early stages of degradation, and the weight of semi-crystalline PLA plateaus in later stages as amorphous regions are crystallized (**Fig. 9C**).

Initial crystallinity of semi-crystalline polymers can be tuned *via* polymer configuration, architecture, crosslinking, blending, or processing. Crystallinity is often quantified by wide- or small-angle X-ray scattering (WAXS or SAXS, respectively), or differential scanning calorimetry (DSC); however, it is important to simultaneously monitor the mechanical properties as the crystalline fraction changes and degradation progresses. In summary, increasing crystallinity can be used to reduce the effective diffusivity D_{eff} , regulate swelling, and reduce the overall degradation rate of a semi-crystalline polymer, but its general influence on degradation behavior on a simple polymer system is highly debated.¹²⁹

3. Methods for evaluating degradation behavior

The following sections highlight current methods used to characterize degradation behavior *in vitro* and monitor degradation, biodistribution, and pharmacokinetics *in vivo*. Within these

discussions, we note controversial issues and unmet needs regarding these methods and provide potential solutions.

3.1. *In vitro*

Degradation behavior is evaluated by monitoring relevant material properties at various times during *in vitro* studies. Typically, the weight lost to solution of solid-state polymers is measured gravimetrically by drying the polymer and weighing after exposure to simulated conditions; molecular weight by size exclusion or gel permeation chromatography; morphology by scanning electron or atomic force microscopy (SEM and AFM, respectively); wettability by contact angle or swelling; crystallinity, glass, and melting temperature (T_c , T_g , and T_m , respectively) and degree of crystallinity by DSC; and degradation byproducts by mass spectrometry, nuclear magnetic resonance (NMR), or high-performance liquid chromatography (HPLC).¹³⁰⁻¹³² Changes in chemical composition during degradation can also be monitored *via* Fourier transform infrared¹³³ and Raman spectroscopy.¹³⁴ *In vitro* studies of cytotoxicity of the polymer and degradation products, along with hemocompatibility and intracellular fate, enable time- and cost-effective optimization of the polymer before *in vivo* studies.¹³²

Many of these techniques are well-established, but inconsistencies with the weight loss and morphology evaluations are subjected to critique. Importantly, weight loss does not directly indicate the degree of degradation within the film, instead indicating the solubilization and/or erosion of material. Additionally, morphological evaluations by SEM and AFM are limited to surfaces, although the evolution of bulk degradation is more consequential in many polymer systems. Furthermore, conventional SEM places samples under vacuum which can distort morphologies of soft materials.¹³⁵ Rather than surface characterization, confocal laser scanning

microscopy may provide more representative dimensional characterization, although not at nanoscale resolution.¹³⁶

Current conventional characterization methods also lack real-time measurement techniques, which would be preferable to removing samples from solution and drying repeatedly. *In situ* techniques, like sum-frequency generation (SFG)¹³⁷ and *in situ* AFM¹²³, have been used to characterize chemical and morphological surface changes but are not as accessible as other techniques. Recently, selective electrochemical sensors were developed to trace polymer degradation in real time by measuring pH and degradation product concentrations, but the samples were still removed from solution, washed, and dried for weight-loss measurements.¹³⁸ Sensors have also been used to track biodegradation of polymers by enzymes and cell supernatants.¹³⁹ These advancements in real-time measurements may improve the accuracy of sequential *in vitro* screenings by reducing the perturbation of the samples from rinsing and drying steps.

Additionally, these evaluation methods rarely represent conditions *in vivo* and do not sustain a homeostatic environment. Because the pH of the surrounding solution may change as byproducts form, static conditions have been shown to significantly accelerate PLA-PGA degradation compared to flow conditions.¹⁴⁰ Furthermore, the buildup of localized concentration gradients in static conditions may challenge the sink conditions desirable for realistic characterization of drug dissolution.¹⁴¹ In an attempt to address these issue, some elect to replace the solution at specified time periods or after the pH drops, but ideally, the evaluation should implement a closed- or open-loop flow-through chamber to simulate the conditions representative of the intended application.¹⁴⁰ Recently, a flow-through chamber was designed for easier and more accurate evaluation of biomaterial degradation.¹⁴² The accessible design and preliminary results promote its potential as a uniting *in vitro* evaluation method.

The aforementioned evaluation methods for three-dimensional materials are commonly reported, but current research lacks insight on the differences between degradation behavior of monolayers and 3D systems. To approach this knowledge gap, we suggest a hierarchical method for evaluating degradation behavior. Characterization of a monolayer *via* SFG or LMD eliminates the influence of diffusion of water within a 3D material. The degradation behavior of the monolayer and 3D material can be compared to identify the influence of diffusion, leading to a multi-dimensional understanding of degradation. Additionally, the monolayer degradation method can be used to isolate the influence of hydrolytic, oxidative, and enzymatic reaction rates and strategically evaluate the effects of environmental and chemical properties.

3.2. *In vivo*

Although *in vitro* characterization gives useful insight on the mechanism of cell-mediated degradation, the efficacy of biomaterials must be demonstrated *in vivo* by monitoring the biodistribution of polymers and their pharmacokinetic-pharmacodynamic (PK/PD) correlations.¹⁴³ *In vitro* degradation is often reported in the literature yet reports of the long-term fates and clearance profiles of degradable polymers *in vivo* are less common, especially for new polymer formulations.

In both degradable and non-degradable water-soluble systems, the polymer chemistry and architecture have been shown to influence the *in vivo* behavior of the polymer. The circulation half-life and biodistribution are largely influenced by the ability of a polymer to reptate through pores; therefore, the properties affecting the polymer size (*e.g.*, molecular weight, structure [linear, cyclic, branched, *etc.*], conformation, flexibility) are important to controlling the retention time *in vivo*.¹⁴⁴⁻¹⁴⁷ These factors controlling *in vivo* behavior have been previously reviewed in depth for water-soluble³⁷ and solid-state polymers.

Advances in non-invasive, real-time methods for monitoring pharmacokinetics and biodistribution have enabled improvements in measurement precision and efficiency. Now, radiolabeling is commonly used to label drugs or molecular probes, and various techniques are employed for continuous monitoring of the labeled species *in vivo*.^{148,149} Positron-emission tomography¹⁵⁰ and single photon emission computed tomography^{151,152} enable radionuclide imaging with high sensitivity. Alternatively, optical imaging techniques, such as fluorescence imaging^{153,154} and Čerenkov luminescence imaging,^{155,156} may also be used to monitor labeled compounds. These techniques can be combined with planar imaging *via* magnetic resonance imaging or computed tomography to provide morphological information.^{157,158}

4. Recent advances toward control of degradation behavior

The section highlights recent physical and chemical approaches that have been taken to manipulate degradation behavior. Advances in physical approaches are primarily applied to commercially available poly(α -hydroxy ester)s, such as PLA, PLGA, and PCL, and involve processing methods that tune material properties and architecture to achieve control over degradation and release profiles. Alternatively, the opportunity for precise control over degradation for both water-soluble and hydrophobic polymers can be achieved by novel “designer polymer” chemical approaches. In the following sections, these emerging solutions to common challenges in the field are analyzed and compared: designer polymers, polymer blends and composites, and architectural modifications.

4.1. Designer polymers

Chemical modifications, such as synthesis of new polymer families, functionalization of side groups, control of tacticity, or formation of stable polymer networks, can be used to precisely control degradation behavior. Importantly, this approach is most favored to modulate the

degradation behavior of water-soluble polymers, while degradation of hydrophobic polymers will be addressed in the following sections. By designing the chemical reactivity, hydrophobicity, ionizability, and inter-/intramolecular interactions of water-soluble polymers, tunable degradation profiles can be achieved and applied in biological situations that require high precision.

Water-soluble, dispersible, and two-dimensional stimuli-responsive systems, especially pH-, redox-, and enzyme-responsive systems, are at the forefront of biomedical applications.¹⁵⁹ In recent years, significant progress toward stimuli-controlled degradation has enabled new approaches to smart-release polymers. Stimuli-controlled degradable polymers commonly invoke stimuli-sensitive linkages in the polymer backbone or side chains that enable polymer stability until triggered, leading to fragmentation of the polymer chain and eventual complete degradation. Although limited to hydrophobic polyesters, a recent review details advances in pH-, reductive-, reactive oxygen species (ROS)-, and enzyme-labile linkages that enable selective, stimuli-controlled degradation.¹⁶⁰ These advances have been applied to other polymer families, including responsive PPZs with self-immolative moieties¹⁶¹ and stimuli-responsive phosphorous-based polymers.¹¹⁹ Many recent works focus on enhancing the stimulus sensitivity, creating multi-stimuli-responsive systems, or combatting unintended degradation with gated linkages.¹⁶²⁻¹⁶⁵

In addition to previously mentioned chemical modifications for modulating degradation behavior, self-immolative polymers (SIPs) represent an extreme case of precise control over degradation behavior. Although random scission is the typical hydrolysis mechanism for common polyesters, controlled scission, *e.g.*, scission only at end chains, would be preferable for applications requiring more precise degradation modelling, as represented in **Fig. 10**. Since end scission has a near-linear effect on the average molecular weight, no sharp initial reduction in

molecular weight is predicted for this mechanism. The applicability of these “chain-unzipping” SIPs has been limited because of harmful byproducts, high dispersity, and low degree of polymerization.¹⁶⁶ For example, a widely used type of SIP, poly(benzyl carbamate)s, generates highly reactive intermediate species during degradation which can interact with proteins and induce toxicity.¹⁶⁶ However, an SIP was recently reported to generated degradation products that were as well-tolerated as PLGA in an MTT assay, but degradation was triggered by light which limits its practical applications.¹⁶⁷ Designs of SIPs have allowed for unzipping by enzymes¹⁶⁸ and ROS;¹⁶⁹ however, there are few reports of these stimuli-responses. Further work on the toxicity and host response of other SIPs is needed, along with alternative methods of initiation. However, the precision of engineered SIPs make them ideal candidates for application in self-destructing electronics such as those desired for hardware security systems and temporary medical implants,¹⁷⁰ and other biomedical applications.

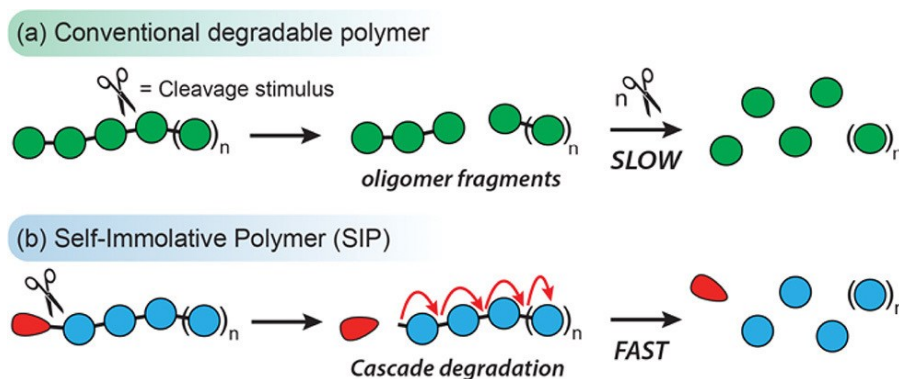


Figure 10. Cleavage mechanisms of conventional degradable polymers (a) *versus* self-immolative polymers (b). Reproduced from reference ¹⁷¹ (CC BY-NC 3.0) with permission from the Royal Society of Chemistry.

Although some control over degradation can be tuned by extending the length of the polymer backbone, the degradation profile of a monodisperse SIP system should be compared with a blend

of molecular weights to confirm if the bulk degradation profile can be tuned, although not relevant if rapid degradation after a trigger is desired. Also, continuous development of SIPs with different methods of stimulating endcap cleavage would contribute to the biomedical field. Finally, morphological changes of SIP materials are largely unreported, so the extent of their applicability is limited.

4.2. Polymer blends and composites

Local acidification from polyester byproducts, combined with cracks or pores formed during bulk or surface erosion, can lead to unpredictable and uncontrollable degradation, inflammation *in vivo*, and accelerated device failure. Furthermore, bioactives loaded into the polymer matrix may be sensitive to pH changes. To regulate the acidity, polymer blends and composites have been designed that either facilitate the removal of byproducts or incorporate buffering agents. These approaches are generally preferred for applications that have structural requirements.

Composites of magnesium compounds with clinically used poly(α -hydroxy ester)s PLA, PLGA, and PCL¹⁷²⁻¹⁷⁴ have demonstrated a buffering effect on the acidic byproducts, therefore regulating degradation rates while improving mechanical properties. Inclusion of magnesium hydroxide particles in PLGA was shown to significantly reduce the effect of acidic PLGA byproducts on inflammation.^{173, 175-178} Composites incorporating hydroxyapatite have also been of interest in biomedical applications for similar reasons.¹⁷⁹ Additionally, recent works have investigated the effect of the shape of magnesium oxide (MgO) filler on the long term degradation behavior,^{172, 180} noting that the crystalline regions around MgO whiskers are more difficult to degrade, possibly due to enhanced interface bonding.^{172, 181, 182} The importance of interfacial effects has been further highlighted in recent research, as the poor interfacial interactions between

the hydrophilic magnesium compounds and hydrophobic PLGA affect the dispersion of filler and crystalline formation, and therefore impacting degradation, swelling, and mechanical behaviors.¹⁸³ Surface modification of magnesium compounds with dispersants cetyltrimethylammonium bromide and polyethylenimine improved filler dispersion and extrusion processes.¹⁸³ However, biomedical applications that value these properties, such as tissue engineering scaffolds, also prefer porous networks for cell proliferation.

Interconnected porous networks had dual functions when common polyesters were implemented; they facilitate transfer of acidic byproducts to prevent acidic microenvironments and have architectural properties desired for tissue engineering applications. These networks can be attained by selective degradation of a continuous phase in a polymer blend. Recently, this behavior was demonstrated with PPZ-PLGA blends.¹⁸⁴ PPZs with differing side groups (with or without hydrogen bonding capability) were blended with PLGA to demonstrate the effect of side groups on hydrolytic degradation in a phase-separated system. As shown in **Fig. 11**, the amorphous PLGA preferentially degraded out of the blends to reveal nearly inverse morphologies depending on the PPZ side chain. Furthermore, the resulting structures supported cell attachment and growth, and the PPZs buffered the pH of the system, likely due to the ammonium phosphates generated from hydrolysis of PPZs.¹⁸⁴

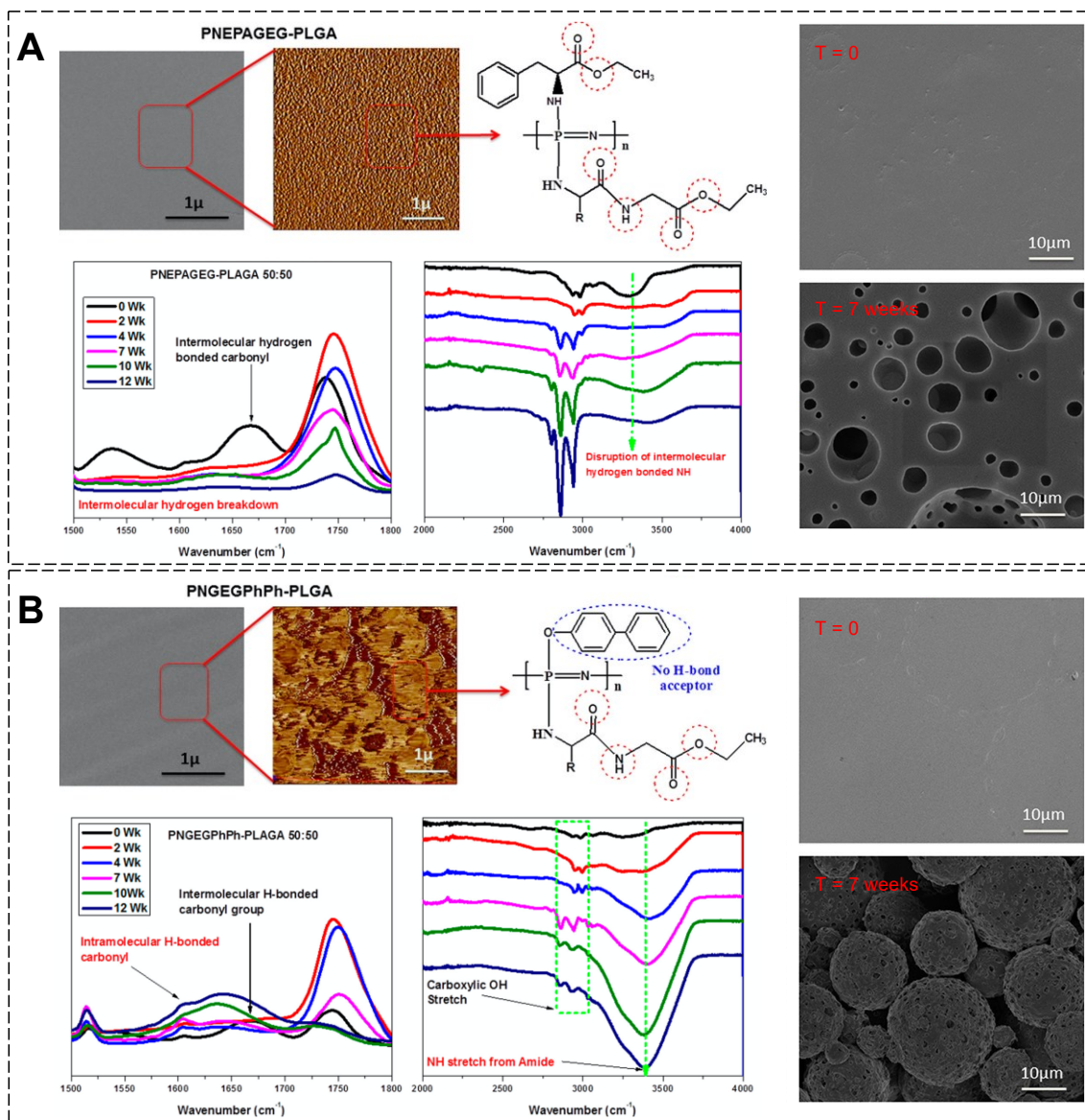


Figure 11. Morphological changes and FTIR spectra of hydrogen-bonding (a) and non-hydrogen-bonding (b) PPZ-PLGA films after incubating in phosphate-buffered saline. Adapted with permission from reference ¹⁸⁴. Copyright 2020 American Chemical Society.

For a more precise control over physical factors important to degradation behavior, such as crystallinity and swelling, mixed polymer systems can be crosslinked to form semi-interpenetrating networks (semi-IPNs). Crosslinking can be used to reduce crystallinity, regulate

swelling, and occupy hydrolysable bonds to reduce hydrolysis rates, depending on the degree of crosslinking. Semi-IPNs of crosslinked poly(ϵ -caprolactone) diacrylate and PLLA were shown to have tunable, uniquely accelerated degradation while creating structures capable of conformal fit within a defect.^{6, 185-187} The accelerated degradation was attributed to reduced crystallinity of crosslinked PCL and phase separation of PLLA domains, possibly leading to enhanced solution diffusion. This tunable degradation behavior attributed to enhanced solution diffusion was also demonstrated for formulations of PLGA and water-miscible solvent N-methyl-2-pyrrolidone for controlled delivery of various antiretroviral drugs.¹⁸⁸

4.3. Architectural modifications

Architectural modifications can be strategically used to seemingly circumvent the detailed material design needed to control bulk degradation, allowing for efficient application of common polyesters with suitable rates of degradation needed for a specific application. Although these processes are considered scalable, these modifications are still subjected to the effects of material size on accelerated autocatalytic degradation. Additionally, processes using heat to achieve structures, such as thermal fiber drawing, melt spinning, and fused deposition modeling, can cause preliminary thermal degradation and damage heat-sensitive active molecules if loaded into the polymer matrix. However, based on recent work and concerns about solvent-based processing, thermal drawing is recognized as a promising route to achieve controllable degradation and release profiles for fiber-relevant applications like sutures, surgical mesh, and wound dressing.^{116, 189}

Recently, customizable release profiles were achieved *via* degradation of thermally drawn microfibers.¹¹⁶ The customizable preform-to-fiber cross-sectional geometry allowed for simple loading and functionalization of fibers. PLGA films with varying L:G ratios covered channels in

a poly(methyl methacrylate) (PMMA) fiber to controllably release loaded materials at staggered times. In **Fig. 12**, the engineered preform-to-fiber geometry showed a high control over the release profiles. Furthermore, the alignment of PLGA chains during drawing increased the mechanical strength of the fiber. The shrinking associated with chain alignment was mitigated by adding a PCL core. Based on these results and the scalability of the technique, thermal drawing has great potential to design degradation profiles with burst and gradual release patterns.

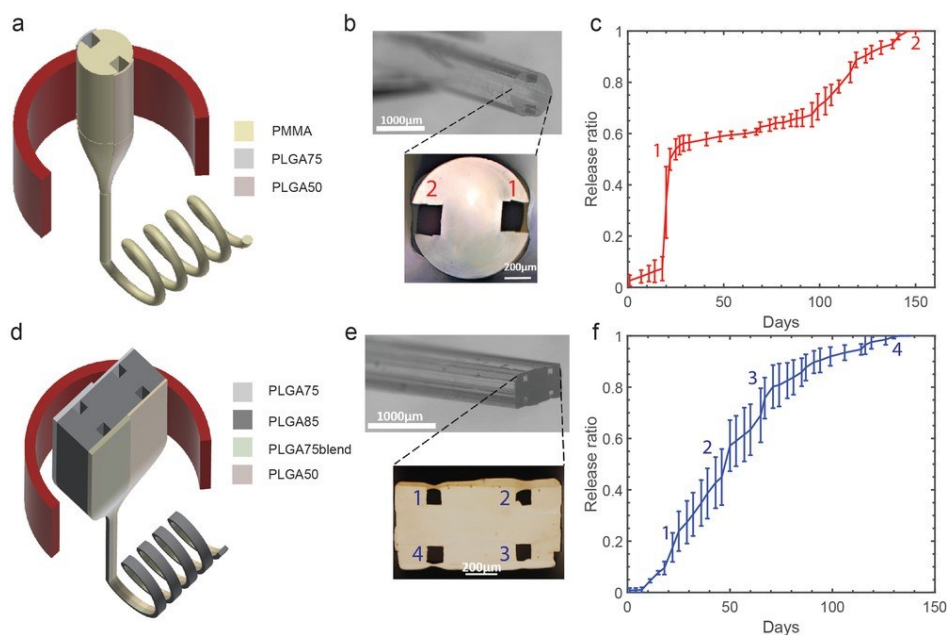


Figure 12. Preform-to-fiber designs (a,b,d,e) and release profiles (c,f) of PLGA-based thermally drawn nanofibers for drug delivery. Reproduced with permission from reference ¹¹⁶. Copyright 2020 John Wiley and Sons.

5. Conclusions and perspectives

Synthetic biodegradable polymers are increasingly investigated for use in tissue regeneration and drug delivery.³⁰⁻³⁵ The rational design of degradable polymers would benefit these needs, along with other applications in life sciences. In pursuit of the rational design of degradable polymers, this critical Review highlighted the ways degradation behavior can be influenced by

increasingly complex sets of their molecular properties, as well as physical state of the polymer. Specifically, the chemical composition, intramolecular autocatalytic effects, and environmental conditions are most important to modulating the rate of solution-state polymer degradation; however, in 3D polymer materials, geometrical effects, crystallinity, and hydrophilicity have large roles in regulating the diffusion of water into the bulk.

To understand and prove the process of surface erosion *versus* bulk erosion, a combination of surface-sensitive and bulk characterization techniques should be used concurrently. For example, chemical changes made during surface degradation can be monitored *via* ATR-FTIR or SFG, while bulk degradation may be observed chemically with transmission FTIR and physically with SEM or AFM. Furthermore, time-resolved *in situ* measurements of degradation, *e.g.*, using *in situ* AFM and SFG, would further the understanding of degradation kinetics and allow a correlation of degradation products with morphological changes in bulk materials. Expanding the use of surface-sensitive and *in situ* techniques may provide valuable insight into the dynamic and autocatalytic effects of hydrolysis in 3D systems.

Also critically lacking in this field are studies that separate chemical and physical parameters for the same system. For example, studies of water-soluble polymers can be compared to the same polymer but cross-linked, formulated into interpolymer complexes, or simply made insoluble *in situ* under physiological conditions so that their chemical degradation mechanisms can be established in solution. Moving from water-soluble polymers, degradation mechanisms of thin coatings, films, and nano- and microparticulate systems where interfacial effects can dominate, which are crucial to both hydrolytic and enzymatic degradation, should also be further investigated. These further studies to bridge this gap may enlighten unanswered questions or

contentious hypotheses about fundamental relationships between physico-chemical properties and degradation. Ideally, as new polymer compositions are developed, a standardized set of results would contribute to a cohesive understanding of new formulations.

By implementing the previous suggestions for cohesive and comparable results, the future of biodegradable polymers may combine with machine-learning opportunities. Computer-aided design of designer polymer formulations and engineered architectures of biodegradable materials with tailored physicochemical properties can contribute significantly to the advancement of the field.¹⁹⁰⁻¹⁹² This suggestion has been proposed in reviews from past decades,^{193, 194} but with the advent of new processing techniques that allow precise architectural design for biodegradable materials, optimized design simulations could accelerate progress and innovation.

Finally, by accelerating the progress in the field of engineered degradable polymers through standardized degradation studies and computer-aided design, we envision many advances in the near future including: ultraprecise degradation profiles *via* SIPs, with a focus on creating SIPs that are triggered by bio-relevant stimuli and degrade into biocompatible products; multifunctional degradable polymers that release active molecules (*e.g.*, therapeutic drugs, antibacterial agents, enzymes, etc.) upon degradation of the polymer backbone; degradable polymer networks, such as IPNs or semi-IPNS, that maintain structural integrity for the intended timeline of implantation; and an increased prevalence of efficient eco-friendly plastic alternatives to approach a circular economy, confronting the biological impacts of global waste and pollution.

6. List of acronyms and variables

AFM - atomic force microscopy

ATR-FTIR - attenuated total reflectance - Fourier transform infrared

D - water diffusivity

D_{eff} - effective diffusivity of water

DSC - differential scanning calorimetry

HPLC - high-performance liquid chromatography

IPNs - interpenetrating networks

L - bulk thickness

L_{crit} - critical thickness

LMD - Langmuir monolayer degradation

$\overline{M}_n$ - number average molecular weight

MEEP - poly[di(methoxyethoxyethoxy)phosphazene]

MgO - magnesium oxide

N - degree of polymerization

NMR - nuclear magnetic resonance

PBS - phosphate-buffered saline

PCL - poly(ϵ -caprolactone)

PCPP - poly[di(carboxylatophenoxy)phosphazene]

PDLLA - poly(D,L-lactic acid)

PDLLGA - poly(D,L-lactic-*co*-glycolic acid)

PEG - poly(ethylene glycol)

PGA - poly(glycolic acid)

PK/PD - pharmacokinetic and pharmacodynamic

PLA - poly(lactic acid)

PLGA - poly(lactic-*co*-glycolic acid)

PMMA - poly(methyl methacrylate)

PPEs - polyphosphoesters

PPZs - polyphosphazenes

ROS - reactive oxygen species

SAXS - small-angle X-ray scattering

SEM - scanning electron microscopy

SFG - sum-frequency generation

SIPs - self-immolative polymers

T_c - crystallinity temperature

T_g - glass transition temperature

T_m - melting temperature

WAXS - wide-angle X-ray scattering

WCA - water contact angle

$\langle x \rangle$ - mean distance travelled by water

ε - erosion number

λ' - hydrolytic reaction rate constant

ρ - polymer density

Author Information

Corresponding Authors

Svetlana A. Sukhishvili – Department of Materials Science & Engineering, Texas A&M University, College Station, Texas 77843, United States; orcid.org/0000-0002-2328-4494; Email: svetlana@tamu.edu

Alexander K. Andrianov – Institute for Bioscience and Biotechnology Research, University of Maryland, Rockville, Maryland 20853, United States; orcid.org/0000-0001-6186-6156; Email: aandrianov@umd.edu

Authors

Jordan Brito – Department of Materials Science & Engineering, Texas A&M University, College Station, Texas 77843, United States; orcid.org/0000-0002-0401-9724

Notes

The authors declare no competing financial interest.

Acknowledgments

This work was supported in part by the National Science Foundation under Award DMR-1808483 (S.S.) and DMR-1808531 (A.A.). J.B. acknowledges financial support from the Texas A&M University Graduate Diversity Excellence Fellowship and National Science Foundation Graduate Research Fellowship Program.

7. References

- (1) Fadare, O. O.; Okoffo, E. D. Covid-19 Face Masks: A Potential Source of Microplastic Fibers in the Environment. *Sci. Total Environ.* **2020**, *737*, 140279. DOI: 10.1016/j.scitotenv.2020.140279.
- (2) Aragaw, T. A. Surgical Face Masks as a Potential Source for Microplastic Pollution in the Covid-19 Scenario. *Mar. Pollut. Bull.* **2020**, *159*, 111517. DOI: 10.1016/j.marpolbul.2020.111517.
- (3) Jędruchiewicz, K.; Ok, Y. S.; Oleszczuk, P. Covid-19 Discarded Disposable Gloves as a Source and a Vector of Pollutants in the Environment. *J. Hazard. Mater.* **2021**, *417*, 125938. DOI: 10.1016/j.jhazmat.2021.125938.
- (4) Ikada, Y.; Tsuji, H. Biodegradable Polyesters for Medical and Ecological Applications. *Macromol. Rapid Commun.* **2000**, *21* (3), 117-132. DOI: 10.1002/(Sici)1521-3927(20000201)21:3<117::Aid-Marc117>3.0.Co;2-X.
- (5) Brown, A.; Zaky, S.; Ray, H., Jr.; Sfeir, C. Porous Magnesium/Plga Composite Scaffolds for Enhanced Bone Regeneration Following Tooth Extraction. *Acta Biomater.* **2015**, *11*, 543-553. DOI: 10.1016/j.actbio.2014.09.008.
- (6) Woodard, L. N.; Kmetz, K. T.; Roth, A. A.; Page, V. M.; Grunlan, M. A. Porous Poly(Epsilon-Caprolactone)-Poly(L-Lactic Acid) Semi-Interpenetrating Networks as Superior, Defect-Specific Scaffolds with Potential for Cranial Bone Defect Repair. *Biomacromolecules* **2017**, *18* (12), 4075-4083. DOI: 10.1021/acs.biomac.7b01155.
- (7) Zilberman, M.; Nelson, K. D.; Eberhart, R. C. Mechanical Properties and in Vitro Degradation of Bioresorbable Fibers and Expandable Fiber-Based Stents. *J. Biomed. Mater. Res. B Appl. Biomater.* **2005**, *74* (2), 792-799. DOI: 10.1002/jbm.b.30319.

- (8) Agrawal, C. M.; Clark, H. G. Deformation Characteristics of a Bioabsorbable Intravascular Stent. *Invest. Radiol.* **1992**, 27 (12), 1020-1024. DOI: 10.1097/00004424-199212000-00007.
- (9) Mehdikhani-Nahrkhalaji, M.; Fathi, M. H.; Mortazavi, V.; Mousavi, S. B.; Akhavan, A.; Haghighat, A.; Hashemi-Beni, B.; Razavi, S. M.; Mashhadiabbas, F. Biodegradable Nanocomposite Coatings Accelerate Bone Healing: In Vivo Evaluation. *Dent. Res. J. (Isfahan)* **2015**, 12 (1), 89-99. DOI: 10.4103/1735-3327.150342.
- (10) Abdal-hay, A.; Hwang, M. G.; Lim, J. K. In Vitro Bioactivity of Titanium Implants Coated with Bicomponent Hybrid Biodegradable Polymers. *J. Sol-Gel Sci. Technol.* **2012**, 64 (3), 756-764. DOI: 10.1007/s10971-012-2912-6.
- (11) Chen, F. M.; Liu, X. Advancing Biomaterials of Human Origin for Tissue Engineering. *Prog. Polym. Sci.* **2016**, 53, 86-168. DOI: 10.1016/j.progpolymsci.2015.02.004.
- (12) Lee, F.; Chung, J. E.; Xu, K.; Kurisawa, M. Injectable Degradation-Resistant Hyaluronic Acid Hydrogels Cross-Linked Via the Oxidative Coupling of Green Tea Catechin. *ACS Macro Lett.* **2015**, 4 (9), 957-960. DOI: 10.1021/acsmacrolett.5b00544.
- (13) Shin, M.; Lee, H. Gallol-Rich Hyaluronic Acid Hydrogels: Shear-Thinning, Protein Accumulation against Concentration Gradients, and Degradation-Resistant Properties. *Chem. Mater.* **2017**, 29 (19), 8211-8220. DOI: 10.1021/acs.chemmater.7b02267.
- (14) Gopferich, A. Mechanisms of Polymer Degradation and Erosion. *Biomaterials* **1996**, 17 (2), 103-114. DOI: 10.1016/0142-9612(96)85755-3.
- (15) Manavitehrani, I.; Fathi, A.; Badr, H.; Daly, S.; Negahi Shirazi, A.; Dehghani, F. Biomedical Applications of Biodegradable Polyesters. *Polymers (Basel)* **2016**, 8 (1), 20. DOI: 10.3390/polym8010020.

- (16) Obst, M.; Steinbuchel, A. Microbial Degradation of Poly(Amino Acid)S. *Biomacromolecules* **2004**, *5* (4), 1166-1176. DOI: 10.1021/bm049949u.
- (17) Guelcher, S. A. Biodegradable Polyurethanes: Synthesis and Applications in Regenerative Medicine. *Tissue Eng. Part B Rev.* **2008**, *14* (1), 3-17. DOI: 10.1089/teb.2007.0133.
- (18) Gopferich, A.; Tessmar, J. Polyanhydride Degradation and Erosion. *Adv. Drug Deliv. Rev.* **2002**, *54* (7), 911-931. DOI: 10.1016/s0169-409x(02)00051-0.
- (19) Andrianov, A. K.; Allcock, H. R., *Polyphosphazenes in Biomedicine, Engineering & Pioneering Synthesis*. American Chemical Society: Washington, DC, 2018; Vol. 1298, ACS Symposium Series.
- (20) Zhao, Z.; Wang, J.; Mao, H. Q.; Leong, K. W. Polyphosphoesters in Drug and Gene Delivery. *Adv. Drug Deliv. Rev.* **2003**, *55* (4), 483-499. DOI: 10.1016/s0169-409x(03)00040-1.
- (21) Zhong, H.; Chan, G.; Hu, Y.; Hu, H.; Ouyang, D. A Comprehensive Map of Fda-Approved Pharmaceutical Products. *Pharmaceutics* **2018**, *10* (4), 263. DOI: 10.3390/pharmaceutics10040263.
- (22) Gentile, P.; Chiono, V.; Carmagnola, I.; Hatton, P. V. An Overview of Poly(Lactic-Co-Glycolic) Acid (PLGA)-Based Biomaterials for Bone Tissue Engineering. *Int. J. Mol. Sci.* **2014**, *15* (3), 3640-3659. DOI: 10.3390/ijms15033640.
- (23) Teng, Y. D.; Lavik, E. B.; Qu, X.; Park, K. I.; Ourednik, J.; Zurakowski, D.; Langer, R.; Snyder, E. Y. Functional Recovery Following Traumatic Spinal Cord Injury Mediated by a Unique Polymer Scaffold Seeded with Neural Stem Cells. *Proc. Natl. Acad. Sci.* **2002**, *99* (5), 3024-3029. DOI: 10.1073/pnas.052678899.

- (24) Bostman, O.; Pihlajamäki, H. Clinical Biocompatibility of Biodegradable Orthopaedic Implants for Internal Fixation: A Review. *Biomaterials* **2000**, *21* (24), 2615-2621. DOI: 10.1016/S0142-9612(00)00129-0.
- (25) Nair Pn, P.; Schug, J. Observations on Healing of Human Tooth Extraction Sockets Implanted with Bioabsorbable Polylactic-Polyglycolic Acids (Plga) Copolymer Root Replicas: A Clinical, Radiographic, and Histologic Follow-up Report of 8 Cases. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2004**, *97* (5), 559-569. DOI: 10.1016/S1079210403006334.
- (26) Böstman, O. M.; Pihlajamäki, H. K. Late Foreign-Body Reaction to an Intraosseous Bioabsorbable Polylactic Acid Screw. A Case Report*. *J. Bone Joint Surg.* **1998**, *80* (12), 1791-1794. DOI: 10.2106/00004623-199812000-00010.
- (27) Sung, H. J.; Meredith, C.; Johnson, C.; Galis, Z. S. The Effect of Scaffold Degradation Rate on Three-Dimensional Cell Growth and Angiogenesis. *Biomaterials* **2004**, *25* (26), 5735-5742. DOI: 10.1016/j.biomaterials.2004.01.066.
- (28) Zandstra, J.; Hiemstra, C.; Petersen, A. H.; Zuidema, J.; van Beuge, M. M.; Rodriguez, S.; Lathuile, A. A.; Veldhuis, G. J.; Steendam, R.; Bank, R. A.; Popa, E. R. Microsphere Size Influences the Foreign Body Reaction. *Eur. Cell. Mater.* **2014**, *28*, 335-347. DOI: 10.22203/ecm.v028a23.
- (29) Amini, A. R.; Wallace, J. S.; Nukavarapu, S. P. Short-Term and Long-Term Effects of Orthopedic Biodegradable Implants. *J. Long. Term Eff. Med. Implants* **2011**, *21* (2), 93-122. DOI: 10.1615/jlongtermeffmedimplants.v21.i2.10.
- (30) Marin, E.; Briceno, M. I.; Caballero-George, C. Critical Evaluation of Biodegradable Polymers Used in Nanodrugs. *Int. J. Nanomedicine* **2013**, *8*, 3071-3090. DOI: 10.2147/IJN.S47186.

- (31) Doppalapudi, S.; Jain, A.; Khan, W.; Domb, A. J. Biodegradable Polymers-an Overview. *Polym. Adv. Technol.* **2014**, 25 (5), 427-435. DOI: 10.1002/pat.3305.
- (32) BaoLin, G.; Ma, P. X. Synthetic Biodegradable Functional Polymers for Tissue Engineering: A Brief Review. *Sci. China Chem.* **2014**, 57 (4), 490-500. DOI: 10.1007/s11426-014-5086-y.
- (33) Ulery, B. D.; Nair, L. S.; Laurencin, C. T. Biomedical Applications of Biodegradable Polymers. *J. Polym. Sci. B Polym. Phys.* **2011**, 49 (12), 832-864. DOI: 10.1002/polb.22259.
- (34) Wang, J.; Wang, L.; Zhou, Z.; Lai, H.; Xu, P.; Liao, L.; Wei, J. Biodegradable Polymer Membranes Applied in Guided Bone/Tissue Regeneration: A Review. *Polymers* **2016**, 8 (4). DOI: 10.3390/polym8040115.
- (35) Hou, L. D.; Li, Z.; Pan, Y.; Sabir, M.; Zheng, Y. F.; Li, L. A Review on Biodegradable Materials for Cardiovascular Stent Application. *Front. Mater. Sci.* **2016**, 10 (3), 238-259. DOI: 10.1007/s11706-016-0344-x.
- (36) Iyer, A. K.; Khaled, G.; Fang, J.; Maeda, H. Exploiting the Enhanced Permeability and Retention Effect for Tumor Targeting. *Drug Discov. Today* **2006**, 11 (17-18), 812-818. DOI: 10.1016/j.drudis.2006.07.005.
- (37) Fox, M. E.; Szoka, F. C.; Frechet, J. M. Soluble Polymer Carriers for the Treatment of Cancer: The Importance of Molecular Architecture. *Acc. Chem. Res.* **2009**, 42 (8), 1141-1151. DOI: 10.1021/ar900035f.
- (38) Kadajji, V. G.; Betageri, G. V. Water Soluble Polymers for Pharmaceutical Applications. *Polymers* **2011**, 3 (4), 1972-2009. DOI: 10.3390/polym3041972.

- (39) Ekladios, I.; Colson, Y. L.; Grinstaff, M. W. Polymer-Drug Conjugate Therapeutics: Advances, Insights and Prospects. *Nat. Rev. Drug Discov.* **2019**, *18* (4), 273-294. DOI: 10.1038/s41573-018-0005-0.
- (40) Thomas, T. J.; Tajmir-Riahi, H. A.; Pillai, C. K. S. Biodegradable Polymers for Gene Delivery. *Molecules* **2019**, *24* (20). DOI: 10.3390/molecules24203744.
- (41) Andrianov, A. K.; Langer, R. Polyphosphazene Immunoadjuvants: Historical Perspective and Recent Advances. *J. Control. Release* **2021**, *329*, 299-315. DOI: 10.1016/j.jconrel.2020.12.001.
- (42) Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U. S. Poly(Ethylene Glycol) in Drug Delivery: Pros and Cons as Well as Potential Alternatives. *Angew. Chem. Int. Ed.* **2010**, *49* (36), 6288-6308. DOI: 10.1002/anie.200902672.
- (43) Fox, M. E.; Szoka, F. C.; Fréchet, J. M. J. Soluble Polymer Carriers for the Treatment of Cancer: The Importance of Molecular Architecture. *Acc. Chem. Res.* **2009**, *42* (8), 1141-1151. DOI: 10.1021/ar900035f.
- (44) Etrych, T.; Kovar, L.; Subr, V.; Braunova, A.; Pechar, M.; Chytil, P.; Rihova, B.; Ulbrich, K. High-Molecular-Weight Polymers Containing Biodegradable Disulfide Bonds: Synthesis and in Vitro Verification of Intracellular Degradation. *J. Bioact. Compat. Polym.* **2010**, *25* (1), 5-26. DOI: 10.1177/0883911509353485.
- (45) Yang, J.; Luo, K.; Pan, H.; Kopeckova, P.; Kopecek, J. Synthesis of Biodegradable Multiblock Copolymers by Click Coupling of Raft-Generated HeterotelechelicpolyHPMA Conjugates. *React. Funct. Polym.* **2011**, *71* (3), 294-302. DOI: 10.1016/j.reactfunctpolym.2010.10.005.

- (46) Yang, J.; Kopecek, J. The Light at the End of the Tunnel-Second Generation Hpma Conjugates for Cancer Treatment. *Curr. Opin. Colloid Interface Sci.* **2017**, *31*, 30-42. DOI: 10.1016/j.cocis.2017.07.003.
- (47) Pan, H.; Yang, J.; Kopeckova, P.; Kopecek, J. Backbone Degradable Multiblock N-(2-Hydroxypropyl)Methacrylamide Copolymer Conjugates Via Reversible Addition-Fragmentation Chain Transfer Polymerization and Thiol-Ene Coupling Reaction. *Biomacromolecules* **2011**, *12* (1), 247-252. DOI: 10.1021/bm101254e.
- (48) Pan, H.; Sima, M.; Miller, S. C.; Kopeckova, P.; Yang, J.; Kopecek, J. Efficiency of High Molecular Weight Backbone Degradable HPMA Copolymer-Prostaglandin E1 Conjugate in Promotion of Bone Formation in Ovariectomized Rats. *Biomaterials* **2013**, *34* (27), 6528-6538. DOI: 10.1016/j.biomaterials.2013.05.003.
- (49) Larson, N.; Yang, J.; Ray, A.; Cheney, D. L.; Ghandehari, H.; Kopecek, J. Biodegradable Multiblock Poly(N-2-Hydroxypropyl)Methacrylamide Gemcitabine and Paclitaxel Conjugates for Ovarian Cancer Cell Combination Treatment. *Int. J. Pharm* **2013**, *454* (1), 435-443. DOI: 10.1016/j.ijpharm.2013.06.046.
- (50) Etrych, T.; Strohalm, J.; Sirova, M.; Tomalova, B.; Rossmann, P.; Rihova, B.; Ulbrich, K.; Kovar, M. High-Molecular Weight Star Conjugates Containing Docetaxel with High Anti-Tumor Activity and Low Systemic Toxicity in Vivo. *Polym. Chem.* **2015**, *6* (1), 160-170. DOI: 10.1039/c4py01120a.
- (51) Rani, S.; Gupta, U. Hpma-Based Polymeric Conjugates in Anticancer Therapeutics. *Drug Discov. Today* **2020**, *25* (6), 997-1012. DOI: 10.1016/j.drudis.2020.04.007.
- (52) Bendele, A.; Seely, J.; Richey, C.; Sennello, G.; Shopp, G. Short Communication: Renal Tubular Vacuolation in Animals Treated with Polyethylene-Glycol-Conjugated Proteins. *Toxicol. Sci.* **1998**, *42* (2), 152-157. DOI: 10.1006/toxs.1997.2396.

- (53) Ishida, T.; Ichihara, M.; Wang, X.; Yamamoto, K.; Kimura, J.; Majima, E.; Kiwada, H. Injection of PEGylated Liposomes in Rats Elicits PEG-Specific IgM, Which Is Responsible for Rapid Elimination of a Second Dose of PEGylated Liposomes. *J. Control. Release* **2006**, *112* (1), 15-25. DOI: 10.1016/j.jconrel.2006.01.005.
- (54) Rudmann, D. G.; Alston, J. T.; Hanson, J. C.; Heidel, S. High Molecular Weight Polyethylene Glycol Cellular Distribution and PEG-Associated Cytoplasmic Vacuolation Is Molecular Weight Dependent and Does Not Require Conjugation to Proteins. *Toxicol. Pathol.* **2013**, *41* (7), 970-983. DOI: 10.1177/0192623312474726.
- (55) Abu Lila, A. S.; Kiwada, H.; Ishida, T. The Accelerated Blood Clearance (ABC) Phenomenon: Clinical Challenge and Approaches to Manage. *J. Control. Release* **2013**, *172* (1), 38-47. DOI: 10.1016/j.jconrel.2013.07.026.
- (56) Baumann, A.; Tuerck, D.; Prabhu, S.; Dickmann, L.; Sims, J. Pharmacokinetics, Metabolism and Distribution of PEGs and PEGylated Proteins: Quo Vadis? *Drug Discov. Today* **2014**, *19* (10), 1623-1631. DOI: 10.1016/j.drudis.2014.06.002.
- (57) Yang, Q.; Lai, S. K. Anti-PEG Immunity: Emergence, Characteristics, and Unaddressed Questions. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2015**, *7* (5), 655-677. DOI: 10.1002/wnan.1339.
- (58) Butcher, N. J.; Mortimer, G. M.; Minchin, R. F. Drug Delivery: Unravelling the Stealth Effect. *Nat. Nanotechnol.* **2016**, *11* (4), 310-311. DOI: 10.1038/nnano.2016.6.
- (59) Zhang, P.; Sun, F.; Liu, S.; Jiang, S. Anti-PEG Antibodies in the Clinic: Current Issues and Beyond PEGylation. *J. Control. Release* **2016**, *244* (Pt B), 184-193. DOI: 10.1016/j.jconrel.2016.06.040.

- (60) Pelegri-O'Day, E. M.; Lin, E. W.; Maynard, H. D. Therapeutic Protein-Polymer Conjugates: Advancing Beyond PEGylation. *J. Am. Chem. Soc.* **2014**, *136* (41), 14323-14332. DOI: 10.1021/ja504390x.
- (61) Schottler, S.; Becker, G.; Winzen, S.; Steinbach, T.; Mohr, K.; Landfester, K.; Mailander, V.; Wurm, F. R. Protein Adsorption Is Required for Stealth Effect of Poly(Ethylene Glycol)- and Poly(Phosphoester)-Coated Nanocarriers. *Nat. Nanotechnol.* **2016**, *11* (4), 372-377. DOI: 10.1038/nnano.2015.330.
- (62) Steinbach, T.; Wurm, F. R. Degradable Polyphosphoester-Protein Conjugates: "PPEylation" of Proteins. *Biomacromolecules* **2016**, *17* (10), 3338-3346. DOI: 10.1021/acs.biomac.6b01107.
- (63) Clochard, M. C. D.; Rankin, S.; Brocchini, S. Synthesis of Soluble Polymers for Medicine That Degrade by Intramolecular Acid Catalysis. *Macromol. Rapid Commun.* **2000**, *21* (12), 853-859. DOI: 10.1002/1521-3927(20000801)21:12<853::AID-MARC853>3.0.CO;2-M.
- (64) Iturmendi, A.; Teasdale, I. Water Soluble (Bio)Degradable Poly(Organo)Phosphazenes. In *Polyphosphazenes in Biomedicine, Engineering, and Pioneering Synthesis*, Acs Symposium Series, Vol. 1298; American Chemical Society, 2018; pp 183-209.
- (65) Rothmund, S.; Teasdale, I. Preparation of Polyphosphazenes: A Tutorial Review. *Chem. Soc. Rev.* **2016**, *45* (19), 5200-5215. DOI: 10.1039/c6cs00340k.
- (66) Wang, Y. C.; Yuan, Y. Y.; Du, J. Z.; Yang, X. Z.; Wang, J. Recent Progress in Polyphosphoesters: From Controlled Synthesis to Biomedical Applications. *Macromol. Biosci.* **2009**, *9* (12), 1154-1164. DOI: 10.1002/mabi.200900253.

- (67) Cini, N.; Ball, V. Polyphosphates as Inorganic Polyelectrolytes Interacting with Oppositely Charged Ions, Polymers and Deposited on Surfaces: Fundamentals and Applications. *Adv. Colloid Interface Sci.* **2014**, *209*, 84-97. DOI: 10.1016/j.cis.2014.01.011.
- (68) Duro-Castano, A.; England, R. M.; Razola, D.; Romero, E.; Oteo-Vives, M.; Morcillo, M. A.; Vicent, M. J. Well-Defined Star-Shaped Polyglutamates with Improved Pharmacokinetic Profiles as Excellent Candidates for Biomedical Applications. *Mol. Pharmaceutics* **2015**, *12* (10), 3639-3649. DOI: 10.1021/acs.molpharmaceut.5b00358.
- (69) Yavvari, P. S.; Awasthi, A. K.; Sharma, A.; Bajaj, A.; Srivastava, A. Emerging Biomedical Applications of Polyaspartic Acid-Derived Biodegradable Polyelectrolytes and Polyelectrolyte Complexes. *J. Mater. Chem. B* **2019**, *7* (13), 2102-2122. DOI: 10.1039/c8tb02962h.
- (70) Monge, S.; Canniccion, B.; Graillot, A.; Robin, J.-J. Phosphorus-Containing Polymers: A Great Opportunity for the Biomedical Field. *Biomacromolecules* **2011**, *12* (6), 1973-1982. DOI: 10.1021/bm2004803.
- (71) Luten, J.; van Steenis, J. H.; van Someren, R.; Kemmink, J.; Schuurmans-Nieuwenbroek, N. M.; Koning, G. A.; Crommelin, D. J.; van Nostrum, C. F.; Hennink, W. E. Water-Soluble Biodegradable Cationic Polyphosphazenes for Gene Delivery. *J. Control. Release* **2003**, *89* (3), 483-497. DOI: 10.1016/s0168-3659(03)00127-5.
- (72) Andrianov, A. K.; Svirkin, Y. Y.; LeGolván, M. P. Synthesis and Biologically Relevant Properties of Polyphosphazene Polyacids. *Biomacromolecules* **2004**, *5* (5), 1999-2006. DOI: 10.1021/bm049745d.
- (73) Andrianov, A. K.; Marin, A.; Peterson, P. Water-Soluble Biodegradable Polyphosphazenes Containing N-Ethylpyrrolidone Groups. *Macromolecules* **2005**, *38* (19), 7972-7976. DOI: 10.1021/ma0509309.

- (74) Decolibus, D. P.; Marin, A.; Andrianov, A. K. Effect of Environmental Factors on Hydrolytic Degradation of Water-Soluble Polyphosphazene Polyelectrolyte in Aqueous Solutions. *Biomacromolecules* **2010**, *11* (8), 2033-2038. DOI: 10.1021/bm100395u.
- (75) Bi, Y. M.; Yin, Y. F.; Huang, R.; Li, Y. M. Synthesis, Characterization, in Vitro Degradation and Cytotoxicity of Polyphosphazenes Containing N-Ethoxypyrrolidone Side Groups. *Polym. Int.* **2010**, *59* (2), 269-275. DOI: 10.1002/pi.2720.
- (76) Wilfert, S.; Iturmendi, A.; Schoefberger, W.; Kryeziu, K.; Heffeter, P.; Berger, W.; Bruggemann, O.; Teasdale, I. Water-Soluble, Biocompatible Polyphosphazenes with Controllable and pH-Promoted Degradation Behavior. *J. Polym. Sci. A Polym. Chem.* **2014**, *52* (2), 287-294. DOI: 10.1002/pola.27002.
- (77) Andrianov, A. K.; Marin, A.; Martinez, A. P.; Weidman, J. L.; Fuerst, T. R. Hydrolytically Degradable PEGylated Polyelectrolyte Nanocomplexes for Protein Delivery. *Biomacromolecules* **2018**, *19* (8), 3467-3478. DOI: 10.1021/acs.biomac.8b00785.
- (78) Allcock, H. R.; Pucher, S. R.; Scopelianos, A. G. Poly[(Amino-Acid-Ester)Phosphazenes] - Synthesis, Crystallinity, and Hydrolytic Sensitivity in Solution and the Solid-State. *Macromolecules* **1994**, *27* (5), 1071-1075. DOI: DOI 10.1021/ma00083a001.
- (79) Weikel, A. L.; Cho, S. Y.; Morozowich, N. L.; Nair, L. S.; Laurencin, C. T.; Allcock, H. R. Hydrolysable Polylactide-Polyphosphazene Block Copolymers for Biomedical Applications: Synthesis, Characterization, and Composites with Poly(Lactic-Co-Glycolic Acid). *Poly. Chem.* **2010**, *1* (9), 1459-1466. DOI: 10.1039/c0py00150c.
- (80) Teasdale, I.; Bruggemann, O. Polyphosphazenes: Multifunctional, Biodegradable Vehicles for Drug and Gene Delivery. *Polymers* **2013**, *5* (1), 161-187. DOI: 10.3390/polym5010161.

- (81) Andrianov, A. K.; Chen, J.; Payne, L. G. Preparation of Hydrogel Microspheres by Coacervation of Aqueous Polyphosphazene Solutions. *Biomaterials* **1998**, *19* (1-3), 109-115. DOI: 10.1016/s0142-9612(97)00227-5.
- (82) Andrianov, A. K.; Payne, L. G.; Visscher, K. B.; Allcock, H. R.; Langer, R. Hydrolytic Degradation of Ionically Cross-Linked Polyphosphazene Microspheres. *J. Appl. Polym. Sci.* **1994**, *53* (12), 1573-1578. DOI: 10.1002/app.1994.070531203.
- (83) Teasdale, I.; Wilfert, S.; Nischang, I.; Bruggemann, O. Multifunctional and Biodegradable Polyphosphazenes for Use as Macromolecular Anti-Cancer Drug Carriers. *Polym. Chem.* **2011**, *2* (4), 828-834. DOI: 10.1039/c0py00321b.
- (84) Rydholm, A. E.; Anseth, K. S.; Bowman, C. N. Effects of Neighboring Sulfides and pH on Ester Hydrolysis in Thiol-Acrylate Photopolymers. *Acta Biomater.* **2007**, *3* (4), 449-455. DOI: 10.1016/j.actbio.2006.12.001.
- (85) Andrianov, A. K.; Sargent, J. R.; Sule, S. S.; Le Golvan, M. P.; Woods, A. L.; Jenkins, S. A.; Payne, L. G. Synthesis, Physico-Chemical Properties and Immunoadjuvant Activity of Water-Soluble Phosphazene Polyacids. *J. Bioact. Compat. Polym.* **1998**, *13* (4), 243-256. DOI: 10.1177/088391159801300401.
- (86) Allcock, H. R.; Pucher, S. R.; Scopelianos, A. G. Poly[(Amino Acid Ester)Phosphazenes] as Substrates for the Controlled-Release of Small Molecules. *Biomaterials* **1994**, *15* (8), 563-569. DOI: Doi 10.1016/0142-9612(94)90205-4.
- (87) Allcock, H. R.; Kim, Y. B. Synthesis, Characterization, and Modification of Poly(Organophosphazenes) with Both 2,2,2-Trifluoroethoxy and Phenoxy Side-Groups. *Macromolecules* **1994**, *27* (14), 3933-3942. DOI: 10.1021/ma00092a038.

- (88) Mack, L. L.; Fitzpatrick, R. J.; Allcock, H. R. Langmuir-Adam Trough Studies of Hydrophobicity, Hydrophilicity, and Amphilicity in Small-Molecule and High-Polymeric Phosphazenes. *Langmuir* **1997**, *13* (7), 2123-2132. DOI: 10.1021/la950453v.
- (89) Allcock, H. R.; Steely, L. B.; Singh, A. Hydrophobic and Superhydrophobic Surfaces from Polyphosphazenes. *Polym. Int.* **2006**, *55* (6), 621-625. DOI: 10.1002/pi.2030.
- (90) Allcock, H. R.; Steely, L.; Singh, A.; Hindenlang, M. Hydrophobic and Superhydrophobic Polyphosphazenes. *J. Adhes. Sci. Technol.* **2009**, *23* (3), 435-445. DOI: 10.1163/156856108x369967.
- (91) Andrianov, A. K.; Marin, A. Degradation of Polyaminophosphazenes: Effects of Hydrolytic Environment and Polymer Processing. *Biomacromolecules* **2006**, *7* (5), 1581-1586. DOI: 10.1021/bm050959k.
- (92) Tian, Z.; Hess, A.; Fellin, C. R.; Nulwala, H.; Allcock, H. R. Phosphazene High Polymers and Models with Cyclic Aliphatic Side Groups: New Structure-Property Relationships. *Macromolecules* **2015**, *48* (13), 4301-4311. DOI: 10.1021/acs.macromol.5b00946.
- (93) Andrianov, A. K.; Marin, A.; Peterson, P.; Chen, J. P. Fluorinated Polyphosphazene Polyelectrolytes. *J. Appl. Polym. Sci.* **2007**, *103* (1), 53-58. DOI: 10.1002/app.23963.
- (94) Selin, V.; Albright, V.; Ankner, J. F.; Marin, A.; Andrianov, A. K.; Sukhishvili, S. A. Biocompatible Nanocoatings of Fluorinated Polyphosphazenes through Aqueous Assembly. *ACS Appl. Mater. Interfaces* **2018**, *10* (11), 9756-9764. DOI: 10.1021/acsami.8b02072.
- (95) Albright, V.; Selin, V.; Hlushko, H.; Palanisamy, A.; Marin, A.; Andrianov, A. K.; Sukhishvili, S. A. Fluorinated Polyphosphazene Coatings Using Aqueous Nano-Assembly of Polyphosphazene Polyelectrolytes. In *Polyphosphazenes in Biomedicine, Engineering,*

and Pioneering Synthesis, ACS Symposium Series, Vol. 1298; American Chemical Society, 2018; pp 101-118.

- (96) Albright, V.; Marin, A.; Kaner, P.; Sukhishvili, S. A.; Andrianov, A. K. New Family of Water-Soluble Sulfo-Fluoro Polyphosphazenes and Their Assembly within Hemocompatible Nanocoatings. *ACS Appl. Bio Mater.* **2019**, 2 (9), 3897-3906. DOI: 10.1021/acsabm.9b00485.
- (97) Albright, V.; Penarete-Acosta, D.; Stack, M.; Zheng, J.; Marin, A.; Hlushko, H.; Wang, H.; Jayaraman, A.; Andrianov, A. K.; Sukhishvili, S. A. Polyphosphazenes Enable Durable, Hemocompatible, Highly Efficient Antibacterial Coatings. *Biomaterials* **2021**, 268, 120586. DOI: 10.1016/j.biomaterials.2020.120586.
- (98) Marin, A.; Brito, J.; Sukhishvili, S. A.; Andrianov, A. K. Cationic Fluoropolyphosphazenes: Synthesis and Assembly with Heparin as a Pathway to Hemocompatible Nanocoatings. *ACS Appl. Bio Mater.* **2022**, 5 (1), 313-321. DOI: 10.1021/acsabm.1c01099.
- (99) Brito, J.; Asawa, K.; Marin, A.; Andrianov, A. K.; Choi, C.-H.; Sukhishvili, S. A. Hierarchically Structured, All-Aqueous-Coated Hydrophobic Surfaces with Ph-Selective Droplet Transfer Capability. *ACS Appl. Mater. Interfaces* **2022**, 14 (22), 26225-26237. DOI: 10.1021/acsami.2c04499.
- (100) Von Burkersroda, F.; Schedl, L.; Göpferich, A. Why Degradable Polymers Undergo Surface Erosion or Bulk Erosion. *Biomaterials* **2002**, 23 (21), 4221-4231. DOI: 10.1016/S0142-9612(02)00170-9.
- (101) Weir, N. A.; Buchanan, F. J.; Orr, J. F.; Farrar, D. F.; Dickson, G. R. Degradation of Poly-L-Lactide. Part 2: Increased Temperature Accelerated Degradation. *Proc. Inst. Mech. Eng. H* **2004**, 218 (5), 321-330. DOI: 10.1243/0954411041932809.

- (102) Reiche, J.; Kratz, K.; Hofmann, D.; Lendlein, A. Current Status of Langmuir Monolayer Degradation of Polymeric Biomaterials. *Int. J. Artif. Organs* **2011**, *34* (2), 123-128. DOI: 10.5301/ijao.2011.6401.
- (103) Machatschek, R.; Lendlein, A. Fundamental Insights in PLGA Degradation from Thin Film Studies. *J. Control. Release* **2020**, *319*, 276-284. DOI: 10.1016/j.jconrel.2019.12.044.
- (104) Schöne, A.-C.; Falkenhagen, S.; Travkova, O.; Schulz, B.; Kratz, K.; Lendlein, A. Influence of Intermediate Degradation Products on the Hydrolytic Degradation of Poly[(Rac-Lactide)-Co-Glycolide] at the Air-Water Interface. *Polym. Adv. Technol.* **2015**, *26* (12), 1402-1410. DOI: 10.1002/pat.3701.
- (105) Gopferich, A.; Langer, R. Modeling of Polymer Erosion. *Macromolecules* **1993**, *26* (16), 4105-4112. DOI: 10.1021/ma00068a006.
- (106) Laycock, B.; Nikolić, M.; Colwell, J. M.; Gauthier, E.; Halley, P.; Bottle, S.; George, G. Lifetime Prediction of Biodegradable Polymers. *Prog. Polym. Sci.* **2017**, *71*, 144-189. DOI: 10.1016/j.progpolymsci.2017.02.004.
- (107) Ford Versypt, A. N.; Pack, D. W.; Braatz, R. D. Mathematical Modeling of Drug Delivery from Autocatalytically Degradable PLGA Microspheres — a Review. *J. Control. Release* **2013**, *165* (1), 29-37. DOI: 10.1016/j.jconrel.2012.10.015.
- (108) Fick, A. Ueber Diffusion. *Ann. Phys. (Berlin, Ger.)* **1855**, *170* (1), 59-86. DOI: 10.1002/andp.18551700105.
- (109) Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons, 2020.
- (110) Atkins, P.; Atkins, P. W.; Paula, J. D. *Atkins' Physical Chemistry*; OUP Oxford, 2014.

- (111) Kiss, É.; Vargha-Butler, E. I. Novel Method to Characterize the Hydrolytic Decomposition of Biopolymer Surfaces. *Colloids Surf. B. Biointerfaces* **1999**, *15* (3), 181-193. DOI: 10.1016/S0927-7757(99)00009-6.
- (112) Paragkumar N, T.; Edith, D.; Six, J.-L. Surface Characteristics of PLA and PLGA Films. *Appl. Surf. Sci.* **2006**, *253* (5), 2758-2764. DOI: 10.1016/j.apsusc.2006.05.047.
- (113) Grizzi, I.; Garreau, H.; Li, S.; Vert, M. Hydrolytic Degradation of Devices Based on Poly(DL-Lactic Acid) Size-Dependence. *Biomaterials* **1995**, *16* (4), 305-311. DOI: 10.1016/0142-9612(95)93258-F.
- (114) Washington, M. A.; Balmert, S. C.; Fedorchak, M. V.; Little, S. R.; Watkins, S. C.; Meyer, T. Y. Monomer Sequence in PLGA Microparticles: Effects on Acidic Microclimates and in Vivo Inflammatory Response. *Acta Biomater.* **2018**, *65*, 259-271. DOI: 10.1016/j.actbio.2017.10.043.
- (115) Fu, K.; Pack, D. W.; Klibanov, A. M.; Langer, R. Visual Evidence of Acidic Environment within Degrading Poly(Lactic-Co-Glycolic Acid) (PLGA) Microspheres. *Pharm. Res.* **2000**, *17* (1), 100-106. DOI: 10.1023/A:1007582911958.
- (116) Shadman, S.; Nguyen-Dang, T.; Gupta, T. D.; Page, A. G.; Richard, I.; Leber, A.; Ruza, J.; Krishnamani, G.; Sorin, F. Microstructured Biodegradable Fibers for Advanced Control Delivery. *Adv. Funct. Mater.* **2020**, *30* (13), 1910283. DOI: 10.1002/adfm.201910283.
- (117) Lakshmi, S.; Katti, D. S.; Laurencin, C. T. Biodegradable Polyphosphazenes for Drug Delivery Applications. *Adv. Drug Deliv. Rev.* **2003**, *55* (4), 467-482. DOI: 10.1016/s0169-409x(03)00039-5.
- (118) Carriedo, G. A.; Alonso, F. J. G.; Alvarez, J. L. G.; Soto, A. P.; Tarazona, M. P.; Laguna, M. T. R.; Marcelo, G.; Mendicuti, F.; Saiz, E. Experimental and Theoretical Study of the

- Acidic Degradation of Poly(2,2'-Dioxy-1,1'-Biphenyl)Phosphazene. *Macromolecules* **2008**, *41* (22), 8483-8490. DOI: 10.1021/ma8015568.
- (119) Teasdale, I. Stimuli-Responsive Phosphorus-Based Polymers. *Eur. J. Inorg. Chem.* **2019**, *2019* (11-12), 1445-1456. DOI: 10.1002/ejic.201801077.
- (120) Martinez, A. P.; Qamar, B.; Fuerst, T. R.; Muro, S.; Andrianov, A. K. Biodegradable "Smart" Polyphosphazenes with Intrinsic Multifunctionality as Intracellular Protein Delivery Vehicles. *Biomacromolecules* **2017**, *18* (6), 2000-2011. DOI: 10.1021/acs.biomac.7b00537.
- (121) Khakbaz, M.; Hejazi, I.; Seyfi, J.; Jafari, S.-H.; Khonakdar, H. A.; Davachi, S. M. A Novel Method to Control Hydrolytic Degradation of Nanocomposite Biocompatible Materials Via Imparting Superhydrophobicity. *Appl. Surf. Sci.* **2015**, *357*, 880-886. DOI: 10.1016/j.apsusc.2015.09.101.
- (122) Vargha-Butler, E. I.; Kiss, E.; Lam, C. N. C.; Keresztes, Z.; Kálmán, E.; Zhang, L.; Neumann, A. W. Wettability of Biodegradable Surfaces. *Colloid. Polym. Sci.* **2001**, *279* (12), 1160-1168. DOI: 10.1007/s003960100549.
- (123) Shakesheff, K. M.; Davies, M. C.; Roberts, C. J.; Tendler, S. J. B.; Shard, A. G.; Domb, A. In Situ Atomic Force Microscopy Imaging of Polymer Degradation in an Aqueous Environment. *Langmuir* **1994**, *10* (12), 4417-4419. DOI: 10.1021/la00024a005.
- (124) Tsuji, H.; Mizuno, A.; Ikada, Y. Properties and Morphology of Poly(L-Lactide). III. Effects of Initial Crystallinity on Long-Term in Vitro Hydrolysis of High Molecular Weight Poly(L-Lactide) Film in Phosphate-Buffered Solution. *J. Appl. Polym. Sci.* **2000**, *77* (7), 1452-1464. DOI: 10.1002/1097-4628(20000815)77:7<1452::AID-APP7>3.0.CO;2-S.

- (125) Tsuji, H.; Ikada, Y. Blends of Crystalline and Amorphous Poly(Lactide). III. Hydrolysis of Solution-Cast Blend Films. *J. Appl. Polym. Sci.* **1997**, *63* (7), 855-863. DOI: 10.1002/(SICI)1097-4628(19970214)63:7<855::AID-APP5>3.0.CO;2-P.
- (126) Cho, K.; Lee, J.; Kwon, K. Hydrolytic Degradation Behavior of Poly(Butylene Succinate)s with Different Crystalline Morphologies. *J. Appl. Polym. Sci.* **2001**, *79* (6), 1025-1033. DOI: 10.1002/1097-4628(20010207)79:6<1025::AID-APP50>3.0.CO;2-7.
- (127) Vert, M.; Li, S.; Garreau, H. More About the Degradation of LA/GA-Derived Matrices in Aqueous Media. *J. Control. Release* **1991**, *16* (1), 15-26. DOI: 10.1016/0168-3659(91)90027-B.
- (128) Li, S.; Garreau, H.; Vert, M. Structure-Property Relationships in the Case of the Degradation of Massive Poly(A-Hydroxy Acids) in Aqueous Media. *J. Mater. Sci. Mater. Med.* **1990**, *1* (4), 198-206. DOI: 10.1007/BF00701077.
- (129) Alexis, F. Factors Affecting the Degradation and Drug-Release Mechanism of Poly(Lactic Acid) and Poly[(Lactic Acid)-Co-(Glycolic Acid)]. *Polym. Int.* **2005**, *54* (1), 36-46. DOI: 10.1002/pi.1697.
- (130) Bennett, S.; Zhang, X. 14 - Degradation Characterisation of Biodegradable Polymers. In *Science and Principles of Biodegradable and Bioresorbable Medical Polymers*, Zhang, X. Ed.; Woodhead Publishing, 2017; pp 415-425.
- (131) Engineer, C.; Parikh, J.; Raval, A. Review on Hydrolytic Degradation Behavior of Biodegradable Polymers from Controlled Drug Delivery System. *Trends Biomater. Artif. Organs* **2011**, *25* (2).
- (132) Wang, M. O.; Piard, C. M.; Melchiorri, A.; Dreher, M. L.; Fisher, J. P. Evaluating Changes in Structure and Cytotoxicity During in Vitro Degradation of Three-Dimensional Printed

- Scaffolds. *Tissue Eng. Part A* **2015**, *21* (9-10), 1642-1653. DOI: 10.1089/ten.tea.2014.0495.
- (133) Partini, M.; Pantani, R. FTIR Analysis of Hydrolysis in Aliphatic Polyesters. *Polym. Degrad. Stab.* **2007**, *92* (8), 1491-1497. DOI: 10.1016/j.polymdegradstab.2007.05.009.
- (134) Bian, L.; Mohammed, H. S.; Shipp, D. A.; Goulet, P. J. G. Raman Microspectroscopy Study of the Hydrolytic Degradation of Polyanhydride Network Polymers. *Langmuir* **2019**, *35* (19), 6387-6392. DOI: 10.1021/acs.langmuir.8b04334.
- (135) Woodard, L. N.; Grunlan, M. A. Hydrolytic Degradation and Erosion of Polyester Biomaterials. *ACS Macro Lett.* **2018**, *7* (8), 976-982. DOI: 10.1021/acsmacrolett.8b00424.
- (136) Teng, X.; Li, F.; Lu, C. Visualization of Materials Using the Confocal Laser Scanning Microscopy Technique. *Chem. Soc. Rev.* **2020**, *49* (8), 2408-2425. DOI: 10.1039/C8CS00061A.
- (137) Yang, F.; Zhang, X.; Song, L.; Cui, H.; Myers, J. N.; Bai, T.; Zhou, Y.; Chen, Z.; Gu, N. Controlled Drug Release and Hydrolysis Mechanism of Polymer–Magnetic Nanoparticle Composite. *ACS Appl. Mater. Interfaces* **2015**, *7* (18), 9410-9419. DOI: 10.1021/acsami.5b02210.
- (138) Fuoco, T.; Cuartero, M.; Parrilla, M.; García-Guzmán, J. J.; Crespo, G. A.; Finne-Wistrand, A. Capturing the Real-Time Hydrolytic Degradation of a Library of Biomedical Polymers by Combining Traditional Assessment and Electrochemical Sensors. *Biomacromolecules* **2021**, *22* (2), 949-960. DOI: 10.1021/acs.biomac.0c01621.
- (139) Schusser, S.; Krischer, M.; Molin, D. G. M.; van den Akker, N. M. S.; Bäcker, M.; Poghosian, A.; Schöning, M. J. Sensor System for in-Situ and Real-Time Monitoring of

Polymer (Bio)Degradation. *Procedia Eng.* **2015**, *120*, 948-951. DOI: 10.1016/j.proeng.2015.08.815.

- (140) Agrawal, C. M.; McKinney, J. S.; Lancot, D.; Athanasiou, K. A. Effects of Fluid Flow on the in Vitro Degradation Kinetics of Biodegradable Scaffolds for Tissue Engineering. *Biomaterials* **2000**, *21* (23), 2443-2452. DOI: 10.1016/S0142-9612(00)00112-5.
- (141) Phillips, D. J.; Pygall, S. R.; Cooper, V. B.; Mann, J. C. Overcoming Sink Limitations in Dissolution Testing: A Review of Traditional Methods and the Potential Utility of Biphasic Systems. *J. Pharm. Pharmacol.* **2012**, *64* (11), 1549-1559. DOI: 10.1111/j.2042-7158.2012.01523.x.
- (142) Kruppke, B.; Weiß, J.; Rößler, S.; Heinemann, C.; Hanke, T. Novel Degradation Flow-through Chamber for in Vitro Biomaterial Characterization. *J. Biomed. Mater. Res., Part B* **2020**, *108* (8), 3124-3133. DOI: 10.1002/jbm.b.34638.
- (143) Duncan, R.; Kopeček, J. Soluble Synthetic Polymers as Potential Drug Carriers. 1984, 1984; Springer: Berlin, Heidelberg, pp 51-101. DOI: 10.1007/3-540-12796-8_10.
- (144) Nasongkla, N.; Chen, B.; Macaraeg, N.; Fox, M. E.; Frechet, J. M.; Szoka, F. C. Dependence of Pharmacokinetics and Biodistribution on Polymer Architecture: Effect of Cyclic Versus Linear Polymers. *J. Am. Chem. Soc.* **2009**, *131* (11), 3842-3843. DOI: 10.1021/ja900062u.
- (145) Venturoli, D.; Rippe, B. Ficoll and Dextran Vs. Globular Proteins as Probes for Testing Glomerular Permselectivity: Effects of Molecular Size, Shape, Charge, and Deformability. *Am. J. Physiol. Renal Physiol.* **2005**, *288* (4), F605-F613. DOI: 10.1152/ajprenal.00171.2004.

- (146) Chen, B.; Jerger, K.; Fréchet, J. M. J.; Szoka, F. C. The Influence of Polymer Topology on Pharmacokinetics: Differences between Cyclic and Linear PEGylated Poly(Acrylic Acid) Comb Polymers. *J. Control. Release* **2009**, *140* (3), 203-209. DOI: 10.1016/j.jconrel.2009.05.021.
- (147) Imran ul-haq, M.; Lai, B. F. L.; Chapanian, R.; Kizhakkedathu, J. N. Influence of Architecture of High Molecular Weight Linear and Branched Polyglycerols on Their Biocompatibility and Biodistribution. *Biomaterials* **2012**, *33* (35), 9135-9147. DOI: 10.1016/j.biomaterials.2012.09.007.
- (148) Fischman, A. J.; Alpert, N. M.; Rubin, R. H. Pharmacokinetic Imaging: A Noninvasive Method for Determining Drug Distribution and Action. *Clin. Pharmacokinet.* **2002**, *41* (8), 581-602. DOI: 10.2165/00003088-200241080-00003.
- (149) Massoud, T. F.; Gambhir, S. S. Molecular Imaging in Living Subjects: Seeing Fundamental Biological Processes in a New Light. *Genes Dev.* **2003**, *17* (5), 545-580. DOI: 10.1101/gad.1047403.
- (150) Aboagye, E. O.; Price, P. M.; Jones, T. In Vivo Pharmacokinetics and Pharmacodynamics in Drug Development Using Positron-Emission Tomography. *Drug Discov. Today* **2001**, *6* (6), 293-302. DOI: 10.1016/S1359-6446(01)01684-1.
- (151) Merkel, O. M.; Librizzi, D.; Pfestroff, A.; Schurrat, T.; Buyens, K.; Sanders, N. N.; De Smedt, S. C.; Béhé, M.; Kissel, T. Stability of Sirna Polyplexes from Poly(Ethylenimine) and Poly(Ethylenimine)-G-Poly(Ethylene Glycol) under in Vivo Conditions: Effects on Pharmacokinetics and Biodistribution Measured by Fluorescence Fluctuation Spectroscopy and Single Photon Emission Computed Tomography (SPECT) Imaging. *J. Control. Release* **2009**, *138* (2), 148-159. DOI: 10.1016/j.jconrel.2009.05.016.

- (152) Sonaje, K.; Lin, K.-J.; Wey, S.-P.; Lin, C.-K.; Yeh, T.-H.; Nguyen, H.-N.; Hsu, C.-W.; Yen, T.-C.; Juang, J.-H.; Sung, H.-W. Biodistribution, Pharmacodynamics and Pharmacokinetics of Insulin Analogues in a Rat Model: Oral Delivery Using Ph-Responsive Nanoparticles Vs. Subcutaneous Injection. *Biomaterials* **2010**, *31* (26), 6849-6858. DOI: 10.1016/j.biomaterials.2010.05.042.
- (153) Frangioni, J. V. In Vivo near-Infrared Fluorescence Imaging. *Curr. Opin. Chem. Biol.* **2003**, *7* (5), 626-634. DOI: 10.1016/j.cbpa.2003.08.007.
- (154) Poon, Z.; Lee, J. B.; Morton, S. W.; Hammond, P. T. Controlling in Vivo Stability and Biodistribution in Electrostatically Assembled Nanoparticles for Systemic Delivery. *Nano Lett.* **2011**, *11* (5), 2096-2103. DOI: 10.1021/nl200636r.
- (155) Mitchell, G. S.; Gill, R. K.; Boucher, D. L.; Li, C.; Cherry, S. R. In Vivo Cerenkov Luminescence Imaging: A New Tool for Molecular Imaging. *Philos. Trans. Royal Soc. A* **2011**, *369* (1955), 4605-4619. DOI: 10.1098/rsta.2011.0271.
- (156) Black, K. C. L.; Ibricevic, A.; Gunsten, S. P.; Flores, J. A.; Gustafson, T. P.; Raymond, J. E.; Samarajeewa, S.; Shrestha, R.; Felder, S. E.; Cai, T.; Shen, Y.; Löbs, A.-K.; Zhegalova, N.; Sultan, D. H.; Berezin, M.; Wooley, K. L.; Liu, Y.; Brody, S. L. In vivo Fate Tracking of Degradable Nanoparticles for Lung Gene Transfer Using PET and Cerenkov Imaging. *Biomaterials* **2016**, *98*, 53-63. DOI: 10.1016/j.biomaterials.2016.04.040.
- (157) Merkel, O. M.; Librizzi, D.; Pfestroff, A.; Schurrat, T.; Béhé, M.; Kissel, T. In Vivo SPECT and Real-Time Gamma Camera Imaging of Biodistribution and Pharmacokinetics of siRNA Delivery Using an Optimized Radiolabeling and Purification Procedure. *Bioconjugate Chem.* **2009**, *20* (1), 174-182. DOI: 10.1021/bc800408g.
- (158) Wang, Y.; Ye, F.; Jeong, E.-K.; Sun, Y.; Parker, D. L.; Lu, Z.-R. Noninvasive Visualization of Pharmacokinetics, Biodistribution and Tumor Targeting of Poly[N-(2-

- Hydroxypropyl)Methacrylamide] in Mice Using Contrast Enhanced MRI. *Pharm. Res.* **2007**, *24* (6), 1208-1216. DOI: 10.1007/s11095-007-9252-1.
- (159)Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-Responsive Nanocarriers for Drug Delivery. *Nat. Mater.* **2013**, *12* (11), 991-1003. DOI: 10.1038/nmat3776.
- (160)Urbánek, T.; Jäger, E.; Jäger, A.; Hrubý, M. Selectively Biodegradable Polyesters: Nature-Inspired Construction Materials for Future Biomedical Applications. *Polymers* **2019**, *11* (6). DOI: 10.3390/polym11061061.
- (161)Iturmendi, A.; Monkowius, U.; Teasdale, I. Oxidation Responsive Polymers with a Triggered Degradation Via Arylboronate Self-Immolative Motifs on a Polyphosphazene Backbone. *ACS Macro Lett.* **2017**, *6* (2), 150-154. DOI: 10.1021/acsmacrolett.7b00015.
- (162)Zhang, M.; Song, C.-C.; Du, F.-S.; Li, Z.-C. Supersensitive Oxidation-Responsive Biodegradable PEG Hydrogels for Glucose-Triggered Insulin Delivery. *ACS Appl. Mater. Interfaces* **2017**, *9* (31), 25905-25914. DOI: 10.1021/acsami.7b08372.
- (163)Lin, Y.; Kouznetsova, T. B.; Craig, S. L. Mechanically Gated Degradable Polymers. *J. Am. Chem. Soc.* **2020**, *142* (5), 2105-2109. DOI: 10.1021/jacs.9b13359.
- (164)Lin, Y.; Kouznetsova, T. B.; Chang, C.-C.; Craig, S. L. Enhanced Polymer Mechanical Degradation through Mechanochemically Unveiled Lactonization. *Nat. Commun.* **2020**, *11* (1), 4987. DOI: 10.1038/s41467-020-18809-7.
- (165)Hsu, T.-G.; Zhou, J.; Su, H.-W.; Schrage, B. R.; Ziegler, C. J.; Wang, J. A Polymer with “Locked” Degradability: Superior Backbone Stability and Accessible Degradability Enabled by Mechanophore Installation. *J. Am. Chem. Soc.* **2020**, *142* (5), 2100-2104. DOI: 10.1021/jacs.9b12482.

- (166) Yardley, R. E.; Kenaree, A. R.; Gillies, E. R. Triggering Depolymerization: Progress and Opportunities for Self-Immolative Polymers. *Macromolecules* **2019**, *52* (17), 6342-6360. DOI: 10.1021/acs.macromol.9b00965.
- (167) de Gracia Lux, C.; McFearin, C. L.; Joshi-Barr, S.; Sankaranarayanan, J.; Fomina, N.; Almutairi, A. Single UV or near IR Triggering Event Leads to Polymer Degradation into Small Molecules. *ACS Macro Lett.* **2012**, *1* (7), 922-926. DOI: 10.1021/mz3002403.
- (168) Grinda, M.; Clarhaut, J.; Renoux, B.; Tranoy-Opalinski, I.; Papot, S. A Self-Immolative Dendritic Glucuronide Prodrug of Doxorubicin. *MedChemComm* **2012**, *3* (1), 68-70. DOI: 10.1039/C1MD00193K.
- (169) Höcherl, A.; Jäger, E.; Jäger, A.; Hrubý, M.; Konefał, R.; Janoušková, O.; Spěváček, J.; Jiang, Y.; Schmidt, P. W.; Lodge, T. P.; Štěpánek, P. One-Pot Synthesis of Reactive Oxygen Species (ROS)-Self-Immolative Polyoxalate Prodrug Nanoparticles for Hormone Dependent Cancer Therapy with Minimized Side Effects. *Polym. Chem.* **2017**, *8* (13), 1999-2004. DOI: 10.1039/C7PY00270J.
- (170) Shin, J.-W.; Chan Choe, J.; Lee, J. H.; Han, W. B.; Jang, T.-M.; Ko, G.-J.; Yang, S. M.; Kim, Y.-G.; Joo, J.; Lim, B. H.; Park, E.; Hwang, S.-W. Biologically Safe, Degradable Self-Destruction System for on-Demand, Programmable Transient Electronics. *ACS Nano* **2021**, *15* (12), 19310-19320. DOI: 10.1021/acsnano.1c05463.
- (171) Maschmeyer, P. G.; Liang, X.; Hung, A.; Ahmadzai, O.; Kenny, A. L.; Luong, Y. C.; Forder, T. N.; Zeng, H.; Gillies, E. R.; Roberts, D. A. Post-Polymerization ‘Click’ End-Capping of Polyglyoxylate Self-Immolative Polymers. *Poly. Chem.* **2021**, *12* (47), 6824-6831. DOI: 10.1039/d1py01169c.

- (172) Zhao, Y.; Liang, H.; Zhang, S.; Qu, S.; Jiang, Y.; Chen, M. Effects of Magnesium Oxide (MgO) Shapes on in Vitro and in Vivo Degradation Behaviors of PLA/MgO Composites in Long Term. *Polymers* **2020**, *12* (5). DOI: 10.3390/polym12051074.
- (173) Lih, E.; Kum, C. H.; Park, W.; Chun, S. Y.; Cho, Y.; Joung, Y. K.; Park, K.-S.; Hong, Y. J.; Ahn, D. J.; Kim, B.-S.; Kwon, T. G.; Jeong, M. H.; Hubbell, J. A.; Han, D. K. Modified Magnesium Hydroxide Nanoparticles Inhibit the Inflammatory Response to Biodegradable Poly(Lactide-Co-Glycolide) Implants. *ACS Nano* **2018**, *12* (7), 6917-6925. DOI: 10.1021/acsnano.8b02365.
- (174) Abdal-hay, A.; Raveendran, N. T.; Fournier, B.; Ivanovski, S. Fabrication of Biocompatible and Bioabsorbable Polycaprolactone/ Magnesium Hydroxide 3D Printed Scaffolds: Degradation and in Vitro Osteoblasts Interactions. *Compos. B Eng.* **2020**, *197*, 108158. DOI: 10.1016/j.compositesb.2020.108158.
- (175) Park, K.-S.; Kim, B.-J.; Lih, E.; Park, W.; Lee, S.-H.; Joung, Y. K.; Han, D. K. Versatile Effects of Magnesium Hydroxide Nanoparticles in PLGA Scaffold-Mediated Chondrogenesis. *Acta Biomater.* **2018**, *73*, 204-216. DOI: 10.1016/j.actbio.2018.04.022.
- (176) Lih, E.; Park, W.; Park, K. W.; Chun, S. Y.; Kim, H.; Joung, Y. K.; Kwon, T. G.; Hubbell, J. A.; Han, D. K. A Bioinspired Scaffold with Anti-Inflammatory Magnesium Hydroxide and Decellularized Extracellular Matrix for Renal Tissue Regeneration. *ACS Cent. Sci.* **2019**, *5* (3), 458-467. DOI: 10.1021/acscentsci.8b00812.
- (177) Go, E. J.; Kang, E. Y.; Lee, S. K.; Park, S.; Kim, J. H.; Park, W.; Kim, I. H.; Choi, B.; Han, D. K. An Osteoconductive PLGA Scaffold with Bioactive B-TCP and Anti-Inflammatory Mg(OH)₂ to Improve in Vivo Bone Regeneration. *Biomater. Sci.* **2020**, *8* (3), 937-948. DOI: 10.1039/C9BM01864F.

- (178)Ko, K.-W.; Choi, B.; Kang, E. Y.; Shin, S.-W.; Baek, S.-W.; Han, D. K. The Antagonistic Effect of Magnesium Hydroxide Particles on Vascular Endothelial Activation Induced by Acidic Plga Degradation Products. *Biomaterials Science* **2020**. DOI: 10.1039/D0BM01656J.
- (179)Jiang, L.; Li, Y.; Xiong, C.; Su, S.; Ding, H. Preparation and Properties of Bamboo Fiber/Nano-Hydroxyapatite/Poly(Lactic-Co-Glycolic) Composite Scaffold for Bone Tissue Engineering. *ACS Appl. Mater. Interfaces* **2017**, 9 (5), 4890-4897. DOI: 10.1021/acsami.6b15032.
- (180)Cifuentes, S. C.; Gavilán, R.; Lieblich, M.; Benavente, R.; González-Carrasco, J. L. In Vitro Degradation of Biodegradable Polylactic Acid/Magnesium Composites: Relevance of Mg Particle Shape. *Acta Biomater.* **2016**, 32, 348-357. DOI: 10.1016/j.actbio.2015.12.037.
- (181)Wen, W.; Luo, B.; Qin, X.; Li, C.; Liu, M.; Ding, S.; Zhou, C. Strengthening and Toughening of Poly(L-Lactide) Composites by Surface Modified MgO Whiskers. *Appl. Surf. Sci.* **2015**, 332, 215-223. DOI: 10.1016/j.apsusc.2015.01.167.
- (182)Zhao, Y.; Liu, B.; You, C.; Chen, M. Effects of MgO Whiskers on Mechanical Properties and Crystallization Behavior of PLLA/MgO Composites. *Mater. Des.* **2016**, 89, 573-581. DOI: 10.1016/j.matdes.2015.09.157.
- (183)Ferrández-Montero, A.; Lieblich, M.; Benavente, R.; González-Carrasco, J. L.; Ferrari, B. Study of the Matrix-Filler Interface in PLA/Mg Composites Manufactured by Material Extrusion Using a Colloidal Feedstock. *Addit. Manuf.* **2020**, 33, 101142. DOI: 10.1016/j.addma.2020.101142.
- (184)Ogueri, K. S.; Ogueri, K. S.; Allcock, H. R.; Laurencin, C. T. A Regenerative Polymer Blend Composed of Glycylglycine Ethyl Ester-Substituted Polyphosphazene and

- Poly(Lactic-Co-Glycolic Acid). *ACS Appl. Polym. Mater.* **2020**, 2 (3), 1169-1179. DOI: 10.1021/acsapm.9b00993.
- (185) Woodard, L. N.; Grunlan, M. A. Hydrolytic Degradation of PCL–PLLA Semi-IPNs Exhibiting Rapid, Tunable Degradation. *ACS Biomater. Sci. Eng.* **2019**, 5 (2), 498-508. DOI: 10.1021/acsbiomaterials.8b01135.
- (186) Pfau, M. R.; McKinzey, K. G.; Roth, A. A.; Grunlan, M. A. PCL-Based Shape Memory Polymer Semi-IPNs: The Role of Miscibility in Tuning the Degradation Rate. *Biomacromolecules* **2020**, 21 (6), 2493-2501. DOI: 10.1021/acs.biomac.0c00454.
- (187) Woodard, L. N.; Page, V. M.; Kmetz, K. T.; Grunlan, M. A. Pcl–Plla Semi-Ipn Shape Memory Polymers (SMPs): Degradation and Mechanical Properties. *Macromol. Rapid Commun.* **2016**, 37 (23), 1972-1977. DOI: 10.1002/marc.201600414.
- (188) Benhabbour, S. R.; Kovarova, M.; Jones, C.; Copeland, D. J.; Shrivastava, R.; Swanson, M. D.; Sykes, C.; Ho, P. T.; Cottrell, M. L.; Sridharan, A.; Fix, S. M.; Thayer, O.; Long, J. M.; Hazuda, D. J.; Dayton, P. A.; Mumper, R. J.; Kashuba, A. D. M.; Garcia, J. V. Ultra-Long-Acting Tunable Biodegradable and Removable Controlled Release Implants for Drug Delivery. *Nat. Comm.* **2019**, 10 (1), 4324. DOI: 10.1038/s41467-019-12141-5.
- (189) Han, G.; Bedair, T. M.; Kim, D. H.; Park, K.-H.; Park, W.; Han, D. K. Improved Mechanical and Biological Properties of Biodegradable Thinner Poly(L-Lactic Acid) Tubes by Bi-Directional Drawing. *J. Ind. Eng. Chem.* **2020**, 90, 85-94. DOI: 10.1016/j.jiec.2020.06.029.
- (190) Anderson, D. G.; Lynn, D. M.; Langer, R. Semi-Automated Synthesis and Screening of a Large Library of Degradable Cationic Polymers for Gene Delivery. *Angew. Chem. Int. Ed.* **2003**, 42 (27), 3153-3158. DOI: 10.1002/anie.200351244.

- (191) Upadhyaya, R.; Kosuri, S.; Tamasi, M.; Meyer, T. A.; Atta, S.; Webb, M. A.; Gormley, A. J. Automation and Data-Driven Design of Polymer Therapeutics. *Adv. Drug Del. Rev.* **2021**, *171*, 1-28. DOI: 10.1016/j.addr.2020.11.009.
- (192) Webb, M. A.; Jackson, N. E.; Gil, P. S.; de Pablo, J. J. Targeted Sequence Design within the Coarse-Grained Polymer Genome. *Sci. Adv.* **2020**, *6* (43), eabc6216. DOI: 10.1126/sciadv.abc6216.
- (193) Kohn, J.; Welsh, W. J.; Knight, D. A New Approach to the Rationale Discovery of Polymeric Biomaterials. *Biomaterials* **2007**, *28* (29), 4171-4177. DOI: 10.1016/j.biomaterials.2007.06.022.
- (194) Costache, A. D.; Ghosh, J.; Knight, D. D.; Kohn, J. Computational Methods for the Development of Polymeric Biomaterials. *Adv. Eng. Mater.* **2010**, *12* (1-2), B3-B17. DOI: 10.1002/adem.200980020.

Table of Content Figure

Degradation of Polymeric Biomaterials: Roles of Microenvironment, Autocatalysis, and Physical State

Jordan Brito¹, Alexander K. Andrianov,² and Svetlana A. Sukhishvili^{1}*

¹Department of Materials Science & Engineering, Texas A&M University, College Station, TX
77843, USA

²Institute for Bioscience and Biotechnology Research, University of Maryland, Rockville,
MD 20850, USA

