Drug Delivery Technology®

May 2010 Vol 10 No 4 www.drugdeliverytech.com

A Decade in Drug Delivery

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

Poonam Velagaleti, PhD
A Novel Mixed Nanomicellar Technology to Treat Diseases of the Anterior & Posterior Segments of the Eye

Josef Bossart, PhD
Drug Delivery Products & Technologies, a Decade in Review

John Lynch
Validating Oral Delivery With Absorption Enhancing Technology

IN THIS ISSUE

INTERVIEW WITH MALLINCKRODT BAKER, INC.'S DIRECTOR GLOBAL MARKETING

HERMAN MITCHELL

FEATURING

SPECIALTY PHARMA Strategies For Business Development

CONTROLLED RELEASE

Amino Acid-Containing Degradable Polymers & Their Potential in Controlled Drug Delivery

By: Aylvin A. Dias, PhD, MSc, and Marc Hendriks, PhD, MBA

ABSTRACT

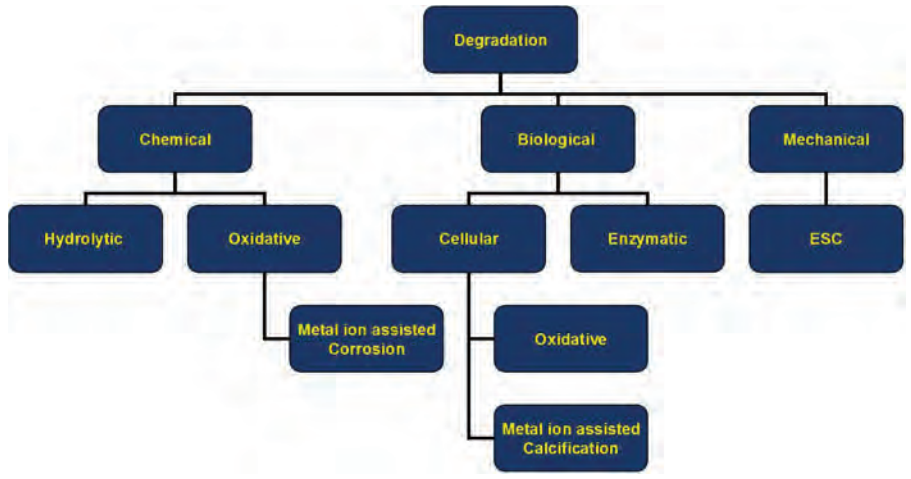
Biodegradable polymers allow for avoidance of re-interventions related to removal of the drug delivery implant, and therefore minimize risk of complications and adverse events associated with long-term implantable materials. However, it should be noted that these benefits have to be weighed against potential risks caused by degradation products and intermediates. The manner in which degradation proceeds has an influence on drug-release behavior and can influence the form the polymer has to adopt. Surface versus bulk degradation is dependent on whether the degradation is via a hydrolytic mechanism (eg, ester hydrolysis) or via an enzymatic mechanism. In case of degradation by hydrolysis, bulk degradation takes place, but can be controlled by exerting control over 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 hydrolytic or oxidative mechanisms. These degradation mechanisms can occur as a result of the inflammatory foreign body response that occurs upon implantation of the polymeric drug delivery system. Enzymes typically involved in biodegradation are esterases, proteases, elastases, and peroxidases. Thus, in the design of degradable polymer-based drug delivery systems, it is worthwhile evaluating both chemically degradable and enzymatically biodegradable polymers and scrutinize the in vitro and in vivo testing results to define the optimal system.

INTRODUCTION

Drug delivery materials to aid pharmacotherapy utilize polymers to stabilize medication during production and sterilization to obtain desired pharmacokinetics and/or achieve locally controlled and targeted drug delivery.[1]

Polymers are preferred matrices for controlled drug delivery because of the large degree of variables that can be used to tune release as well as achieve other functional properties. Polymers may be divided into linear (thermoplastic) or cross-linkable (thermoset) polymers. In either of these two classes, there is further opportunity to tune the composition of the polymer 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,

FIGURE 1



Various mechanisms that contribute to the degradation of polymers.

hyperbranched, and comb-like polymers. Finally, polymers can be formulated either as linear polymer blends, linear-cross-linked polymer blends (semi-interpenetrating networks), and blends of cross-linked polymers (interpenetrating networks).

This tool box of parameters that can be used to adjust and manipulate polymers offers numerous possibilities to develop solutions when drug delivery needs have to be reconciled against a number of other requirements related to shape, mechanical properties, biocompatibility, process, and biostability.

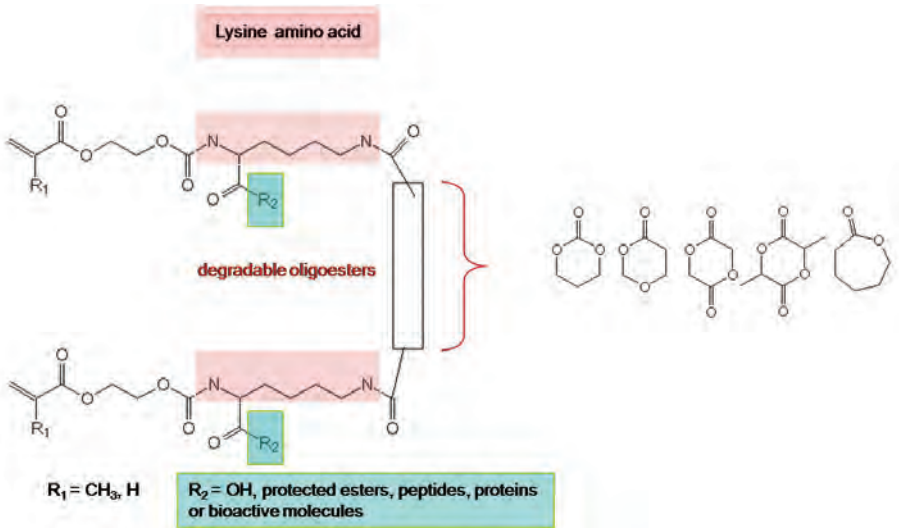
When considering polymers for drug delivery applications, an important feature is the form the polymer will have as a drug delivery matrix. Polymers can be fabricated into films, coatings, tablets, microspheres, nanoparticles, gels, complex 3-D monoliths, and components, as well as polymer prodrugs. So development of an eventual drug delivery matrix is a delicate interplay between the drug-polymer compatibility and the form required for the selected method of administration.

BIODEGRADABLE POLYMERS

In polymer-based drug delivery, a major area of research and development is on design of biodegradable polymer systems. Biodegradable polymers allow for avoiding re-interventions related to removal of the drug delivery implant, and thus minimize 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 potential risks caused by degradation products and intermediates.

The term biodegradable polymers is rather all-encompassing, and often, derivative idioms are interchangeably used when describing such polymers. For the sake of clarity, degradable polymers are those in which bonds can be broken by chemical or enzymatic mechanisms.

FIGURE 2



Cross-linkable biodegradable polyesterurethane in which the amino acid side-group can be further chemically modified for additional functionality.

Degradation can occur by various mechanisms that can be classified according to Figure 1.

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 biological and/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 behavior and can influence the form the polymer has to adopt. Surface versus bulk degradation is dependent upon whether the degradation is via a hydrolytic mechanism (eg, ester hydrolysis) or via an enzymatic mechanism. In case of degradation by hydrolysis, bulk degradation takes place but can be controlled by exerting control over 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 that degrade via 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 provide for better control over drug release due to their surface erosion-based degradation behavior. In addition, enzymatically degradable polymers offer advantages in that they exhibit greater storage and packaging robustness when compared to hydrolytically degradable polymers, largely because of the latter's sensitivity to moisture.

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

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 drug is dispersed within the polymer materials and is released both by diffusion through the polymer and as the polymer degrades.

Whereas these systems have successfully demonstrated the ability to deliver drugs in a controlled manner over prolonged periods of time, they are associated with significant limitations for further expansion of their use, related to items such as acidic degradation products, the relative hydrophobicity, etc.

The follwing presents the next evolution in biodegradable materials that are prepared via synthetic incorporation of amino acid building blocks. The incorporation of amino acid building blocks provides not only a natural degradation end product but the possibility to address the limitations of the conventional degradable polymers.

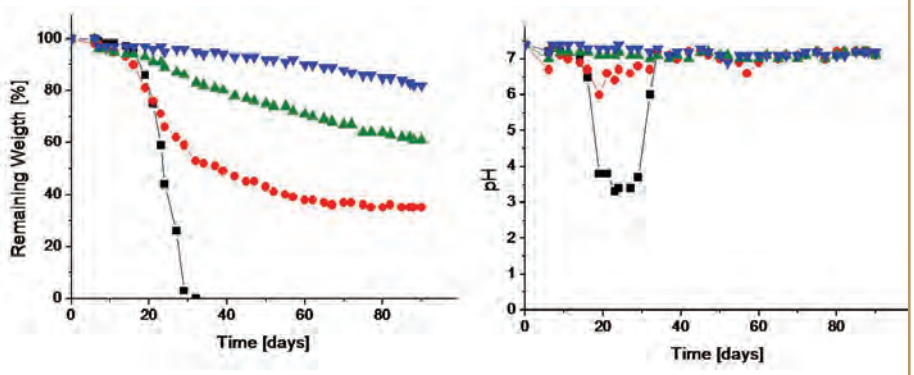
A thermoset degradable polymer (polyesterurethane) and a thermoplastic polyester amide both bearing amino acid building blocks and their degradation characteristics are described.

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 synthesize a degradable polymer. The nature of the resultant degradation by-products is as important as selecting building blocks for achieving 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 has been the incorporation of amino acid-based building blocks. Amino acids offer more than being biodegradable and metabolizable building blocks; they may moreover provide one or more 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 their low level systemic toxicity upon degradation. To address these limitations, amino acid-based polyester urethanes, polyester amides, and polycarbonates were developed.

FIGURE 3

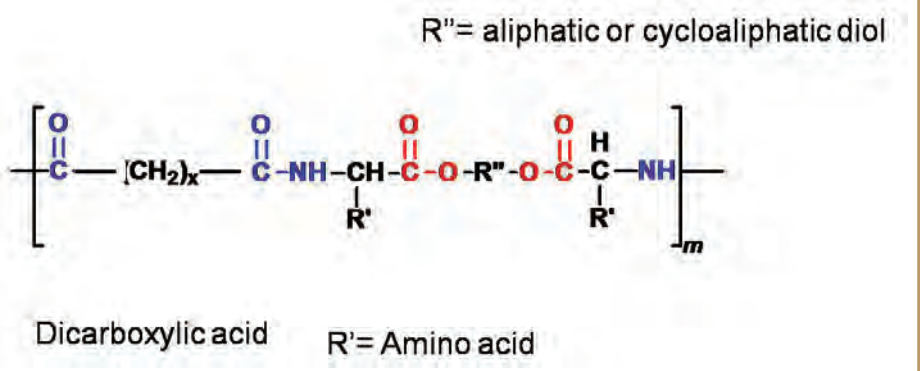


Degradation of polyester urethanes showing reduced pH drop compared to analogous non-lysine-bearing hydroxyester-based microspheres, and the varying degradation rates obtained by varying the hydroxyester backbone.

POLYESTERURETHANES

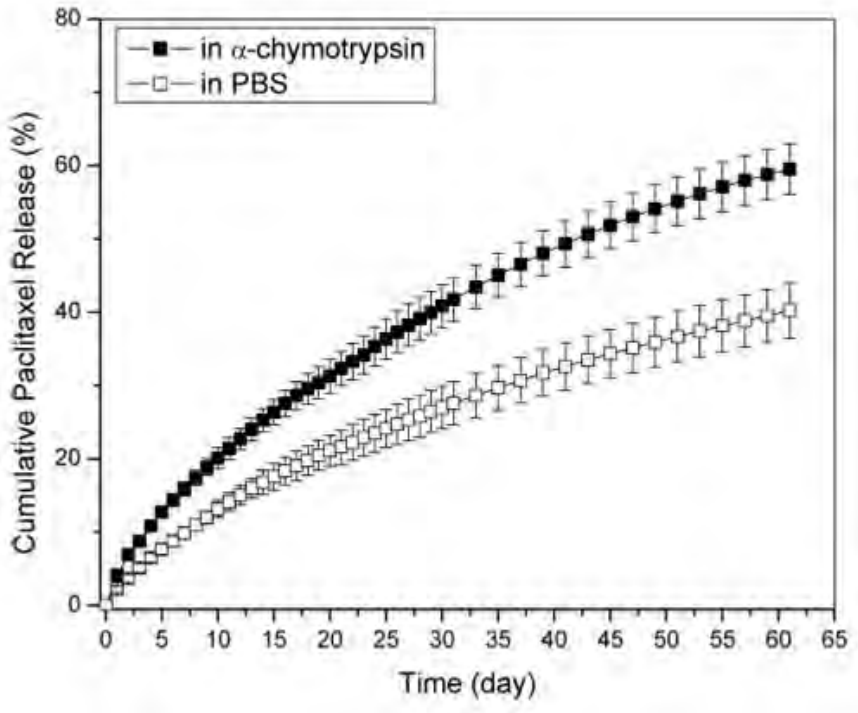
The incorporation of amino acids in polyurethanes originally stemmed from observations that supposedly biostable polyurethanes were in fact degraded due to inflammation-derived enzymatic activity, thus generating non-natural and often toxic amine-functional degradation products. The isocyanates used to produce the polyurethanes resulted in non-natural amine degradation products and triggered the development of isocyanates that generated natural amine-based degradation by-products. These were most notably the use of butanediisocyanate and

FIGURE 4



A new generation of amino acid-based biodegradable polyesteramides for drug delivery and other medical applications.

FIGURE 5



In vitro paclitaxel release profiles from cross-linked phenylalanine-based polyesteramide hydrogels in pure PBS buffer and in an alpha-chymotrypsin solution at 37°C.[5]

lysine diisocyanate that generated putrescein and lysine, respectively, as degradation end products of the resultant polymer.

Furthermore, amino acid building blocks can provide one or more reactive sites that allow further modification of the polymer, such as is exemplified schematically with a cross-linkable amino acid-based polyesterurethane in Figure 2. Such polymers can be further modified to introduce functionalities related to imaging or molecular targeting, but also, drugs can be chemically conjugated to the polymer this way.[3]

One of the main advantages that can be attributed to these amino acid-based polyurethanes is the reduced pH drop upon degradation. This reduced pH drop has been demonstrated in both coatings and microspheres. Cross-linked 40- to 60-micron microspheres prepared by emulsion photopolymerization were degraded by hydrolysis in phosphate-buffered saline are shown in Figure 3. The results show that the lysine-containing lactide glycolide-based urethane microspheres result in a lower pH drop compared to the analogous lactide glycolide microphores. Furthermore, by changing the hydroxyester backbone, it is possible to change the degradation rates while maintaining the same cross-link density, also shown in Figure 3.

AMINO ACID-BASED POLYESTERAMIDES

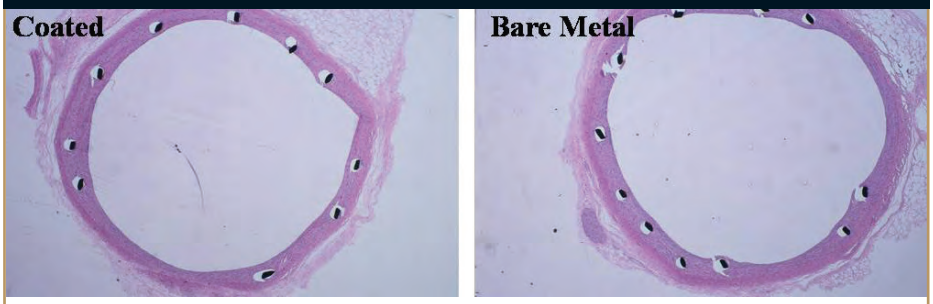
Amino acid-based polyesteramides are based on alpha-amino acids, aliphatic dicarboxylic acids, and aliphatic alpha-omega diols as shown in Figure 4.[4]

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, and biocompatibility as well as 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 they predominantly degrade by an enzymatic mechanism; because of consequential surface erosion degradation, drug release follows mainly 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 5.[5]

These amino acid-based polyesteramides have been tested extensively and showed good tissue and blood compatibility in applications like coatings for stents. As an example, the in vivo biocompatibility was tested in porcine coronary arteries by comparing the polymer-coated stents with bare metal stents in pigs. These porcine preclinical trials reveal that the polyesteramide-coated stents had similar injury and inflammation scores to a bare metal stent.[6] Exemplary photomicrographs of the porcine coronary arteries 28 days following implantation with a polyesteramide-coated stent and a bare metal stent are shown in Figure 6.

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.[7] A recent in vitro study looking at polyesteramide nanoparticles and their ability to transfect rat smooth muscle cells revealed that first, these polyester amides have a high degree of plasmid DNA binding, and second, they could be used in wide dosage ranges

FIGURE 6



Photomicrographs of the porcine coronary arteries 28 days following implantation with a polyesteramide-coated stent and a bare metal stent.[6]

without adversely affecting cell morphology, viability, and apoptosis. Rhodamine labeling of the plasmid confirmed cellular incorporation via endocytosis and revealed close to 100% transfection efficiency. These are promising results, but further optimization of this delivery system is still required because 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.

SUMMARY

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 means to further chemically modify these polymers with additional functionality not least as a means to chemically bind drugs.

It is our strong belief that hydrolytically degradable polymers as well as 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 available, the diversity provided in control over chemistry, molecular architecture, formulation, and processing methods to fabricate these polymers into a given form or shape presents one a unique ability to design drug delivery solutions around the drug and therapy rather than the trial-and-error approach that has been pervasive thus far.

ACKNOWLEDGEMENTS

The authors would like to thank Drs. Z. Gomurashvilli and B. Turnell for their assistance on the polyesteramides, B. Plum and T. Handels for their assistance on the polyesterurethanes.

REFERENCES

1. Ratner BD, Hoffmann AS, Schoen FJ, Lemons JE. Biomaterials science. 2nd ed. An Introduction to Materials in Medicine. Elsevier, ISBN -10: 0-12-582463-7; 2004.
2. Dias AA, Petit AA. Microparticles comprising a crosslinked polymer. WO 2007/107358 A1;2007.
3. Dias AA, Boerakker M, Nijenhuis AJ. Polymers comprising polythioester bonds. WO 2007 /028612 A;2007.
4. Gomursahvili Z, Zhang H, Da J, Jenkins TD, Hughes J, Wu M, Lanbert L, Grako KA, Defife KM, Macpherson K, Vassilev V, Katsarave R, Turnell WG. From drug eluting stents to biopharmaceuticals: poly(esteramide) a versatile new bioabsorbable biopolymer. ACS Synposium series 977; Polymers for Biomedical Applications. Mahapatro A, Kulshresthra AS, eds. ISBN 978-0-8412-3966-1; 2008.
5. Guo K, Chu CC. Controlled release of paclitaxel from biodegradable unsaturated pol(ester amide) polytheylene glycol diacrylate hydrogels. J Biomater Sci Polymer Edn. 2007;18:489.
6. Lee SH, et. al. In-vivo biocompatibility evaluation of stents coated with a new biodegradable elastomeric and functional polymer. Coronary Artery Dis. 2002;13:237-241.
7. Yamanouici D, Wu J, Lazar AN, Craig Kent K, Chu CC, Liu B. Biodegradable arginine based poly(esteramides) as non viral gene delivery reagents. Biomater. 2008;29:3269.

BIOGRAPHIES

Dr. Aylvin A. Dias is R&D Manager at DSM Biomedical, Geleen, The Netherlands, where he currently manages research in drug delivery and tissue engineering for ophthalmic and cardiovascular applications. He earned his BSc and PhD in Biological and Polymer Chemistry at the University of Kent at Canterbury. In 1994, after his PhD, he worked at Total Chemie on materials for food packaging. In 1996, he joined DSM in the Netherlands. In the first 5 years, he worked on coating resins, optical fibre, and stereolithographic materials. In the subsequent 4 years, he established the biomedical research program and thereby was one of the founding fathers of DSM Biomedical. He managed the start-up of an application development laboratory in medical coatings. The research program lead to the launch of two new medical coatings, a lubricious coating, and an antimicrobial coating. Dr. Dias has over 30 patents and 20 peer-reviewed publications to his credit.

Dr. Marc Hendriks is R&D and Technology Director at DSM Biomedical, Geleen, The Netherlands, where he provides scientific and strategic leadership in establishing the company's R&D portfolio and ensuring it encompasses the development of novel polymeric materials and material technologies for the enhancement of existing and creation of new biomedical products or therapies. He joined DSM Biomedical in 2006 after spending 15 years at Medtronic's Bakken Research Center in Maastricht, the Netherlands. During his time with Medtronic, Dr. Hendriks served in various roles, including Research Director, where he led various R&D projects on surface modification technologies, drug delivery, and cross-linking technologies for bioprosthetic tissues; Manager of Biomaterials Technology; Scientist, and Engineer. He holds over 25 US patents, with several more pending. He has also co-authored over 30 journal articles and various book chapters in the field of biomedical materials research. Dr. Hendriks earned his PhD and MSc from Eindhoven University of Technology and his MBA from University Maastricht Business School.