Poly(ester amide)s: recent insights into synthesis, stability and biomedical applications

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Poly(ester amide)s (PEAs) are very important synthetic polymers with applications in many fields. The combination of the thermal and mechanical properties of polyamides with the biocompatibility and biodegradability of polyesters affords biomaterials of great interest especially for tissue engineering and drug delivery. Recent advances are elucidated herein with focus on synthesis and applications.

1 Introduction

Polyamides (PAs) and polyesters (PEs) are two of the most important polymer classes.1–3 PAs (monomers are connected via amide bonds) were established in the 1930’s with Nylon 6,6 and Nylon 6, and meanwhile a variety of fossil- and bio-based polyamides exist for applications in many fields (commodities, automotive, biomedical).3 Polyesters (monomers are connected via ester bonds) are frequently used as mass plastics for consumables, and meanwhile also for special biomaterials in medicine due to their good mechanical properties, ability to hydrolyze and biocompatibility.1,2

Poly(ester amide)s (PEAs) are prominent polymers, which can combine the stiffness and the excellent thermal and mechanical properties of polyamides with the biocompatibility and biodegradability of polyesters.4,5 They have been investigated and applied as biodegradable plastics for consumables (Bayer, tradename BAK®).6 The first PEAs were synthesized in 1932 by Carothers from diacids, diols and diamines.7 Due to these properties, PEAs are an emerging group of very interesting polymers,8 which have gained an increasing impact within the past few years, especially for medical applications in drug delivery systems, hydrogels, non-viral gene carriers, smart materials, composites and adhesives and especially as scaffolds for tissue

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engineering (TE). Many synthetic polymers have been described for medical applications, e.g. for implants, drug delivery or TE, and though also metals, ceramics or glasses can be used as TE scaffolds, polymers have meanwhile gained most attention for this due to their versatility of properties, which provides a basis for replacement, restoration and regeneration of tissue structure and/or function. Based on their structures, the desirable alteration of hard and soft segments and a tunable amide bond/ester bond ratio, PEAs are very interesting in particular for suchlike applications. Many parameters like this ratio and also the microstructures play a role for their stability and degradation behavior. If the ester content is high, the degradability is favored, and if the amide content is high, the stability against degradation as well as thermal stability are the predominant properties. A lower degradation rate and lower pH drop compared to polyesters are additional important features of PEAs in view of their medical applications. This article describes the basic concepts of PEA synthesis and applications with focus on recent advancements.

2 General aspects of poly(ester amide) synthesis

PEAs can be synthesized via ring-opening polymerization (ROP) of cyclic monomers or via polycondensation of linear monomers. For instance, copolymers of α-hydroxy acids and α-amino acids, polydepsipeptides (PDPs), can be obtained by polymerization of morpholino-2,5-diones (synthesized by cyclization of amino acid derivatives) with different catalysts (e.g. SnOct₂) and enzymes (lipases) (Scheme 1A). Furthermore, copolymerization of lactams and lactones via ROP can afford different PEAs (Scheme 1B). Polycondensation can further be classified into melt polycondensation, interfacial polymerization, solution polycondensation and solid/liquefied state polycondensation. Thus, depending on the exact procedures and the exact monomers used, regular, segmented or random PEAs can be synthesized – the respective reaction design can be complex, and the corresponding details have been reviewed elsewhere in detail. In brief, regular PEAs can e.g. be synthesized by thermal polycondensation of a diol and a diamide-diestier (Scheme 1C), while segmented PEAs are preferably prepared by reaction of diesters with diamide diol units (Scheme 1D). A "classical" way to obtain random PEAs is a thermal polycondensation of diols, dicarboxylic acids and amino acids (Scheme 1E). PEAs can also be afforded by e.g. polycondensation of diamide-diols with a dicarboxylic acid (dichloride) (Scheme 1F) or via reaction of chloroacetate with amino acids (via metal halide salt; Scheme 1G). Furthermore, PEAs can be obtained by other solution polymerizations via reaction of an activated dicarboxylic acid (e.g. p-nitrophenol as the activating group) with an ester diamine salt or a diester diamine salt (e.g. with pTSA; Scheme 1H). In a similar, further developed strategy for PDP synthesis, the p-toluene sulfonic acid salt of bis-α-(l-amino acid)-α,ω-alkylene diesters (BAAD) is made to react with nitrophenyl esters derived from α-hydroxy acids. The latter can be obtained in two steps, the reaction of an α-hydroxy acid with a diacetyl chloride, affording a dicarboxylic acid (1), and reaction of this acid with p-nitrophenol (in the presence of thionyl chloride and pyridine) (Scheme 1I). Another important strategy to obtain PEAs is the interfacial polycondensation of p-toluenesulfonic salts of α-amino acids (or derivatives) and macrodiacyl chlorides from α-hydroxy acids.
3 Recent progress in poly(ester amide)s based on amino acids

Structure variety, biocompatibility, functionalities and stereo-information of α-amino acids, which are in nature building blocks for peptides and proteins, make these components highly interesting for biomaterials and thus for PEAs. Supplemented PEA mats showed upregulation of PDGFRβ dependent on the concentration and cell type. With regard to morpholino-2,5-dione polymerization (see section 2), lipase-catalyzed ROP of isoleucine-based 3(S)-sec-butylmorpholine-2,5-dione (BMD) was described to afford poly(BMD), an optically active PEA with specific stereoregularity (dyads) (Fig. 1B). Different lipases and parameters (enzyme concentration, time, temperature) were screened, and conversions up to 70% and molecular weights from 5500–10 700 were obtained. It was found that water content is an important factor for the control of both conversion and molecular weight: the increasing water content results in enhanced polymerization rates while the MW of poly(BMD) decreases.

Fig. 1 PEAs based on (A) L-Phe; (B) on BMD and (C) tetraaniline-grafted PEAs based on Leu and Glu. Reprinted with permission from ref. 33. Copyright (2012) American Chemical Society. (D) PEAs with pendant C=C double bonds; (E) PEAs derived from amino acids and dianhydrohexitols.

phantom text
Unsaturated PEAs based on other compounds have also been described (which can also be further functionalized via their double bond; see later). Sequential PEAs derived from glycine, diols and dicarboxylic acids were also synthesized by a two-step method that involved a final thermal polyesterification. Similar PEAs were prepared from ε-lysine as the diamine unit. The possibility of linking pharmacologically active compounds to the carboxylic groups of lysine makes these materials even more interesting e.g. for drug delivery systems. Phe- and Lys-based PEAs were also investigated in terms of endothelial cell adhesion and inflammation in vitro, and arginine-based PEAs have been used as non-viral-gene delivery reagents. PEAs based on the chloroacetate derivatives of an ω-amino acid or a diamine are similar examples. With regard to blood and the cellular metal. For copolymerization of CLa or PL with CLo and PL with CLo or preparation of P(CLo-δ-valerolactone and, respectively, the lactam family. Therefore, their double bond; see later). Sequential PEAs derived from glycine, diols and dicarboxylic acids were also synthesized by a two-step method that involved a final thermal polyesterification. Similar PEAs were prepared from ε-lysine as the diamine unit. The possibility of linking pharmacologically active compounds to the carboxylic groups of lysine makes these materials even more interesting e.g. for drug delivery systems. Phe- and Lys-based PEAs were also investigated in terms of endothelial cell adhesion and inflammation in vitro, and arginine-based PEAs have been used as non-viral-gene delivery reagents. PEAs based on the chloroacetate derivatives of an ω-amino acid or a diamine are similar examples.

Poly(ester amide)s based on ε-caprolactone and ε-caprolactam

Cyclic monomers ε-caprolactam (CLa) and ε-caprolactone (CLo) belong to the most relevant representatives of the lactone and, respectively, the lactam family. Therefore, their copolymerization to PEAs by means of ROP has been intensively studied, and many procedures have been used for the preparation of P(CLo-co-CLa). Early studies described the copolymerization of CLa, α-pyrrolidone (PL) or α-piperidone (PP) with CLo or δ-valerolactone (VLo) in the presence of an alkali metal. For copolymerization of CLa or PL with CLo and PL with VLo, conversions of above 70% and reduced viscosities of about 0.5 (in m-cresol) at 35 °C for all compositions were obtained. Copolymerization of CLa with VL at 180 °C, a conversion of 25% and a reduced viscosity of 0.5 were obtained, but the polymer polycapeptide was formed, while at 90 °C the conversion was 50% but the polymer was polyvalerolactone. Copolymerization of PP with CL or VL resulted only in a polyester. The proposed mechanism involves chain propagation by the stepwise addition of the lactam at the end of the chain and by stepwise addition of the lactone at the other end of the chain, resulting effectively in the formation of polyester and polyamide blocks/segments. The results obtained through a reaction with alkali metal salt of the lactam, IR data, elemental analysis and determination of physical properties of these copolymers supported this mechanism. Anionic copolymerization of CLa and CLo has also been described with ε-caprolactam magnesium bromide as the initiator. Polymers with 5–25 wt% CLo were obtained. It was possible to conduct polymerization at 110 °C. CLo-content and temperature influenced the mechanical properties, and it was not possible to restrict exchange transacylation reactions, which progress during polymerization, by kinetic tools. Furthermore, two types of CLo–CLa copolymers were prepared by catalyzed hydrolytic ROP (Scheme 2). First, both cyclic comonomers were simultaneously in the reaction medium, where copolymers with random distribution were afforded (as evidenced by NMR). For the second type, cyclic comonomers were added sequentially, yielding diblock PEAs. Polymers were analyzed by DSC, X-ray scattering (SAXS and WAXS), TEM and SEM, and biodegradation was also studied. Interestingly, in a wide composition range only the CLa units were capable of crystallization. Comparison between block and random copolymers gave a good opportunity to distinguish the dilution effect of CLo units on the crystallization and melting of the polyamide phase from the chemical composition effect for random copolymers, which makes the crystallization of the polymer strongly dependent on composition. Degradation in composted soil showed that much faster degradation was obtained for random PEAs with a CLo content larger than 30% than for neat PCL (synergistic effect).

Further biodegradation studies were conducted under the attack of yeast Cryptococcus laurentii at 20 °C. CLo–CLa copolymers as well as copolymers prepared by a two-step polymerization reaction of hexanediol-1,6, hexanediamine-1,6 and adipoyl chloride were investigated. Under biotic conditions, these copolymers were found to be readily degradable, which was shown by weight loss, GPC, NMR and tensile measurements. Biodegradation occurred much faster under milder conditions compared to abiotic hydrolysis. The enzymatic hydrolysis of ester groups into acids and hydroxyl groups was proved by NMR, while no breakdown of amide bonds was observed under the biotic conditions. Suchlike copolymers were recently studied in a wide composition range and in the wet and dry states. Crystalline and amorphous phases of these PEAs were characterized, the first by wide-angle X-ray scattering and the latter by the thermally stimulated depolarization current technique. A microwave synthesis of PCLa–PLOa has
also been described.\textsuperscript{55} Here, a variable frequency furnace, programed to a set temperature and controlled by a pulsed power on-off system was used to induce anionic copolymerization of these monomers, which showed effective adsorption of microwave energy. Dielectric properties were measured in a range of 0.4–3 GHz, and the polymer yields were 70%. In comparison with conventional thermal and microwave copolymerization studies, it was thus shown that an effective microwave method for CLa/ClO \textsuperscript{c} copolymerization was developed with higher yield, higher amide content and higher $T_m$'s relative to the thermal process. Further studies describe similar anionic ROP of these cyclic monomers as well as their thermo-analytical data in detail.\textsuperscript{56–58}

5 Polyesteramides derived from various linear diacids, diamines and diols

Copolymers of CLa, 1,4-butanediol and adipic acid possess interesting mechanical properties and are suitable for different applications. These polymers have for instance been prepared in a one-batch two-step reaction and manufactured as nonwoven 3D textile scaffolds applicable for tissue engineering scaffolds (Scheme 3A).\textsuperscript{59} Structural conformity of different batches was confirmed by NMR and SEC. Production was successfully performed via simultaneous ROP of CLa and polycondensation with 1,4-butanediol and adipic acid at 230 °C under high vacuum, and Soxhlet extraction allowed optimal cleaning. The effect of scaffold extraction before cell seeding was analyzed by cytotoxicity tests and XPS. The carriers were then seeded with human preadipocytes and examined for cellular proliferation and differentiation, which was shown to be very effective. This makes this kind of PEA suitable for clinical use.

Novel PEAs derived from 1,4-butanediol, dimethyl adipate and a preformed $\alpha,\omega$-amino alcohol from aminobutane and caprolactone were also prepared and electrospun from solution (Scheme 3B).\textsuperscript{60} Many effects on fibre morphology and diameter were investigated, namely by increasing the ratio of amide/ester groups in the copolymer, polymer concentration, solvent mixtures and applied voltage. The obtained fibres were randomly oriented. Increasing amide concentration increased the fiber quality and homogeneity, and the solvent mixture CHCl\textsubscript{3}/HCOOH gave the best electrospinning results. The fibers were characterized by SEM, DSC and FT-IR, showing that they are amorphous compared to the pristine samples. These fibers are thus potential candidates for applications as tissue engineering scaffolds. Aliphatic PEAs with a periodic sequential structure consisting of ester and amide bonds were also synthesized by a two-step polycondensation reaction of adipate, butane-1,4-diamine and linear diols (3–6 methylene units).\textsuperscript{61}

Similarly, PEAs derived from glycolic acid (respectively its dichloride), 1,6-hexanediamine and even aliphatic dicarboxylic acids (adipic acid and dodecanedioic acid) have been synthesized and analyzed (Scheme 3C).\textsuperscript{62} Isothermal crystallization from diol and glycerin solutions resulted in chain-folded lamellar crystals, and the crystalline habit was investigated by real space electron microscopy. Triclinic and monoclinic unit cells were obtained, in which the crystallographic parameter was close to the typical distance between hydrogen-bonded chains. The molecular conformation of both semicrystalline polymers deviates from the all-trans conformation typical of aliphatic PAs and PEs with a large number of methylene groups. In another study, polycondensation of a bio-based sebacic acid, 1,4-butanediol and introduction of 1,4-butanediamine as a comonomer afforded different interesting PEAs.\textsuperscript{63} The homopolymer was semicrystalline with a $T_m$ of 65 °C. An amide content over 10% resulted in two melting endotherms and a significant decrease of their melting enthalpies. The crystallinity decrease with increasing amide content was shown by the WAXD results, and FT-IR measurements confirmed intramolecular as well as intermolecular hydrogen bonding, as well as the fact that the area of the amide–amide hydrogen bonded NH band increases during hydrolysis, while the area of the amide-ester hydrogen bonded NH band decreases. Furthermore, the degradability of the PEA series increased with the amide content. In other work, the Nylon 610 oligomer (PrePA) was prepared from the reaction of Nylon-610 salt with sebacic acid. Polyester prepolymers (PrePEAs) with an amide content from 10–60 mol% were then synthesized via melt polycondensation from adipic acid, 1,4-butanediol and the PrePA with stannous chloride as catalysts. Chain extension of these PrePEAs was then carried out using 2,2′-(1,4-phenylene)-bis(2-oxazoline) (PBOX) and adipoyl bis-caprolactamate as combined chain extenders, resulting in extended biodegradable PEAs (ExtPEAs) with $T_m$ from 95.2 to 156 °C, the initial decomposition temperature over 325.3 °C and the tensile strength up to 33.1 MPa (Scheme 3D).\textsuperscript{64}

Regarding (renewable) sebacic acid, poly(1,3-diamo-no-2-hydroxypropane-co-polyol sebacate) (APS) elastomers have also been synthesized and used for the fabrication of airway stents.\textsuperscript{65} In contrast to airway stents that would have to be sur-
Unsaturated polyesteramides

PEAs with unsaturated amino acid residues have been described in section 3. As another example, PEAs with positively charged guanidine groups and pendant C–C double bonds were also prepared.\(^6\) Furthermore, unsaturated PEAs based on ethylene glycol lactate diol, maleic anhydride and toluene-2,4-disocyanate afford a crosslinked resin with unsaturated double bonds, which is very interesting for biomaterials due to its porous structure (formation of CO\(_2\) during synthesis), flexibility (resulting in shape-memory characteristics) and a \(T_g\) close to human body temperature (Fig. 2).\(^6\)

![Fig. 2 Unsaturated PEAs, crosslinked, containing lactic acid units.](Image)

Polyesteramides from other natural products

In addition to the amino acid and sebacic acid derived PEAs described above, several other natural product based PEAs have been described. Examples are carbohydrate-derived, stereocenter-containing PEAs from \(\alpha\)-arabinose, succinyl and glutaryl moieties (Fig. 3A).\(^7\) For those, the degradation rate can be enhanced by increasing the amount of the sugar-based monomer. Biodegradable PEAs from tartaric acid have also been investigated (\(M > 80000\)), which showed \(T_m\) and \(T_g\) values ranging from 100 to 230 and 50 to 100 °C, respectively (Fig. 3B).\(^7\) Similarly, PEAs derived from \(\gamma\)-malic acid were prepared with ester to amide group ratios from 1 : 50 up to 1 : 2, with \(O\)-methyl-\(\gamma\)-malic acid, 1,6-hexanediol and 1,6-hexamidine as the comonomers (Fig. 3C). The ester linkage was incorporated using 6-aminohexy perchlorophenyl \(O\)-methyl-\(\gamma\)-malate as the comonomer in the polycondensation of bis(pentachlorophenyl)-\(O\)-methyl-\(\gamma\)-malate with 1,6-hexamidine.\(^7\) Isoregic \(ir\)-PEALM (1 : 1) and aregic \(ar\)-PEALM were obtained. The molecular weight of PEALM is between 10 000 and 50 000. The \(T_m\) of these PEALMs decreased with the content of ester groups from 168 to 144 °C, and \(T_g\) falling from 60 to 10 °C. Thermal decomposition of PEALM initiated around 260 °C. Degradation occurred in water at pH 7.4, 37 °C, at a rate that increased with the content of ester groups.

![Fig. 3 PEAs derived from (A) \(\alpha\)-arabinose; (B) tartaric acid and (C) malic acid.](Image)

Conclusion

Polyesteramides are very important biodegradable polymers, which show some improved properties compared to polyesters (e.g. strength) due to the presence of both ester and amide bonds. Many interesting studies refer to the synthesis and application of PEAs with a variety of different architectures, which can afford amorphous, semicrystalline and elastomeric materials. A lot of biomedical applications for these polymers are studied in terms of drug delivery, hydrogels or tissue engineering. Based on their promising property profiles, further effort and research will be spent for PEAs, which are anticipated to play a growing role as high performance...
materials in the future for general and special applications especially in the (bio)medical field.

Notes and references