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Review Article

Pseudo-Proteins: A New Family of Biodegradable Polymers for Sophisticated Biomedical Applications

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Introduction

Biodegradable Polymers

Polymers called as *biodegradable* are a special class of high-molecular-weight compounds that breaks down after its intended purpose by chemical (hydrolysis, redox cleavage) or biological (bacterial, enzyme catalysed) decomposition process to result in low-molecular-weight debris (therefore they are called also as *resorbable* polymers). These polymers are found both naturally occurring and synthetically made, and largely consist of ester, amide (peptide), urethane, ether, and anhydride groups (connecting links in the polymeric backbones). Properties and breakdown mechanism of biodegradable polymers (BPs) are determined by their structure. These polymers are often synthesized by condensation reactions or ring opening polymerization. Today there are vast examples and applications of biodegradable polymers in medicine, agriculture, veterinary, food processing, packaging, as eco-friendly materials. In medicine, biodegradable (resorbable) materials are used as implantable devices such as bone screws, bone plates, contraceptive reservoirs, stents, and vascular stent coatings, wound dressings, surgical sutures, staples, drug delivery vehicles, to name a few. BPs are also employed as membranes, films and patches for depositing and growing cell, as tissue engineering scaffolds, etc.

BPs have a long history, and since many are natural products, the precise timeline of their discovery and use cannot be accurately traced. One of the first medicinal uses of a biodegradable polymer was the catgut suture, which dates back to at least 100 AD [1]. The first catgut sutures were made from the intestines of sheep, but modern catgut sutures are made from purified *collagen* extracted from the small intestines of cattle, sheep, or goats [2]. Today many proteins such as collagen, gelatine, albumin, elastin, fibrin, etc. are used as medicated sponges for burns/wounds, mini-pellets and tablets for protein delivery, carriers for constructing artificial vaccines, gel formulation in combination with liposomes for sustained drug delivery, controlling material for transdermal delivery, microspheres for drug delivery, nanoparticles for drug and gene delivery, as a shell to protect and renders the quantum dots available for in vivo applications, to name a few [3,4]. Along with proteins, among naturally occurring BPs should also be mentioned polysaccharides, hyaluronic acid, nucleic acids, bacterial polyesters (poly-β-hydroxybutyrates).

Synthetic biodegradable polymers and plastics have been intensively developed since 70-80s of the last century [5-7]. Due to the huge commercial interest, many different classes of synthetic biodegradable polymers have been introduced in the art, such as polyesters and poly(ortho esters), polyamides and polyurethanes, poly(ester amide)s and poly (ester urethane)s, polyanhydrides, polyphosphazenes, and amino acid-based polymers (synthetic analogues of proteins).

Even though biodegradable polymers have numerous applications, there are properties that tend to be common among them. All biodegradable polymers should be stable and durable enough for use in their particular application, but upon disposal they should easily break down. Other properties of biodegradable polymers that are common among those used for medicinal usages include being:

- non-toxic;
- capable of maintaining good mechanical integrity until degraded;
- capable of controlled rates of degradation.

They should not to elicit the immune response, and the products of degradation also need not to be toxic, carcinogenic, or teratogenic. These are important as biodegradable polymers are used as resorbable surgical materials and devices as well as for drug delivery where it is critical sustained/controlled release the drug into the body over time instead of all at once. Factors controlling the rate of degradation include molecular weight, hydrophobicity, and degree of crystallinity. The degradation rate depends on the location in the body, which influences the environment surrounding the polymer such as pH, enzymes concentration, and amount of water.

Among the naturally occurring BPs the most applicable for biomedical purposes are proteins. The proteins show a high tissue compatibility owing to a high affinity with tissues that is connected with peptide (NH-CO) bonds. Besides, proteins release α-amino acids upon biodegradation which represent a nutritive material and support cells proliferation and ultimately the regeneration of tissues. However, proteins as biomaterial has some limitations such as batch-to-batch variation, risk of disease transmission and immune rejection. The last limitation is connected with molecular architecture of proteins. It is known that α-amino acids (AAs) in a protein molecule have so-called "head-to-tail" orientation as it is depicted in Figure 1, A (assuming that α-amino group is "head" and α-carboxyl groups is "tail"). This natural proteinaceous architecture of macromolecules containing only amide (peptide) groups is easily recognizable by the immune system

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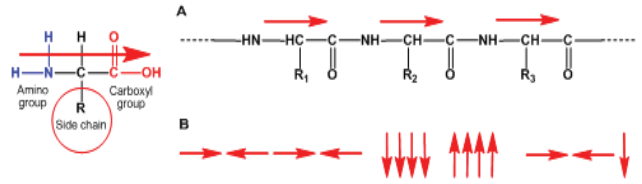

Figure 1: Possible orientations of AAs in macromolecules: A - "head-to-tail" orientation (proteinaceous molecular architecture), B – another types of orientations (non-proteinaceous molecular architecture).

of the body. This can cause immune incompatibility of the biomaterial with the body tissues.

The main advantage of synthetic BPs over the naturally occurring ones consists in low to zero immunogenicity and no risk of disease transmission. However, the most of synthetic BPs listed above do not contain amide (peptide) NH-CO bonds and possess lower compared to the proteins tissue compatibility and, besides, do not release nutritive AAs upon biodegradation. Therefore, more promising from these view-points look AAs-based BPs (AABPs) – man-made analogues of proteins which contain amide NH-CO bonds and release AAs upon biodegradation. These polymers can be designed so to have non-proteinaceous molecular architecture (Figure 2, B) less recognizable by immune system of the organism. Along with amide (peptide) NH-CO bonds AABPs can contain additional hetero-bonds like ester, ether, urea, urethane, etc. in the backbones that can further decrease the immunogenicity of the polymers and, in parallel, to widen the range of their material properties.

The main representatives of synthetic AABBPs introduced in the art since 80s are: poly(amino acid)s (PAAs), pseudo-poly(amino acid) s (PPAAs), poly(depsipeptide)s (PDPs), and pseudo-proteins.

Poly(α-amino acid)s, PAAs

The most rational and commonly used synthesis of PAAs consists in ring-opening polymerization (ROP) of suitable monomers - N-carboxy-α-amino acid anhydrides (NCAs) which readily undergo polymerization with carbon dioxide evolution yielding the corresponding PAAs [8], as it is depicted in Figure 2.

Despite some prospects of the synthetically made PAAs as a potential biomaterials, the studies revealed that most of the PAAs could not be considered as suitable biomedical materials due to their immunogenicity stipulated by proteinaceous molecular architecture [9] along with unfavourable physical-chemical characteristics - with few exceptions, PAAs tend to be insoluble polymers that decompose in the molten state [10,11].

Pseudo-poly(amino acid)s, PPAAs

More promising, compared to PAAs, as biodegradable biomaterials are so called "pseudo-poly(amino acid)s" - the AABPs the backbones of which are constructed by utilizing the side-chain functional groups of suitably modified trifunctional α-L-amino acids or dipeptides made of them [12-14]. Accordingly, pseudo-poly(amino acid)s (PPAAs) have one of the non-proteinaceous molecular architecture (Figure 1,B) and differ from conventional PAAs which have proteinaceous molecular architecture (Figures 1,A and 2). Such an approach offers the opportunity to create polymers from naturally occurring metabolites (AAs) [12-14] but without some of disadvantages of conventional

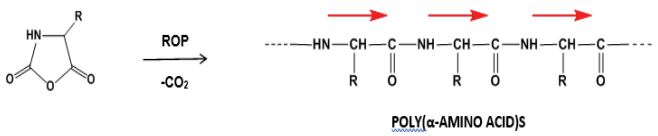

Figure 2: The synthesis of poly(α-amino acid)s via ROP of NCAs.

PAAs. Copolymerization of AAs with non-AA monomers has been achieved through a variety of reactions, leading to PPAAs of various classes - polyesters, polyarylates/poly¬carbo¬nates, polyamides, polyureas, polyurethanes, with a wide range of structures and properties. Synthesis of several samples of the PPAAs are given in brief below.

The PPAA of polyester classes (PPAA-PEs) having valuable material properties were synthesized on the basis of hydroxy-AAs such as hydroxyproline and serine.

High-molecular weight PPAA-PEs (MW up to 42 kDa) were obtained by thermal polycondensation of N-substituted *trans*-4-hydroxy-proline [14-16] as depicted in Figure 3 below:

For synthesizing high-molecular-weight (MW up to 30-40 kDa) serine-based PPAA-PEs better best was found the ring-opening polymerization of N-protected-L-serine β-lactone (Figure 4) [13,17].

One of the most promising representatives of the PPAAs are the polymers on the basis of AA tyrosine [14]. The key monomers for synthesizing these PPAAs are tyrosine based *bis*-phenols such as tyrosine dipeptide and desaminotyrosyl-tyrosine [18-22] (Figure 5).

These monomers were used for synthesizing all classes of heterochain polymers available on the basis of *bis*-phenol type monomers and linked by non-amide bonds such as ester, ether, carbonate or iminocarbonate bonds. Such polymers contain CO-NH bonds in the backbones (which come from the monomers depicted in Figure 5) that provides enhanced affinity and, hence, compatibility of the polymers with tissues [23].

Suitable monomers for synthesizing PPAAs are also three-functional AAs such as α-amino dicarboxylic acids - aspartic and glutamic acids, and diamino α-carboxylic acid lysine which contain side-chain functional groups used for constructing PPAAs (Figure 6).

These AAs after suitable modification were used for synthesizing high-molecular-weight polymers. Aspartic and glutamic acids were used for synthesizing polyamides (PAs) [24]. Lysine was used for

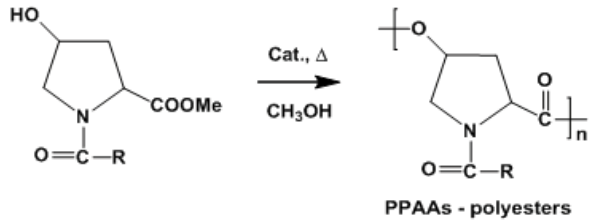

Figure 3: Synthesis of the PPAAs-PEs by thermal polycondensation of N-substituted trans-4-hydroxy-proline methyl ester.

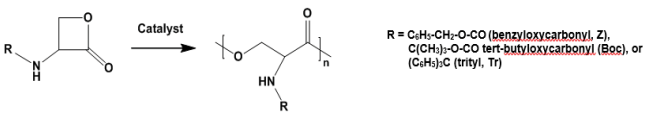

Figure 4: Synthesis of the polyesters by ROP of N-protected serine.

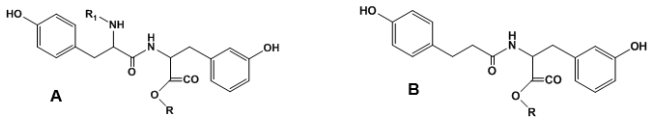

Figure 5: Chemical structure of (A): C- and N-protected tyrosine dipeptide and (B): desaminotyrosyl-tyrosine alkyl esters, DTR; R = C_2H_5, C_4H_9, C_6H_{13}, C_8H_{17}, $C_{12}H_{25}$; R_1 = amino protecting group.

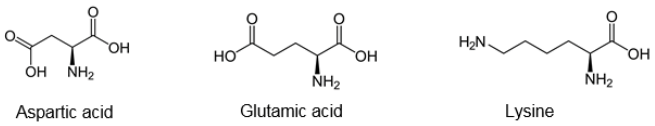

Figure 6: Three-functional AAs containing side-chain functional groups.

synthesizing functional PPAAs with free lateral carboxyl groups. On the basis of lysine were obtained PAs [25] and highly functional PAs [26-29], polyureas [30-31] and polyurethanes [32].

Poly(depsipeptide)s, PDPs

Polydepsipeptides (PDPs) represent an important class of AABPs completely composed of naturally occurring ("physiological") building blocks such as α-amino acids and α-hydroxy acids [33-36]. The most rational way for synthesizing the PDPs is ring-opening polymerization (ROP) of cyclic depsipeptides - morpholine-2,5-diones developed in 1985s [33], as depicted in Figure 7.

Various PDPs were synthesized by ROP and copolymerization of different morpholine-2,5-dione derivatives including random, alternating, diblock, triblock, functional and graft PDPs [37-44]. It has to be noted that though in the backbones of the PDPs the AAs have "head-to-tail" orientation but they are interleaved with ester bonds that provides non-proteinaceous molecular architecture less recognizable by immune system.

Pseudo-proteins, PPs

A huge and highly promising family of the synthetic AABPs destined for broad biomedical applications was obtained on the basis of AAs and other non-toxic and vastly available building blocks such as diols and dicarboxylic acids. We used the name *pseudo-proteins* (PPs) for these polymers to distinguish them from other classes of AABPs discussed above. The first representatives of PPs having valuable material properties were poly(ester amide)s (PEAs) reported in 1994 [45]. Later other classes of PPs such as poly(ester urethanes)s (PEURs) and poly(ester urea)s were reported as well [46,47].

One of the main advantages of the PPs over other classes of the AABPs consist in the key *bis*-nucleophilic monomers – α,α'-diamine-diesters as stable di-p-toluenesulfonic acid salts (TDADEs). These monomers are basically synthesized in high yields (up to 90-95%) *via* very simple and cost-effective procedure - direct thermal condensation of two moles of α-amino acids with one mole of diols in refluxed organic solvent (benzene, toluene or cyclohexane) in the presence of two moles (in case of AA arginine four moles) of p-toluenesulfonic acid (Figure 8) which serves as both amino groups protector and the condensation reaction catalyst [45-51].

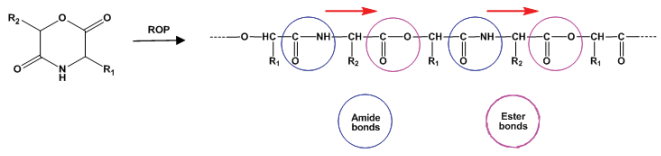

Figure 7: Synthesis of polydepsipeptides by ROP of cyclic depsipetides

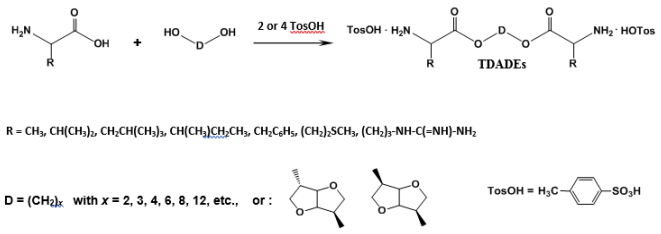

Figure 8: Synthesis of diamine-diester monomers (TDADEs) by direct thermal condensation of AAs with fatty diols. D – a diol residue.

Additional merits of the TDADE-monomers are stability upon storage, highly active terminal amino groups for successful chain growth along with the designed-in non-proteinaceous ("head-to-head") orientation of amino acids, enzyme specific lateral groups R, and labile (hydrolysable) ester bonds (Figure 9).

The TDADEs are universal bis-nucleophilic monomers which, after interacting with various *bis*-electrophiles (Figure 10), lead to the synthesis of three basic classes of the PPs such as poly(ester amide)s (PEAs) [45,48,49], poly(ester urethane)s (PEURs) [46,49], and poly(ester urea)s (PEUs) [46,47,49] depicted in Figure 11. Diacid chlorides and activated diesters of diacids are used for synthesizing the PEAs, diol-*bis*-chloroformates and activated *bis*-carbonates of diols - PEURs, phosgene/triphosgene and activated carbonates – PEUs.

Using the *bis*-electrophilic monomers above, two techniques of the SGP such as Interfacial Poly-condensation (IP) and Solution Active Polycondensation (SAP) can be applied to the synthesis of the PPs [49].

A variety of the classes and synthetic methods for making thereof allow to tune the structure and material properties of the PPs in the widest range. As expected, based on the non-proteinaceous architecture, PPs show low to zero immunogenicity [35,49,52-58].

The most of PPs are well-soluble in organic solvents such as ethanol and isopropanol (approved for medical applications), *N,N*-dimethylformamide, tetrahydrofuran, dioxane, chloroform, methylene chloride, and some of them even in acetone and ethylacetate.

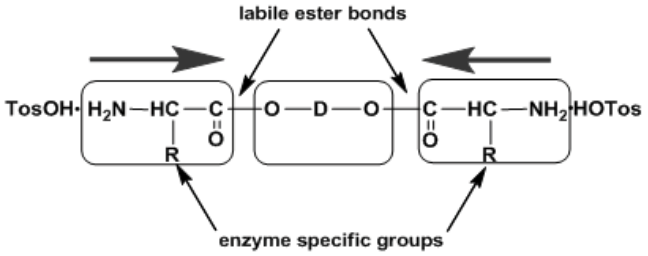

Figure 9: The structure of DADEs – key monomers for synthesizing PPs.

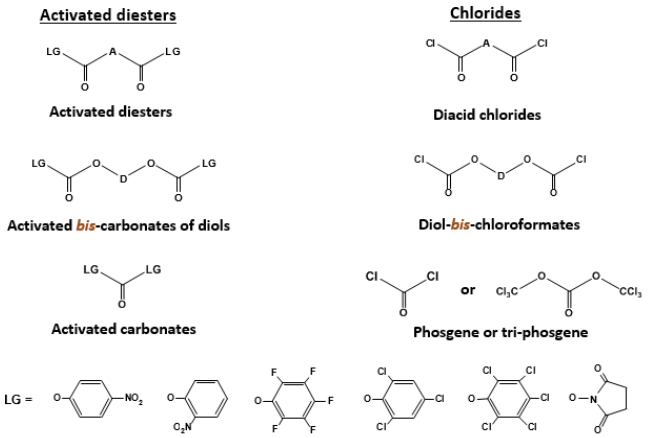

Figure 10: Some key bis-electrophilic monomers for synthesizing PPs. A – a diacid residue, D – a diols residue.

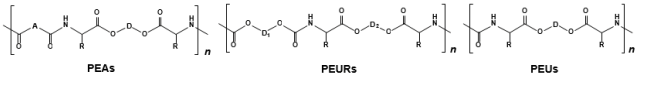

Figure 11: Chemical structures of three classes of PPs: PEAs, PEURs, and PEUs. A – a diacid residue, D_1 and D_2 – diols residues.

The molecular weights of the PPs are reasonably high and vary within 24,000 – 167,000 Da (Mw), polydispersity - within 1.20–1.81. The thermal characteristics of the PPs are also within a wide range: glass transition temperature (Tg) varies within 5 – 102°C and some of the PPs (PEAs and PEUs) are semi-crystalline with melting temperature (Tm) within 103–165°C. The low melting temperatures and solubility of PPs in common organic solvents substantially facilitates their processing into different shapes [48,49].

The chemical structure affects the mechanical properties of PPs, which varies in a wide range: tensile strength from 15-20 (PEURs and some PEAs) to 80-100 MPa (PEUs and some PEAs), elongation at break from 8-100 (PEUs and some PEAs) to 800-1000% (PEURs and some PEAs), Young's modulus up to 6 GPa (some PEAs and PEUs) [49,59,60]. The PPs can be obtained in form of viscous-flow materials promising for sealing cavities.

The PPs can degrade by both chemical (nonspecific) and enzymatic hydrolysis with a reasonable rates ranging within V = 10^{-3}–10^{-1} mg/cm^{2}h [48,54,61]. The biodegradation of the PPs proceeds by erosive mechanism without compromising bulk properties that is important when constructing both resorbable surgical devices and therapeutic (drug delivery) systems. The biodegradation rate can be tuned by impregnated or surface immobilized enzymes [61,62]. The biodegradation of PPs starts from the hydrolysis of the ester bonds since they are 10^3-10^4 times more active as compared with amide groups. The amide, urethane and urea bonds are hydrolyzed at subsequent stages of biodegradation resulting in ultimate products of biodegradation. The ultimate biodegradation products are: for PEAs – AAs, dicarboxylic acids and diols, for PEURs and PEUs – AAs, diols and carbon dioxide.

The scopes of applications of PPs can be substantially expanded by designing functional PPs. This can be achieved (i) by combination of TDADEs with functionalized TDADEs or with other types of functional co-monomers, or (ii) by synthesizing various active pre-polymers with subsequent functionalization by means of polymer-analogous reactions. As a result, various types of functionalized PPs were obtained [55]. One of them - epoxy-functionalized PP-PEAs [63] contain active oxirane rings (Figure 12) and be used for covalent attachment of the compounds containing free amino groups.

Epoxy-PP-PEAs can further be functionalized by interaction with hetero-bifunctional PEG-derivatives such amine-PEG-carboxymethyl (Figure 13, FG=COOH), amine-PEG-thiol (Figure 13, FG=NH_2) or amine-PEG-hydroxyl (Figure 13, FG=OH). After such kind of modification the PPs become water soluble and contain functional groups at attached lateral PEG-substituents remote form the polymeric backbones.

The PP modified with methoxy-PEG-amine (Figure 13, FG = CH_3O), labelled as PEA-mPEG represents a kind of biodegradable surfactant which forms micelles in water solution. A comparative study of PEA-mPEG carried out using known surfactants showed very close characteristics of the all surfactants studied (Table 1) in terms of mean particle diameter (MPD), polydispersity index (PDI) and zeta-potential (ZP).

The PEG-modified PP PEA-mPEG is promising as surfactants for fabricating NPs with simultaneous PEGylation of their surface [64]. The PEGylation of NPs which are used as drug delivery vehicles is important to protect them from the attack of immune system of the organism. The PEGylation decreases affinity of plasma proteins (opsonins) for adsorption on NPs - long chains of PEG form a random cloud around the NPs thereby preventing absorption of opsonins and in that way suppressing phagocytosis. Along with the protection of the NPs from phagocytosis the PEGylation substantially increases the bioavailability of NPs [65]. The functional groups of the PEG cloud (functionalized cloud – Figure 14) can be used for the conjugation of various markers, vectors, etc. to the surface of NPs.

A library of cationic PPs was synthesized on the basis of AA arginine. The cationic PPs showed excellent cell compatibility, transfection (important for potential applications in gene therapy), and bactericidal activity [66-68]. The cationic PPs are also suitable for constructing positively charged nanoparticles. A series of positively charged NPs was prepared by blending of regular (neutral) PP-PEA 8L6 and cationic PP-PEA 8R6 (Figure 15). The NPs were fabricated by cost-effective polymer deposition/solvent displacement (nanoprecipitation) method [69]. The zeta-potential of the NPs was changed from -12.5 mV in case of pure 8L6 to +28.0 mV in case of 50/50 blend of 8L6/8R6 (Table 2).

Positively charged NPs are favourable for penetration through cells and biological barriers - it is known that a positive charge helps with the NPs' adhesion to the surface of cells and stimulates penetration into the cells *via* endocytosis [70].

Table 1: Characteristics of micelles of standard surfactants and new biodegradable PP-based surfactant **PEA-mPEG** from Figure 13 (**FG = CH_3O**).

Surfactant	MPD (nm) ± SD	PDI ± SD	ZP (mV) ± SD
Tween 20	11.3 ± 0.3	0.244 ± 0.029	-9.5 ± 0.8
Brij010	19.2 ± 0.3	0.173 ± 0.016	-11.1 ± 0.5
Kolliphor P188	9.2 ± 0.4	0.373 ± 0.031	-13.9 ± 1.5
Triton X-100	10.4 ± 0.7	0.254 ± 0.021	-6.5 ± 0.5
Mowiol 4-88	20.0 ± 1.3	0.463 ± 0.039	-13.0 ± 1.9
PEA-mPEG	16.2 ±1.0	0.174 ± 0.012	-13.1 ± 1.8

± SD – standard deviation of three parallel measurements.

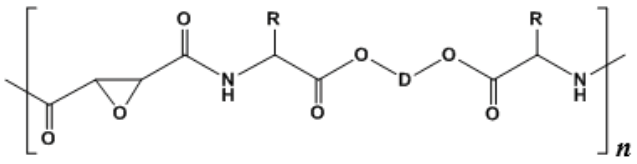

Figure 12: Epoxy-functionalized PP-PEA.

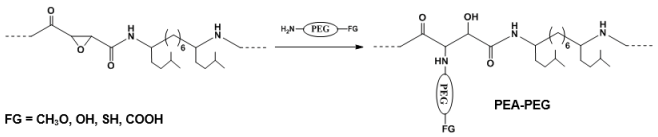

Figure 13: Functionalization of epoxy-PP-PEAs with hetero-bifunctional PEG-derivatives.

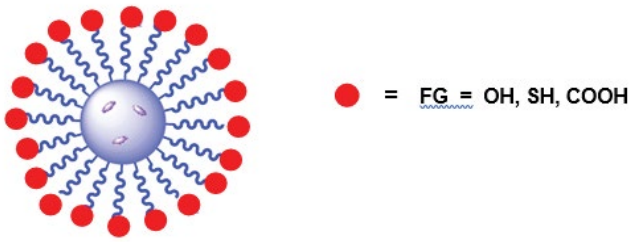

Figure 14: NP with functionalized PEG cloud.

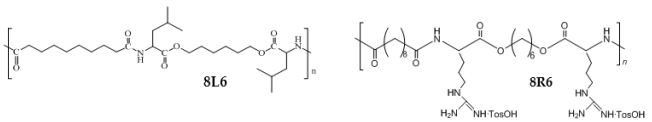

Figure 15: PP-PEAs – neutral **8L6** and cationic **8R6** used for fabricating NPs.

Table 2: The ZP of the NPs made of **8L6/8R6** blends.

Polymer	Weigh ratio 8L6/8R6	Zeta-potential (mV)±SD
8L6	100/0	–12.5 ±1.9
8L6 / 8R6	95/5	+19.6 ± 3.6
	90/10	+23.2 ± 4.7
	80/20	+25.8 ±2.7
	70/30	+27.2 ±3.2
	50/50	+28.0 ±4.9

NPs were fabricated using Tween 20 as a surfactant
± SD – standard deviation of three parallel measurements..

The PPs of PEA and PEU classes were found suitable for fabricating fibrous mats by the electrospinning technique. These mats can be loaded with enzymes and antibacterial drugs including bacteriophages [71-75]. Such loaded fibrous mats are highly promising as soft dressings to treat superficial burns, wounds and ulcers. It is important that the bioresorbable dressing does not stick to the wound and is removed spontaneously after complete healing of the wound/skin.

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