Polymer Sequences

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Precision Synthesis of Biodegradable Polymers**

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The design of bioapplicable polymers and materials is a true dilemma for today's synthetic chemists. Indeed, modern bioapplicable materials have to fulfill antinomic criteria: on one hand, they should exhibit advanced properties and functions,[1] while on the other hand they have to comply with increasingly stringent regulations on sterilization, biocompatibility, and in vivo clearance. Consequently, there nowadays is a huge gap between promising options reported in the scientific literature and real bioapplicable systems. For instance, the overall number of approved polymers for human use is relatively low. Biodegradable aliphatic polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly(lactic-*co*-glycolic acid) (PLGA) are widely used polymers in life sciences.[2] These polymers can be hydrolyzed in vitro and in vivo within weeks to years. In addition, PLA, PGA, and PLGA and their degradation products have been shown to be nontoxic and biocompatible.[3] Therefore, in the past few decades, many homopolymers and copolymers based on lactic and glycolic acid have been used in a variety of bioapplications as diverse as controlled drug release, gene therapy, regenerative medicine, or implants.[4] In particular, the copolymer PLGA that contains both (*S*,*S*)- or *rac*-lactic and glycolic units is the most widely used material for drug-release systems.

Several parameters have been reported to influence the degradation behavior of PLGA; the most important factors are the copolymer composition, the molecular weight and molecular-weight distribution, the crystallinity, and the structure of the copolymer.[5] Other important properties of the polymer matrix that depend on the copolymer composition, such as the glass transition temperature (T_g), have additional indirect effects on degradation rates.[5d] For instance, PLGAs with diverse material properties and degradation rates can be produced by incorporating various monomer ratios. Indeed, PLGA degrades by hydrolysis of its ester linkages and it has been shown that the ester linkages in glycolic units are more sensitive to hydrolysis than their lactic counterparts.[6] However, the simple adjustment of the overall copolymer composition is not necessarily optimal for all applications. For instance, demanding applications such as controlled and sustained drug delivery may require very specific degradation kinetics.

Major problems encountered in time-controlled delivery of drugs from biodegradable PLGA matrices are the overall bioavailability of the released drugs and the fast initial release from the polymer matrix ("burst release").[7] This initial hydrolysis is typically followed by a slow degradation of the residual material. Thus, the preparation of micro- or nanoparticles is usually accompanied by an important loss in activity of the drugs.[8] Therefore, there is still a great need for a safe and effective delivery system for labile and/or large molecules to be delivered to specific targets. Possible alternatives to PLGA are extensively studied and reported every week in specialized journals. However, as mentioned above, the approval of a new biocompatible polymer is a tedious process, which may require years to be completed. In this context, it is sometimes wiser and certainly more straightforward to optimize existing structures rather than to develop new ones. For instance, a finer control of the PLGA structure would allow the proper selection of the rates of both the drug release and the biodegradation of particles.

There is an increasing interest in methods that allow for the preparation of PLGAs in a reproducible and controlled fashion. Current methods to synthesize PLGAs include direct condensation from lactic acid, glycolic acid, and light condensates (i.e. small oligomers) or ring-opening polymerization (ROP) of the related cyclic dimers, namely, lactide and glycolide) in bulk, initiated with metal alkoxides.[9] However, in such ring-opening processes, the number and types of sequences that can be prepared are limited by the dimeric form of the ROP monomers. Moreover, poly(*rac*-lactic acid-*co*-glycolic acid) (*rac*-PLGA) obtained from these dimers has broad composition ranges and a random block nature because of the much higher reactivity of glycolide and the drastic polymerization conditions.[10]

Current PLGAs are therefore far from being optimal and tailor-made structures are certainly needed. However, in the case of simple aliphatic polyesters, the available options for molecular optimization are relatively limited. Indeed, only a

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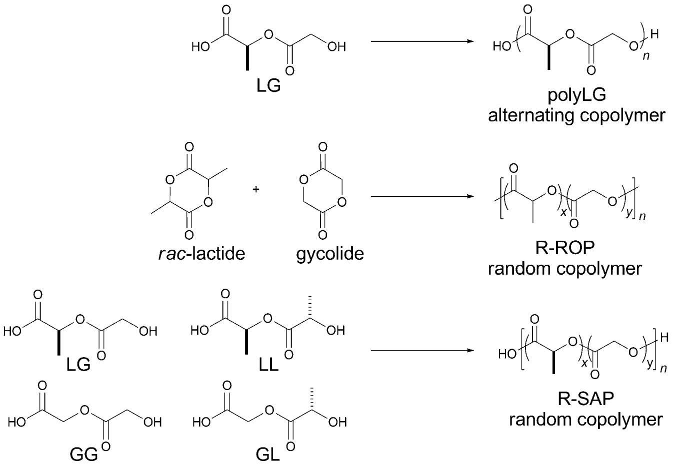
few macromolecular parameters can be varied, for example, chain length, molecular weight distribution, chain ends, architecture, and microstructure. Yet, the opportunities offered by the latter option have been certainly underestimated in recent synthetic polymer science. As learned from biological polymers, the control over chain microstructure (i.e. tacticity and monomer sequences) may lead to highly optimized macromolecules with tailored properties.[11] This simple strategy could also lead to significant advances in the field of synthetic polymer materials. For instance, it has been already demonstrated that tacticity may considerably influence the degradation rates of synthetic polyesters:[12] Stereoregular polymers are usually more crystalline than their atactic counterparts and therefore exhibit slower degradation profiles.

In a very recent paper, Meyer and co-workers reported that—besides tacticity—the primary structure (i.e. the distribution of monomer units in a copolymer chain) may also strongly influence the degradation properties of PLGA.[13] These results are timely. Indeed, it was recently suggested that sequence-controlled polymers may open interesting avenues in materials science.[14] Yet, although some promising options for controlling sequences have been reported,[15] experimental studies that evidence the beneficial effect of ordered monomer sequences on material properties are still rare. In this context, the paper of Meyer and co-workers highlights a clear correlation between momomer sequence and polymer properties. Their original strategy relies on the use of a segmer-assembly polymerization (SAP) approach.[16] Although this strategy is less efficient than ROP, molecular weights suitable for biomedical applications are easily accessible. Also, unlike ROP, this procedure leads to the formation of periodic copolymers and thus allows access to a variety of PLGA sequences

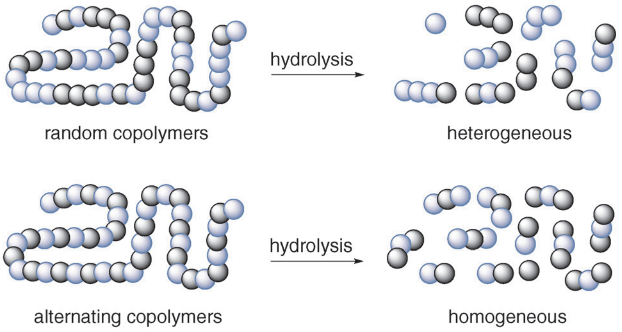
Hence Meyer and co-workers synthesized four PLGA samples with different sequence distributions (Scheme 1). An alternating poly(lactic-*alt*-glycolic acid), polyLG, was prepared with two molecular weights (16 and 26 kDa) by polycondensation of a dimeric precursor (Scheme 1). For comparison, a 1:1 random copolymer (R-ROP) was prepared by ROP of glycolide and *rac*-lactide and a random polyester (R-SAP) was produced from glycolic and stereopure L-lactic precursors by the condensation reaction of the dimeric precursors LG, GG, LL, and GL (Scheme 1). Then, the resulting copolymers were formulated using a standard emulsion method[17] allowing the preparation of microparticles in the range of 2 to 4 µm.[18] Remarkably, it was demonstrated that an alternating PLGA exhibits a dramatically different hydrolysis behavior compared to random analogues. In particular it was shown that the overall rate of degradation is substantially slower for the alternating polymer relative to the random analogues. Also, the sequence-controlled PLGAs degrade with a uniform profile: After an initial rapid drop in weight, the loss becomes remarkably linear. Even the initial weight loss is smaller than that observed for the random controls over the same period.

Moreover, the uniformity of the degradation of the sequence-controlled polymers relative to the random copolyesters was evidenced by the different thermal behavior observed for the polymers. For instance, in the case of polyLG (26 kDa), the glass transition at 50 °C shifts and broadens over time because of the decrease in molecular weight and the appearance of oligomers. However, the persistence of the transition attests that the material has not changed significantly. Also, the constancy of a weak melting transition at 80 °C is in accordance with the presence of crystalline sequenced oligomers, the composition of which does not alter over the period of hydrolysis. Since the sequence-controlled polyLG exhibits a more gradual and controlled degradation relative to the random analogues, the authors proposed that this behavior can be explained by the uniformity of the cleavage sites (Scheme 2). Indeed, the alternating PLGA presents only two types of hydrolytic sites, whereas the random copolymers have a wide variety of sites that would be expected to exhibit a more diverse range of reactivity rates with water. Hence, the linear degradation profile of the sequence-defined polymers seems controllable and therefore suitable for drug-release applications.



Scheme 1. Molecular structures of PLGA copolymers prepared either by SAP or by ROP. L = lactic unit, G = glycolic unit.

These promising results indicate that the control over polymer sequences is an effective strategy for tuning macromolecular properties. Based on this first proof-of-principle, tailor-made biodegradable polymers may be envisioned and



Scheme 2. Schematic representation of the hydrolytic degradation of PLGA samples containing either ill-defined (top) or ordered (bottom) comonomer sequences.

synthesized using SAP or related synthetic approaches.[19] Interestingly, these new results also emphasize that chemical diversity is not always needed for materials innovation. Obviously, even extensively studied polymers such as PLGA can lead to previously unidentified properties, if approached from a different angle. Thus, in terms of polymer chemistry, there is still room for innovation and improvements in highly regulated life science applications.

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