Perfect Polymers

Aylvin A Dias and Marc Hendriks at DSM Biomedical examine degradable polymers and their growing significance in controlled drug delivery

Drug delivery materials can help pharmacotherapy by use of polymers to stabilise medication during both production and sterilisation in order to obtain the desired pharmacokinetics, or to achieve locally controlled and targeted drug delivery (1).

Polymers are the preferred matrices for controlled drug delivery, because of the large degree of variables that can be used to tune release, in addition to their other functional properties. Polymers may be divided into linear (thermoplastic) or cross-linkable (thermoset) polymers. In both of these two classes, the composition of the polymer can be tuned further to give random, alternating or block copolymers. Yet another feature to control drug release is the molecular architecture that can be used to generate linear, branched, hyperbranched and comb-like polymers. Finally, polymers can be formulated either as linear polymer blends, linear-crosslinked polymer blends (semi-interpenetrating networks) and blends of cross-linked polymers (interpenetrating networks).

This toolbox of parameters that can be used to adjust and manipulate polymers means that there are numerous possibilities for developing solutions when drug delivery needs have to be reconciled against a number of other requirements related to shape, mechanical properties, biocompatibility, process and storage conditions.

When considering polymers for drug delivery applications, an important feature is the form that the polymer will have as a drug delivery matrix. Polymers can be fabricated into films, coatings, tablets, microspheres, nanoparticles, gels, complex 3D monoliths and components, as well as polymer prodrugs. The factors that govern the choice of form and polymer are often interdependent, as shown in Figure 2.

Table 1: Various synthetic and biosynthetic degradable polymers and those that have been reported for drug delivery applications (marked *).

Synthetic polymers	Biosynthetic polymers
Polyphosphazenes*	Collagen*
Polycyanaoacrylates*	Fibrin and fibrinogen
Poly(lactic acid), poly(glycolic acid) and copolymers thereof*	Gelatin*
Poly(hydroxyalkanoates)*	Poly(hydroxyalkanoates)
Polycaprolactone *	Cellulose*
Polyanhydrides*	Polysaccharides (chitosan, alginates)
Polydioxanones	Starch and amylose*
Polyorthoesters*	Polythioesters
Poly(propylene fumarates)	
Polyesteramides	
Polyamido amines*	
Polythioesters	

BIODEGRADABLE POLYMERS

Within polymer-based drug delivery, a major area of research and development is the design of biodegradable polymer systems. Biodegradable polymers allow for re-interventions related to removal of the drug delivery implant to be avoided, and thus minimise the risk of complications and adverse events associated with long-term implantable materials. However, it should be noted that these benefits have to be weighed against the potential risks caused by degradation products and intermediates.

Degradable polymers are divided into synthetic and biosynthetic polymers, as classified according to Table 1. Biosynthetic polymers can be derived from plant and animal sources or can be synthesised via microbial or enzymatic methods. The term 'biodegradable polymers' is rather all-encompassing, and often derivative; idioms are used interchangeably when describing such polymers. For the sake of clarity: degradable polymers are those whose bonds can be broken by chemical or enzymatic mechanisms. Degradation can occur by various

Figure 1: Molecular and architectural control levers to tune polymer properties

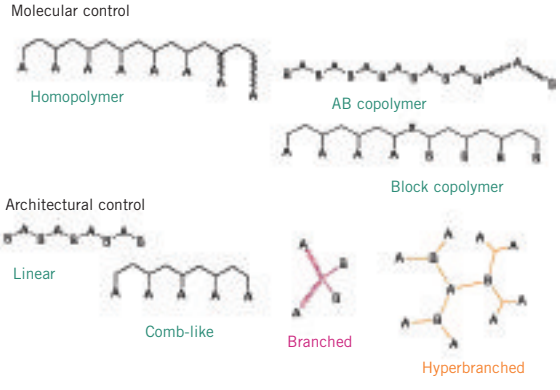
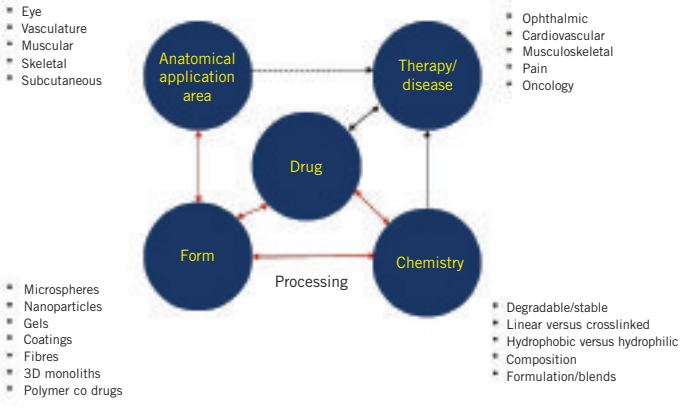


Figure 2: Factors that define the type and form that the polymer will take as a drug delivery matrix



mechanisms that can be classified according to Figure 3.

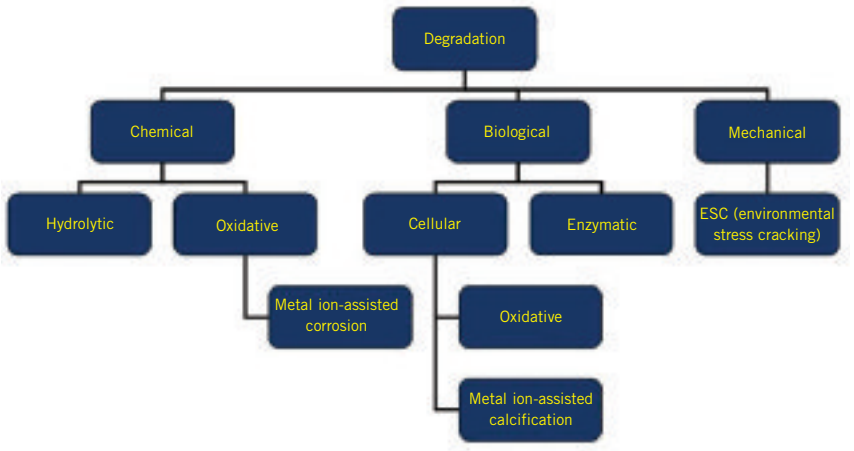
Erodible polymers are those in which the polymer mass or volume is lost by gradual dissolution of the polymer without actual degradation or cleavage of chemical bonds. Biodegradation refers to degradation of polymers in the presence of enzymes, cells or microorganisms. Mechanical degradation often occurs in conjunction with either biological or chemical degradation. It should be noted that, in most cases, degradation proceeds by multiple pathways and rarely via a single mechanism.

The manner in which degradation proceeds has an influence on drug release behaviour and can also influence the form that the polymer has to adopt. Surface versus bulk degradation is dependent on whether the degradation is via a hydrolytic mechanism (such as ester hydrolysis) or via an enzymatic mechanism. In the case of degradation by hydrolysis, bulk degradation takes place, but can be controlled by influencing the rate of water penetration and material swelling, which is governed by the hydrophilicity of the polymer. In the case of enzyme or cellular mediated biodegradation, the mechanism is mainly via surface degradation and erosion.

Enzymatic degradation can occur via enzymatic hydrolysis and enzymatic oxidation. These degradation mechanisms also occur as a result of the inflammatory foreign body response that occurs upon implantation of the polymeric drug delivery system. Enzymatic oxidation is the result of the phagocytic action of inflammatory cells. Enzymes typically involved in biodegradation are esterases, proteases, elastases and peroxidases.

There remains much debate on the pros and cons of hydrolytically degradable versus enzymatically or biodegradable polymers. It has been speculated that polymers which degrade by a chemical hydrolytic mechanism offer much more control over degradation than those that degrade via an enzymatic mechanism. This is on the basis that the inflammatory foreign body response in both patient and implant site are variable. However, polymers that enzymatically degrade give better control over drug release due to their surface erosion-based degradation behaviour. In addition, enzymatically degradable polymers have other advantages, such greater storage and packaging robustness when compared to hydrolytically degradable polymers, largely because of the latter's sensitivity to moisture.

Figure 3: Various degradation mechanisms that contribute to the degradation of polymers



Thus, in the design of degradable polymer-based drug delivery systems, it is worthwhile to evaluate both chemically degradable and enzymatically biodegradable polymers, and scrutinise the *in vitro* and *in vivo* testing results to define the optimal system to proceed with.

HYDROLYTICALLY DEGRADABLE POLYMERS

Polylactic acid (PLA) and copolymers with glycolic acid (PLGA) have been the most widely used materials for drug delivery. PLA- and PLGA-based systems are used as matrix reservoirs in which the drug is dispersed within the polymer materials and is released both by diffusion through the polymer and while the polymer degrades. Whereas these systems have demonstrated successfully their ability to deliver drugs in a controlled manner over prolonged periods of time, there are also significant limitations to further expansion of their use, related to items such as acidic degradation products and the relative hydrophobicity.

As a result of this, several companies have recently been designing hydrolytically degradable polymers using unique linking technologies. For instance, when PLGA oligomers are functionalised with a double bond containing end-groups, they can be photo-crosslinked. Photo-polymerisation makes effective, rapid and controllable crosslinking at low temperatures possible, providing handles to control the physical properties of the networks (such as hydrophilicity and mechanical behaviour) and alter degradation rates. With regard to the latter, by varying crosslink density, burst release of drugs can be minimised, as

Figure 4: Influence of crosslink density on drug release of the terazosin (vasolidator) from biodegradable crosslinked polyester urethane microspheres

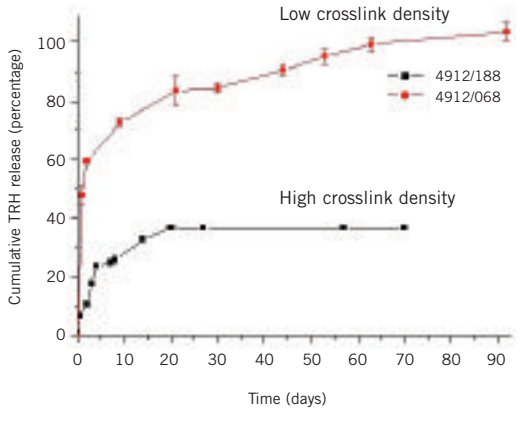
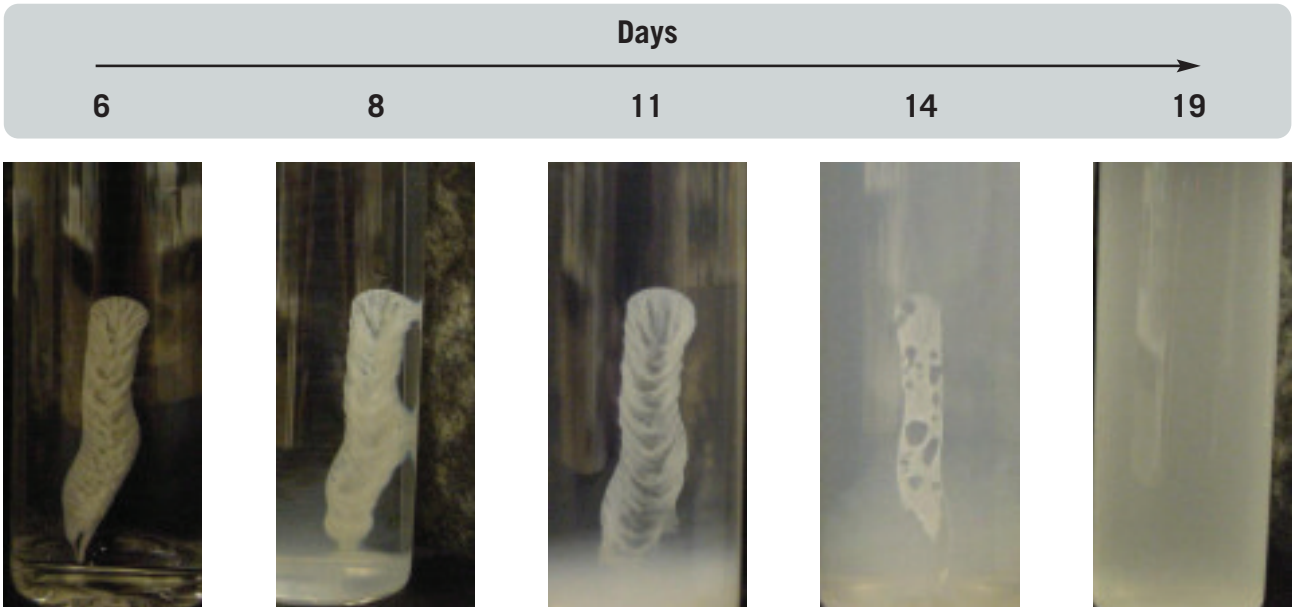


Figure 5: Bulk hydrolytic degradation of a polythioester in phosphate buffer at 37°C



demonstrated in Figure 4. At high crosslink density, the burst release of terazosin from crosslinked polyester urethane microspheres is reduced. The release of the remainder of the drug is then governed by the rate of degradation.

POLYTHIOESTERS

Polythioesters can be synthesised by chemical or biosynthetic pathways. The chemical approaches are:

- Reaction of thiols with acid or activated acids
- Ring opening polymerisation of thiolactides, thioglycolides and thioanhydrides

To date, biodegradable polythioesters that have been used mostly in surgical sealants and medical adhesive applications have been based on the first chemical route. Biosynthetic routes to polythioesters involve microbial biosynthesis from mercaptoalkanoates. However, exploitation of these materials has been mostly restricted to bulk plastic and packaging applications.

One of the reasons for the limited exploitation of polythioesters as degradable polymers for drug delivery has been the limited range of building blocks that are available. Recently however, a synthetic route to biodegradable polythioesters that offer improved flexibility in the ability to tune the properties of the polythioesters has been developed (2). This involves the reaction of thioic acid with unsaturated monomers and oligomers that are widely used in polymer chemistry. This provides a large number of building blocks that can be used to tailor the affinity of the polythioester for the drug, thereby controlling the drug release rate.

This approach allows the preparation of both linear and crosslinked polymers by either thermal or photochemical polymerisation, which provides a broad process window that allows thermally (proteins) or photochemically sensitive (select drugs) compounds to be processed.

The ability to tune both the building blocks provides a means to tune the polymer to achieve either bulk or surface degradation. An example of a bulk degrading polythioester is given in Figure 5.

AMINO ACID-BASED BIODEGRADABLE POLYMERS

With degradation comes the release of degradation products into the body, the toxicity of which should be taken into account when selecting building blocks used to synthesise a degradable polymer. Considering the nature of the resultant degradation by-products is as important as selecting building blocks for achieving the desired mechanical properties, polarity or particular diffusion characteristics of the polymer. This has led to the incorporation of biological building blocks in degradable polymers for medical applications, most notably the incorporation of amino acid-based building blocks. Amino acids have more advantages than simply being biodegradable and metabolisable building blocks: they also provide one or more

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Figure 6: An example of an aromatic non-natural diisocyanate that gives rise to a polyurethane polymer. This degrades to give a non-natural diamine and an amino acid-based diisocyanate, which gives rise to lysine as a degradation product

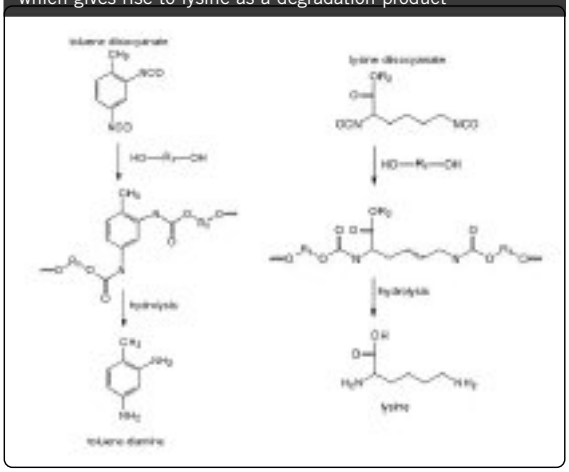
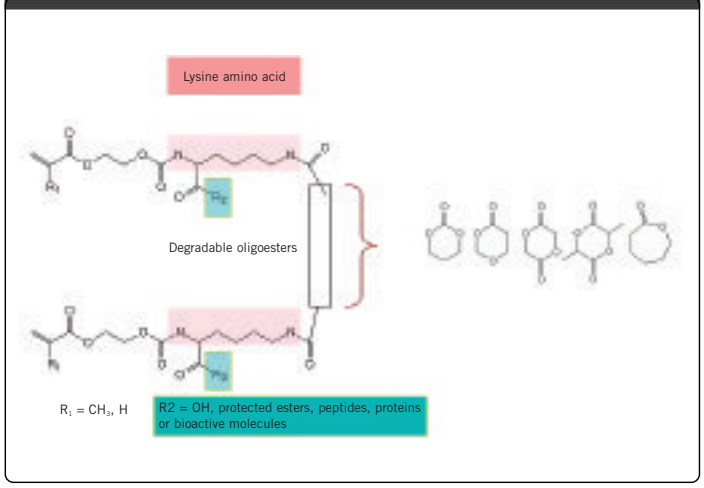


Figure 7: Cross-linkable biodegradable polysterurethane where the peptide may be further chemically modified for additional functionality



reactive sites that allow further modification of the polymer to tailor physicochemical properties, tune cellular response or serve as a handle for the chemical attachment of functional molecules, including drugs.

Initial development on amino acid-based polyamidoamines was complicated by their poor solubility and processability, as well as by their low level systemic toxicity upon degradation. To address these limitations, amino acid-based polyester urethanes, polyester amides and polycarbonates were developed.

POLYESTERURETHANES

The incorporation of amino acids in polyurethanes originally stemmed from observations that supposedly biostable polyurethanes were in fact degraded due to inflammation-derived enzymatic activity, thus giving rise to non-natural and often toxic amine-functional degradation products. This insight yielded the development of new amino acid-based isocyanates as building blocks of polyurethanes, an example of which, lysine diisocyanate, is depicted in Figure 6.

As mentioned before, amino acid-building blocks can provide one or more reactive sites that allow further modification of the polymer, as is exemplified schematically with a crosslinkable amino acid-based polyesterurethane in Figure 7. Such polymers can be further modified to introduce functionalities related to imaging or molecular targeting, but drugs can also be chemically conjugated to the polymer this way (3).

AMINO ACID-BASED POLYESTERAMIDES

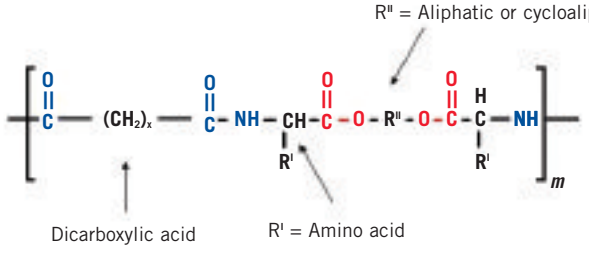
Amino acid based polyesteramides (4) are based on α-amino acids, aliphatic dicarboxylic acids and aliphatic α-ω diols as shown in Figure 8.

The presence of amino acid building blocks not only ensures safe degradation products, but also gives the resultant polymers protein-like physical properties. Variations of the three building blocks allow one to combine the beneficial properties of both polyamides and polyesters. Properties that can be tuned are hydrophilicity, biodegradation, biocompatibility and drug release. Among this class of polymers, it is the AA-BB heterochain polymers that offer the greatest versatility in terms of molecular level design to tailor drug release properties. These polyesteramides have been chemically modified and formulated to deliver a wide variety of small molecule drugs and biologics. Their main advantage is related to the fact that they predominantly degrade by an enzymatic mechanism; because of consequential surface erosion degradation, drug release mainly follows zero-order kinetics. As an example, paclitaxel has been delivered from a cross-linked phenylalanine-based polyesteramides hydrogel. *In vitro* release profiles of paclitaxel in PBS buffer and in chymotrypsin solution have been reported, as shown in Figure 9 (see page 22) (5).

Amino acid based polyesteramides have been extensively tested preclinically and have shown good tissue and blood compatibility. Currently, amino acid-based polyesteramide polymers are in human clinical studies as biodegradable coatings for drug eluting stents.

Apart from small molecule drug delivery, more recently, arginine-based polyester amides were developed for their use as non-viral gene delivery vehicles (6). A recent *in vitro* study looking at polyesteramide nanoparticles and their ability to transfect rat smooth muscle cells

Figure 8: A new generation of amino acid-based biodegradable polysteramides for drug delivery and other medical applications



revealed that, firstly, these polyester amides have a high degree plasmid DNA binding, and secondly, they could be used in a wide dosage range without adversely affecting cell morphology, viability and apoptosis. Rhodamine labelling of the plasmid confirmed cellular incorporation via endocytosis and revealed close to 100 per cent transfection efficiency. Despite these promising results, further optimisation of this delivery system is still required since most of the DNA remained in the endocytotic compartments. Nonetheless, the high cellular uptake combined with low toxicity suggests that polyester amides also show much promise for use in gene therapy.

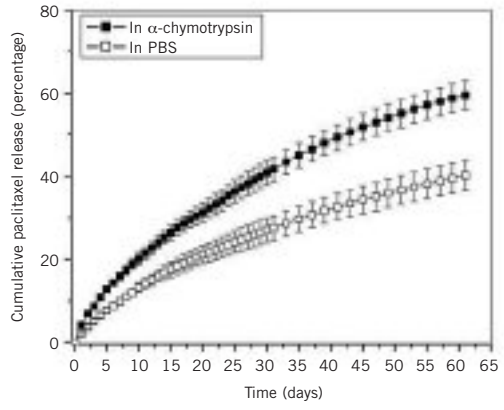
CONCLUSION

Amino acid-based biodegradable polymers represent the next frontier in the use of polymers for drug delivery. The amino acid building blocks reduce the risk of toxic degradation products and provide a means to continue to chemically modify these polymers with additional functionality, not least as a means of chemically binding drugs.

It seems very likely that both hydrolytically degradable polymers and enzymatically biodegradable polymers will be needed in a drug delivery company's armamentarium of solutions. There is no 'one size fits all' in drug delivery; each pharmaceutical compound, be it a small molecular weight drug or a large molecule biologic, brings a variation of challenges for designing an optimal polymer-based controlled release solution.

With both types of polymers in one's 'toolbox', the diversity provided in control of the chemistry, molecular architecture, formulation and processing methods to fabricate these polymers into a given form or shape, presents a unique opportunity to design drug delivery solutions around the drug and therapy, rather than the trial and error approach that has been pervasive thus far.

Figure 9: *In vitro* paclitaxel-release profiles from cross-linked phenylalanine-based polysteramide hydrogels in pure PBS buffer and in α-chymotrypsin solution at 37°C (5)



About the authors

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Marc Hendriks joined DSM Biomedical Materials in 2006, after serving for almost 15 years at Medtronic's Bakken Research Center in Maastricht, the Netherlands. In his current position as R&D/Technology Director, Marc takes care of DSM Biomedical's scientific R&D programme and the formation of technology strategies, including the alignment of these with business and intellectual property strategies. He also leads the development of strong cooperative relationships with key knowledge institutes around the world. Marc graduated from Eindhoven University of Technology in 1992, received his PhD in Chemical Technology from the same institute in 1996, and his *cum laude* MBA degree from the University of Maastricht Business School in 2005. Hendriks holds more than 25 US Patents, with several more pending, and has (co-)authored various publications and book chapters in the field of biomedical materials research. Email: marc.hendriks@dsm.com

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