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

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Part 1: A Brief History Of The Development Of Polyester Amide (PEA) Polymers

Drug delivery systems can enable an improvement in a drug's therapeutic efficacy while minimizing unwanted effects. These systems are often composed of a polymeric vehicle containing an active pharmaceutical ingredient (API) that is designed to release at the site of disease or trauma. Recognizing opportunities for design improvements, an evolution of degradable polymers occurred from aliphatic polyesters to nitrogen bearing biomaterials such as polyurethanes, polyester amides, and polyureas. This evolution was needed to provide biomaterials which demonstrate improved control over degradation, material, and drug release properties. Naturally, this has also led to hybrid material designs, such as combining the biodegradability of polyesters with the excellent biocompatibility and more hydrophilic nature of polyamides.

Polymers comprising both ester and amide linkages in the polymer chain were reported for the first time in the work of Carothers and Hill from 1932[1]. The publication describes a polymeric material that resulted from heating together aminocarpoic acid, dicarboxylic acid and glycol. The authors aimed at obtaining materials with properties between those of low-melting-point and high-solubility polyesters and high-melting-point and low-solubility polyamides. Until 1955, publications on these polyester amides (PEA) were predominantly found in patent literature rather than in academic communications, which implies that this hybrid class of polymers has been considered industrially relevant for more than 70 years! Already then, PEAs had been prepared by different equilibrium polycondensation approaches reacting dicarboxylic acids (or derivatives) with aminoalcohols; diacids with diamines and glycols; aminoalcohols with aminoacids; aminoalcohols and hydroxycarboxylic acids. More complex monomers for preparation of PEAs have been reported as well. For example, the melt condensation of a diol with amide groups containing di-carboxylic acid[2].

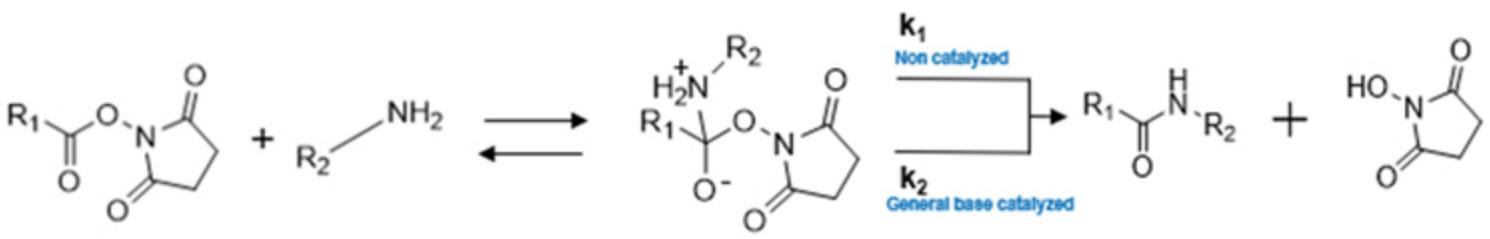

Figure 1: PEA Condensation Process, G. W. Cline, S. B. Hanna., J. Org. Chem. 1988, 53, 3583

A key step in the commercial development of the PEA material is the solution polycondensation method (SPC) published by Katsarava in 1994[3]. The preparation of L-amino acid-containing polymers by SPC was mainly carried out via use of activating groups (hence, often termed as active polycondensation) by reacting di-p-toluenesulfonic acid salts of bis-(L-amino acid) diesters with di-p-nitrophenyl esters of diacids. This active polycondensation approach is remarkably versatile in that:

< >the backbone structure of resulting polyester amides can be tuned by the starting diacids (X) or diols (Y), in which either aliphatic or aromatic and saturated or unsaturated backbones with varying lengths of alkylene units can be prepared; the choice of L-amino acids will lead to degradable polymers with vastly different side groups such as alkyl, amine, and carboxyl functions. In addition, SPC can be carried out under mild conditions without the use of toxic catalysts, making it a highly attractive synthetic approach for degradable medical grade polymers.

In the next decade, DSM further improved this innovative polymerization method to enable the commercial manufacturing of a new family of biodegradable PEAs that combines natural and synthetic building blocks. Specifically, the DSM PEA technology combines α-amino acids, aliphatic dicarboxylic acids and aliphatic α-ω diols into functional building blocks that form AA–BB hetero-chain polymers in a polycondensation process. This advanced method allows polymerization at low temperature (65 °C), affording side-product free polycondensates and predictable degradation products[4]. The manufactured polymers are obtained as amorphous white material of molecular weight (Mn) in the range of 40,000 to 75,000 Dalton. The glass-transition temperature of the polymers varies with the selection of the monomers and is typically in the range of 50 to 70 ^{0}C[6]. The hybrid nature of PEAs provides exceptional shelf-life stability. Dedicated studies have confirmed that these biodegradable materials preserve their functional properties at both refrigerated and room temperature storage conditions for a minimum of five years.

The incorporation of amino acid-based building blocks provides one or more reactive sites that allow further modification of the polymer to tailor physicochemical properties, tune cellular response or to form polymer-drug conjugates. One benefit is the excellent solubility of these polymers in low molecular weight hydrocarbon alcohols (like methanol or ethanol). This flexibility in solubility is an advantage for polymer processing and formulation development, allowing more versatility in solvent selection and the use of a friendlier solvent for the formulator. Building block selection allows control over polymer biodegradation rate and degradation mechanism. That is, the polymers can be designed to degrade predominantly by either hydrolytic or enzymatic mechanisms. The enzymatic degradation mechanism is a unique feature of these polymers, which drives degradation through surface erosion. This means that while the polymer is degrading, its mechanical and barrier properties are preserved longer than with traditional biomaterials. Contrary to typical polymer drug carriers that release their content and degrade by falling apart (akin to a sugar cube in water), the PEAs “dissolve” slowly from the surface inward (akin to a candy cane), providing a higher integrity. This feature is of particular importance for the development of drug eluting coatings, such as intravascular stents, with which these novel PEAs have seen their first commercial application[5].

In the next article, we will continue this introduction to DSM's PEA polymer technology platform by sharing how it has been further developed for application in ophthalmology. Want to learn more? Connect with us at DrugDelivery.Biomedical@dsm.com.

References

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[6] Data available on file at DSM Biomedical.