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Evolution Of A Novel Polymer To Overcome Limitations In Sustained Drug Delivery In Ophthalmology

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Part 2: Developments Inspired By The Challenges In Ophthalmic Drug Delivery

In Part 1 of this article series, a brief history of the development of Polyester Amide biodegradable polymers was introduced. DSM Biomedical's TheraPEA™ family of biodegradable Polyester Amide polymers was originally developed to address the sophisticated requirements of biodegradable coatings on cardiovascular devices, such as Drug Eluting Stents (DES). The unique features of these polymers to promote a natural healing response[1] and enzyme-mediated surface bio-erosion mechanism have contributed to the development of a DES with outstanding performance. Svelte Medical Systems leveraged the TheraPEA™ platform in developing their DISCREET Bioresorbable Drug Coating used to control the delivery of sirolimus. Based on data from a clinical study involving more than 1600 patients, the device showed no difference to a control DES with regards to all primary and secondary endpoints with stent thromboses rates less than 0.4% after 1 year.[2] The proven success of the TheraPEA™ polymer as a biodegradable, drug eluting coating for cardiovascular devices triggered the interest in its applicability in other areas such as ophthalmology, a therapeutic area with a high demand for drug delivery solutions.

Blindness and vision impairment poses an enormous global social, emotional and financial burden. Globally, at least 2.2 billion people have a near or distance vision impairment. In at least 1 billion – or almost half – of these cases, the vision impairment is considered avoidable if treated.[3] A key success factor in any eye therapy is the application of the proper dosage of medicine in the appropriate location over time. Diseases of the retina require delivery of medicine via frequent local needle injections that may cause patients significant discomfort and undesired side-effects. The eye physiology (retina-blood barrier) and the rapid clearance of the medicine from the intravitreal space are often bottlenecks in the development of new therapies. Biodegradable, locally applied drug delivery systems, however, are often not just an improvement, but also an enabler in the treatment of chronic eye conditions.

The first step in exploring the potential of TheraPEA™ polymers as drug delivery vehicles for ophthalmology was to optimize the material properties to the specificity of the eye physiology. While the enzyme mediated bio-erosion of TheraPEA™ PEA III AcBz is an essential feature for the coating integrity and performance on a DES, the biodegradation in the eye vitreous requires a different characteristic. The eye however is one of the immune privileged sites in the body, meaning the inflammatory responses to foreign objects is minimized. While the immune privileged feature defends the eye function, it presents a challenge for the bio-erosion of an enzymatically degradable material where the foreign body response is essential for triggering biodegradation. As result, in ophthalmic applications, a hydrolytically degradable drug delivery carrier would be preferred. Fortunately, the molecular structure of TheraPEA™ allows an elegant handle on the polymer degradation mechanism while still preserving material biocompatibility and drug release properties.

TheraPEA™ PEA III AcBz

TheraPEA™ PEA III X

Scheme 1: Chemical structure of the PEA polymers. Enzymatically degradable: TheraPEA™ PEA III AcBz and hydrolytically degradable: TheraPEA™ PEA III X polymers.

L-lysine is utilized as a di-amino building block in TheraPEA™ polymers (Scheme 1) and provides a carboxyl functionality pendant to the polymer chain. When the carboxyl functionalities are converted to benzyl esters (as in TheraPEA™ PEA III AcBz), the polymers degrade enzymatically. When a partial substitution of the benzyl esters occurs and free carboxyls are produced, a new material property is introduced – hydrolytic degradability[4]. By controlling the ratio between the free and esterified carboxyl groups, a fine tuning of the degradation rate can be achieved to result in an optimal resorption time.

Scheme 2: Biodegradability of TheraPEA™ PEA III X. Excellent correlation noted between in vitro and in vivo data.

The biodegradation of the novel polymers was studied extensively both *in vitro* and *in vivo* (rabbit model) to confirm the hydrolytic degradation mechanism and has demonstrated an excellent correlation between the polymer degradation kinetics *in vitro* and *in vivo*[5] (Scheme 2). This correlation, combined with excellent biocompatibility and a high level of barrier properties, highlights TheraPEA™ polymers as a promising excipient for drug delivery solutions in ophthalmology.

In future articles, we will continue our introduction of DSM Biomedical's TheraPEA™ polymer platform by sharing highlights of the research on material tolerability and biocompatibility. Want to learn more? Connect with us at DrugDelivery.Biomedical@dsm.com or visit DSMBiomedical.com.

References:

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[2] D. Kereiakes at al., Circ Cardiovasc Interv., (2021) 879-892

[3] WHO fact sheet, blindness and visual impairment, October 2022. https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment

[4] DSM Internal reports

[5] DSM Internal reports