Chapter 5
Alternating Copolymers Based on Amino Acids and Peptides

Ishita Mukherjee, Krishna Gopal Goswami and Priyadarsi De

Abstract Controlling the monomer sequence along the polymer chain leads to the development of a special class of synthetic copolymers, and they are known as alternating copolymers when the two comonomers are placed in a regular exchanging fashion. The monomer sequence control plays an important role to regulate the different bulk properties such as conductivity, rigidity, biodegradability, as well as mimic the properties of the sequence defined biopolymers like DNA, RNA, enzymes, and proteins. Very recently, different synthetic strategies have been explored to mimic the monomer sequences in synthetic polymeric materials. An enormous combination of several desired functionalities has been attached with the electron donor styrene, stilbene or electron acceptor maleic anhydride or *N*-substituted maleimide moieties to produce strictly alternating backbone and their properties have been extensively investigated. Nowadays, functionalities like amino acids and peptides, essential and fundamental components of protein biopolymers and alive entities extending from bacteria to humans with a variety of enormities from nano to macro dimension, are widely used to design an extensive range of block or random copolymers with significant assets and applications, as they can play critical responsibility in both functional and structural levels. The multifaceted biological features of these moieties help to generate bioactive and biocompatible materials. However, the properties associated with their alternating architecture have not been broadly studied. By providing a quick look on different types of alternating copolymers, in this book chapter, we aim to focus on recent developments of amino acid and peptide-based alternating architectures, their interesting properties and applications as bioinspired nanomaterials, in inclusion chemistry, catalysis, sensing, tissue engineering, molecular electronics, molecular separation technology, and so on.

Keywords Alternating copolymers · Amino acids and peptides · Biopolymers · Building block

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1 Introduction

The field of macromolecular architecture and its applications has been extensively explored over the last two decades particularly in the devise of complex macromolecular designs with significant advances [1, 2]. Copolymers, a long macromolecular chain comprised of at least two monomers of unlike chemical nature, can be usually classified as random or statistical copolymers, block or segmented copolymers, graft copolymers, star polymers, alternating copolymers, periodic copolymers [3], gradient copolymers [4], and aperiodic copolymers [5] relying on various distributions of monomers along the chain (Fig. 1) [6]. One of the principal objectives in the field of precise macromolecular chemistry is to regulate the sequential arrangement of monomers in the as-prepared polymer chains [7, 8]. Sequence modulation in polymer materials is of tremendous interest as the polymer properties rely both on the monomer constitution and their arrays which critically determine higher-order polymer conformation in addition to polymeric bulk properties and applications [9, 10], as witnessed in various existing biopolymers, for instance, proteins, DNA, and RNA [11]. This molecular facet appears vital for adjusting subnanometric features like molecular recognition, biocatalysis, molecular encoding of information, and therefore emerging novel generations of polymeric materials after learning from biopolymers [12]. Consequently, an extensive array of the novel sequence defined polymer-based nanomaterials have been newly emerged via iterative [13, 14], step-growth [15], chain-growth, template [16], multiblock [17, 18] chain shuttling mechanism to yield periodic pattern or kinetic strategies [19, 20].

In this regard, an alternating copolymer is a special class of sequence defined polymers where two comonomers are arranged in a regular exchanging fashion [21], leading to $r_1 r_2 = 0$ where r_1 and r_2 denote the ratio of the rate constant of homopropagation to cross-propagation [22]. Copolymerizations of electron donor styrene (also

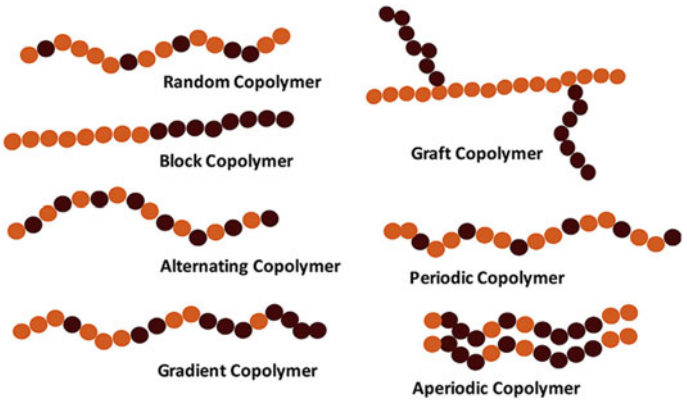

Fig. 1 Various types of copolymers from two different monomers. Reprinted with permission from Ref. [23]. Copyright (2017) Elsevier

stilbene) with electron acceptor maleimide or maleic anhydride are mostly used to produce strictly alternating backbone [23]. The phenyl ring of styrene can be functionalized with desired functionalities, and also various *N*-substituted maleimide moieties can be used to prepare varieties of strictly alternating copolymers. Several emerging applications like nanoelectronics, photonics, biotechnologies, and alternative energies are generated from these novel structures [24].

Amino acids and peptides, the major building block of protein biopolymers, are the natural key ingredients to facilitate life [25]. These molecules have engrossed immense attention over the last few decades as their bioactive, biodegradable, and biocompatible nature leads to potential biomedical applications [26, 27]. Amino acids and peptides offer an exciting platform for the fabrication of nanoscale biocompatible materials as a promising alternative of synthetic compounds through self-assembly or co-assembly of two or more kinds of building blocks ensuing progressively more complex nano-assemblies with distinctly different features comparing to the basic mono-structures [28, 29]. Recently, an extensive range of block or random copolymers with significant properties has been designed with amino acid or peptide-based building block with significant possessions and applications [30, 31], though the properties associated with their alternating architecture have not been broadly studied. This chapter summarizes the recent developments of amino acid and peptide-based alternating constructions by presenting an overall discussion on different types of alternating copolymers with their interesting applicative side as catalyst, bioinspired nanomaterials, tissue engineering scaffold, in inclusion chemistry, molecular electronics, molecular separation technology, etc.

2 Different Synthetic Strategies

Monomer sequence control in polymers can be achieved via numerous synthetic strategies which include both biological (e.g., DNA templates) and synthetic chemistry concepts to countenance the synthesis of macromolecules with diverse chemical structures [12]. The simplest examples of such controlled sequence arrangements are the alternating copolymers, composed of two monomer units [10]. The copolymerization of electron-rich styrene with electron-accepting maleic anhydride or *N*-substituted maleimide representing such monomer pairs has been extensively investigated since the early 1940s [32]. The successful synthesis of the alternating copolymers from these monomers was attained in conventional free-radical copolymerization (FRP) using 2,2′-azobisisobutyronitrile (AIBN) as the initiator [33, 34]. Apart from common organic solvents, for instance, tetrahydrofuran (THF) and *N,N′*-dimethylformamide (DMF), supercritical carbon dioxide (CO_2) was also used to accomplish an ultrahigh molecular weight alternating copolymer from styrene and maleic anhydride. By increasing the free volume and segmental motion of the copolymer chain, CO_2 restricts its precipitation from the solvent leading to the emergence of a high molecular weight polymeric structure [35]. As reported in the literature, UV irradiation was also efficiently incorporated for preparing alternating copolymers at

room temperature [36]. Though traditional free-radical polymerization has been conveniently implemented to fabricate alternating copolymers, it suffers from some limitations while the amount of in feed maleic anhydride is less than 50 mol% resulting in a mixed assemblage of copolymer and homopolymer [23]. A strong compositional drift was reported for two random copolymer samples where the resultant polymer chains were rich in maleic anhydride and styrene content at low and high masses, respectively [37]. Nevertheless, if one starts with imbalanced monomer ratio with low maleic anhydride content, the polymerization will begin as an alternate copolymerization till the entire maleic anhydride is incorporated. After that, the excess styrene will be homopolymerized ensuing the in situ formation of a block copolymer composed of a poly(styrene-*alt*-maleic anhydride) block and a polystyrene segment [38].

Successful utilization of both nitroxide mediated polymerization (NMP) and reversible addition-fragmentation chain transfer (RAFT) polymerization for styrene and maleic anhydride system was reported in the literature. Hawker and coworkers have investigated the controlled copolymerization of maleic anhydride via NMP resulting in the occurrence of a unique, single-step production of functionalized block copolymers from a 9:1 amalgamation of styrene and maleic anhydride [39]. Wang et al. described an effective strategy to prepare poly(styrene-*co*-maleic anhydride)/SiO_2 hybrid composites by NMP which permits a facile control over the molecular weight distributions and architecture of grafted copolymers onto solid surfaces [40]. Williams and coworkers have reported the successful fabrication of alternate copolymers from nucleobase-enclosed styrene monomers with maleic anhydride through the RAFT polymerization process using hexafluoroisopropanol as the solvent [41]. Several other reports are there where RAFT has been found fruitful for synthesizing alternating copolymers [42, 43]. Other than NMP and RAFT polymerization, atom transfer radical polymerization (ATRP) can also be effectively employed to copolymerize styrene and *N*-substituted maleimides [44, 45]. Based on it, Lutz and coworkers have presented a sequence-modulation tactic to tune conventional alternating behaviors by time-dependent introduction of small amounts of ultra-reactive maleimide monomer during the controlled polymerization of an excess of styrene monomer leading to the local functionalization of polymer chains [19, 46]. However, ATRP seems incompatible with styrene and maleic anhydride comonomers, owing to the interaction between maleic anhydride and the copper complex as used for such polymerization process. Apart from this, Heuts et al. successfully employed catalytic chain transfer polymerization to synthesize styrene–maleic anhydride copolymers in presence of low spin [bis(difluoroboryl) dimethylglyoximato] cobalt(II) complex [47].

Still, so far, the above discussion was mainly focused on the alternating copolymerization of styrene and maleic anhydride or *N*-substituted maleimide monomers. There are many other examples where different structural units have been utilized to prepare alternating polymer networks. Coates and coworkers have optimized the ring-opening alternate copolymerization of succinic anhydride with propylene oxide to synthesize a fresh array of semicrystalline polyesters [48]. A catalyst driven sequence

control strategy was developed by Thomas et al. to produce highly alternating copolymers from a combination of enantiomerically pure but dissimilar monomers [49]. The successful synthesis of alternating polyacetylene was recently reported by He and coworkers through the regioselective anionic polymerization of butadiene derivatives [50]. Literature reports also revealed the usefulness of condensation polymerization to formulate the alternating structures [51]. Tsuji and Arakawa have recently employed this process to synthesize alternating stereocopolymer, poly (L-lactic acid-*alt*-D-lactic acid) from chiral hydroxyalkanoic acids [52]. Generally speaking, continuous efforts are still made to design artificial polymeric structures with controlled sequence which may open up numerous opportunities to switch the structure–property relationship in tomorrow's polymer science. Figure 2 schematically represents different synthetic procedure to synthesize alternating copolymer architectures.

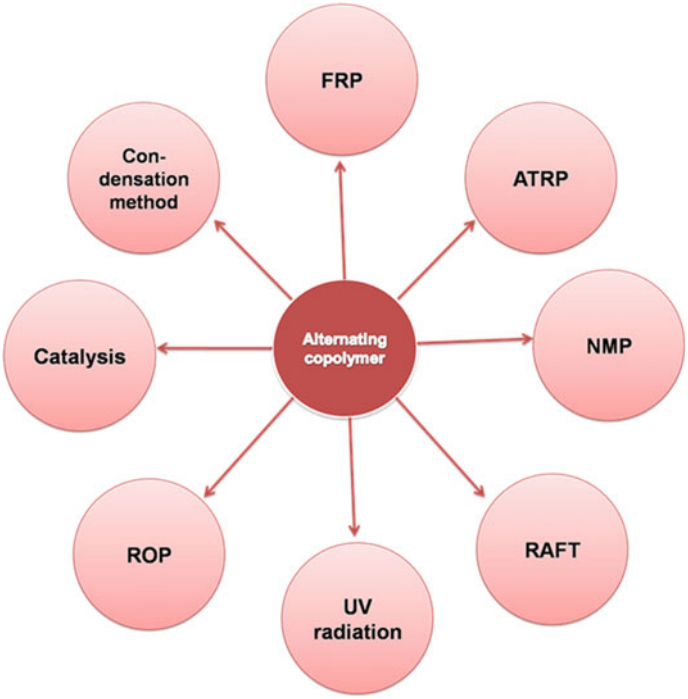

Fig. 2 Schematic illustration of the different synthetic strategies of alternating copolymers

3 Mechanistic Models on Styrene–Maleic Anhydride Radical Copolymerization

There has been a resurgence of attention in the study of styrene–maleic anhydride copolymerization from a mechanistic point of view as it shows a strong tendency to form alternating structures. Numerous studies have been endorsed to ascertain the underlying reason behind this alternating tendency which has been argued very much in the literature [38]. Several models are demonstrated to rationalize this alternation behavior. The earlier Mayo-Lewis model recommended the dependence of the propagation rate constant on both the terminal radical and the arriving monomer [53]. Though it could be successfully utilized to relate the copolymer composition with monomer feed composition, it suffers limitation to justify the correlation of rate constant versus monomer feed composition [23, 54]. Another model is the penultimate unit model (PUM) which could be incorporated to account for the deviation from Mayo-Lewis model [55]. Apart from the terminal radical, the rate constant of monomer addition also depends on the penultimate monomer unit as depicted in this model [56, 57]. The third model is the complex participation model (CPM) which could be employed to elucidate both the copolymerization kinetics and the copolymer composition in addition to monomer sequence distribution [38]. As the styrene monomer is an electron-rich monomer, it is susceptible to form charge-transfer complexes via the interaction with the electron-poor maleic anhydride monomer that has been confirmed by spectroscopic evidences [58, 59]. Based on this, the CPM model has been established, which suggests the participation of single monomer as well as the charge-transfer complex in the copolymerization [60, 61]. Nevertheless, there are still some doubts about the involvement of charge-transfer complexes in the copolymerization as evidenced by literature [62]. The underlying mechanism of the alternating behavior is still a topic of discussion and continuous efforts are made to find out the exact reason behind this copolymerization.

4 Recent Development of Alternating Copolymers Containing Amino Acids and Peptides

Over the last few decades, amino acids and peptides are widely used to design an extensive range of copolymers containing two or more amino acids at the side chain [31] or main chain peptide [63]. Primary synthesis and conformational investigation of alternating poly(γ-benzyl D, L-glutamates) [64] and alternating copolypeptide, poly(Lys-Phe) [65] are already reported in the literature long before. Primarily, the copolymer sequencing toward alternating, block or random orientations is presented and regulated by relative reactivity ratios of two diverse amino acid-based monomers. Further, information on sequencing was dictated by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectroscopy. As dictated by Gross and coworkers, the evident selectivity of several protease enzymes for

addition of either L-Et-Leu or L-$(Et)_2$-Glu to propagate chain ends with extreme sequencing leading to alternating, random, and block orientations was estimated from relative reactivity ratios, which was calculated during protease-catalyzed co-oligomerizations of γ-ethyl-L-glutamate (L-$(Et)_2$-Glu) with L-leucine ethyl ester (L-Et-Leu) monomer (Fig. 3) [66].

Various molecular techniques like solid-phase peptide synthesis, native chemical ligation, Staudinger ligation, *N*-carboxyanhydride (NCA) polymerization, and genetic engineering are adopted facilitating the rapid, adaptable, and orthogonal synthesis of main chain peptide-based materials [23]. The amino acid sequence in a peptide can be regulated by the genetic engineering method, though several limitations are associated with this technique like more laborious technique than others, significantly lower yield, use of natural amino acids only unless additional efforts are applied [67, 68]. The molecular devices required for the assembly of precisely designed sequence defined materials are especially genetic engineering, ring-opening polymerization (ROP), and solid-phase peptide synthesis leading to a fruitful transition from fundamental research to industrial application.

Rationally designed cyclic alternating polypeptide facilitates the production of a novel organic nanotubes with specified internal diameter and surface characteristics having potential applications in several industries and educations like chemistry, biochemistry, and material sciences, which includes mimicking biological channels and porous structures, investigating physical and chemical properties of restricted molecules, controlling properties and expansion of inorganic and metallic clusters, or designing novel optical and electronic devices [69]. An eight-residue cyclic peptide with an alternate sequence *cyclo*[-(D-Ala-Glu-D-Ala-Gln)$_2$-] was considered as a subunit with the postulation of cyclic peptide with an even sequence of alternating D- and L-amino acids. A low-energy flat ring-shaped orientation can be adopted by them with all approximately perpendicular backbone amide functionalities to the plane of the adopted β-sheet structure resulting backbone–backbone intermolecular hydrogen bonding (Fig. 4). The alternating D- and L-sequence results from the peptide side chain necessarily lying at the outside of the ensemble to prepare the most wanted hollow tube structure at the core.

Recently, a unique alternating peptide peptoid copolymer was prepared via one-pot Ugi four-component reaction polymerization of dipeptides in aqueous solution involving a primary amine, an aldehyde, an isocyanide, and a carboxylic acid. Thus,

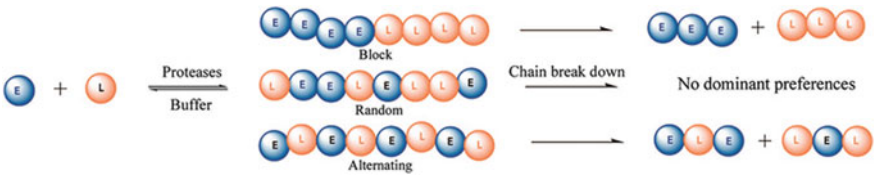

Fig. 3 Possible sequence selectivity of proteases during oligomerization reaction of γ-ethyl-L-glutamate (E) with L-leucine ethyl ester (L) monomer. Reprinted with permission from Ref. [66]. Copyright (2008) American Chemical Society

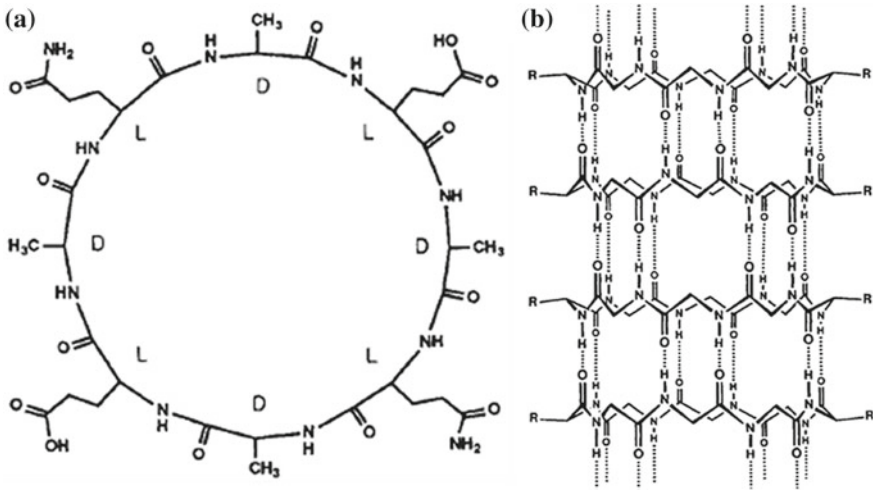

Fig. 4 **a** A two-dimensional representation of the chemical structure of the peptide subunit (D or L refers to the amino acid chirality). **b** Peptide subunits are shown in a self-assembled tubular configuration emphasizing the antiparallel stacking and the extensive network of intermolecular hydrogen bonding interactions (for clarity only backbone structure is presented). Reprinted with permission from Ref. [69]. Copyright (2013) Nature Chemistry

a quasi-quantitative pathway of α-amido amide compounds with high atomic efficiency has been developed due to potential biomedical applications of polypeptides and polypeptoids, analogous to *N*-substituted amino acids [70]. Despite the simplest dipeptide, glycyl-glycine (Gly-Gly), for a trial reaction, the amino acid sequence on the final structure of the peptide-*alt*-peptoid copolymers was highlighted by choosing several dipeptides like glycyl-alanine (Gly-Ala) and L-alanyl-glycine (Ala-Gly) (Fig. 5a). A great attention has been paid on those water-soluble peptide-based alter-

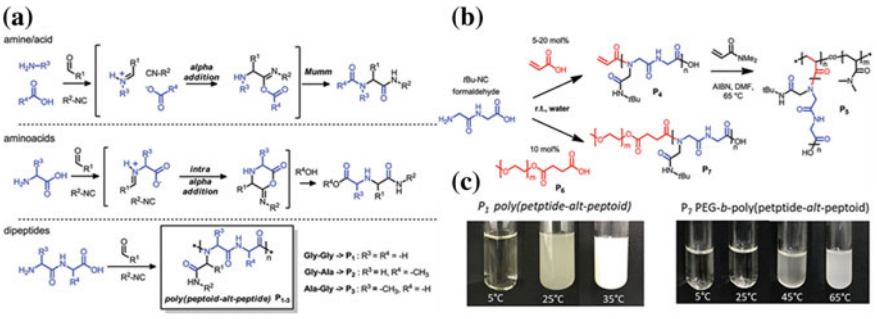

Fig. 5 **a** Synthesis based on Ugi four-component reaction, **b** synthesis of the poly(peptide-*alt*-peptoid) macromonomer as well as the corresponding graft and block copolymers with acrylic acid and *N*,*N*′-dimethylacrylamide (DMA), and **c** their thermoresponsive properties in aqueous solution. Reprinted with permission from Ref. [70]. Copyright (2017) The Royal Society of Chemistry

nating copolymers and their derivatives with acrylic acid, graft copolymerization with *N,N′*-dimethylacrylamide (DMA) by free-radical polymerization or modification with carboxylic acid terminated polyethylene glycol (PEG), due to their significant thermoresponsive properties exhibiting a range of lower critical solution temperature (LCST) leading to several biomedical applications (Fig. 5b, c).

Another interesting example of amino acid-based alternate architecture is MAX1, a sequence defined peptide containing 20 amino acids [71]. It is fully soluble in aqueous media, adopts random coil conformation, and can transfer to β-hairpin conformation to facilitate a targeted self-assembly structure into a rigid cross-linked hydrogel by applying exogenous stimulus like pH [34], temperature [72], ionic strength [73] of cell growth media. Kretsinger et al. demonstrated the cytocompatibility of the hydrogel toward NIH 3T3 murine fibroblasts generated from MAX1 including alternating sequence of lysine and valine residues oriented on two β-strands edges. They can be crinkled and self-assembled under treatment of buffered concentrated saline solution, i.e., cell growth media (Fig. 6) [74]. Cytotoxicity was measured in a qualitative pathway using a live/dead cell viability analysis. Here, calcein-AM hydrolysis in live cells produced a green fluorescent signal while ethidium homodimer generated a red fluorescent signal only in dead cells. The non-cytotoxicity of the hydrogel surface was exhibited by Fig. 7, where that cell viability on the hydrogel surface was comparable to that of the control TCTP surface. Due to non-toxic nature toward fibroblasts cells, porosity, biocompatibility, supportive properties to cell adhesion both in presence and absence of serum protein and proliferation, the hydrogel meets the preliminary mechanical and cytocompatibility requirement to act as an attractive candidate of tissue engineering scaffold.

Selectivity of pH-triggered supramolecular polymerization can be regulated by amino acid-based alternating peptide. In neutral buffer, self-assembly of phenylalanine-lysine (FK)- and phenylalanine-glutamic acid (FE)-composed

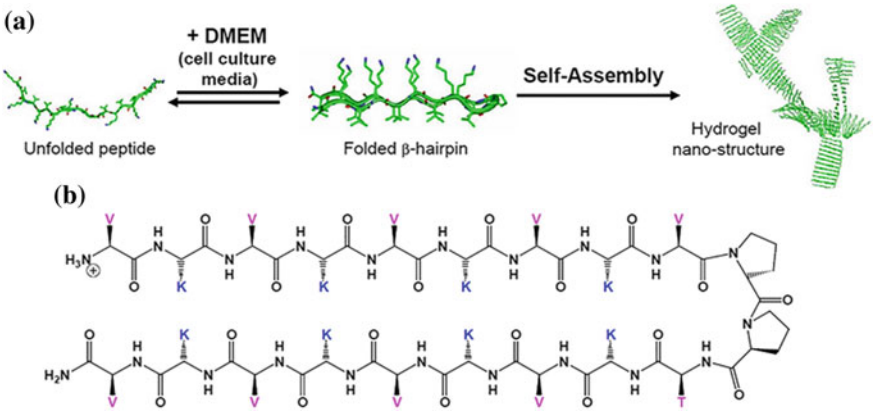

Fig. 6 **a** Model for the folding and self-assembly of MAX1. **b** Folded sequence of MAX1. Reprinted with permission from Ref. [74]. Copyright (2005) Elsevier

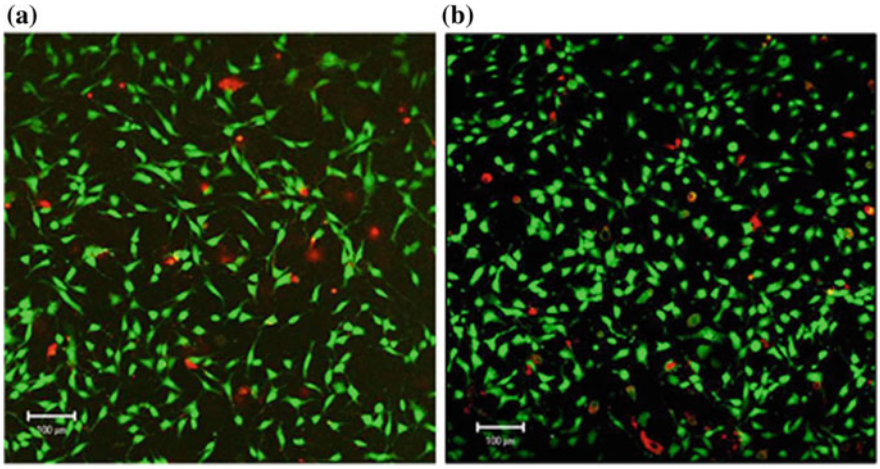

Fig. 7 Live/dead cytotoxicity assay on 40,000 cells/cm^2 murine NIH 3T3 cells 5 h after introduction onto **a** 2 wt% MAX1 hydrogels or **b** TCTP control plates. Viable cells fluoresce green and compromised cells fluoresce red. Scale bar represents 100 μm. Reprinted with permission from Ref. [74]. Copyright (2005) Elsevier

amphiphilic alternating dendron shaped peptides 1 and 2 can happen to generate a distinct 1–2 copolymers. pH can control the selective turn off of the negative or positive charges on the oppositely charged comonomers [75], hence leading to selective homopolymerization based on stimuli-responsive opposite comonomer release phenomenon. This was the first report of a supramolecular polymerization in solution with the ability to reversible switch over between three differential compositions: homopolymer of 1, 1–2 copolymers, and homopolymer of 2 where different states to be homopolymer of 1 (pH > 10), copolymer of 1–2 (neutral pH) and homopolymer of 2 (pH < 4) were postulated (Fig. 8) [76].

Conformational properties of amino acid-based alternating copolymers are regulated by salt effect and pH, though the consequence is somewhat different from amino acid-based statistical copolymers due to differential basic architecture. As reported in the literature, the alternating copoly(L-leucyl-L-lysine), however, does not exhibit coil to α-helix conformational switching like its statistical analog. But the precise alternating arrangement along the polymeric chain could result in a β-sheet orientation composed of hydrophilic and hydrophobic residues at two terminal sides. In the hydrophilic end, salt addition or pH enhancement could neutralize the repulsion among the positively charged amino groups of lysine side chains [77]. Different anions present in the salts are postulated to generate coil to β-sheet conformation of alternate amino acid-based architecture through different mechanism. ClO_4^-, specifically, bind to the positively charged side chain group, whereas β-structural orientation is dictated by SO_4^{2-} due to the intermolecular hydrophobic interactions between the leucyl residues of adjacent chains and ionic interactions between one

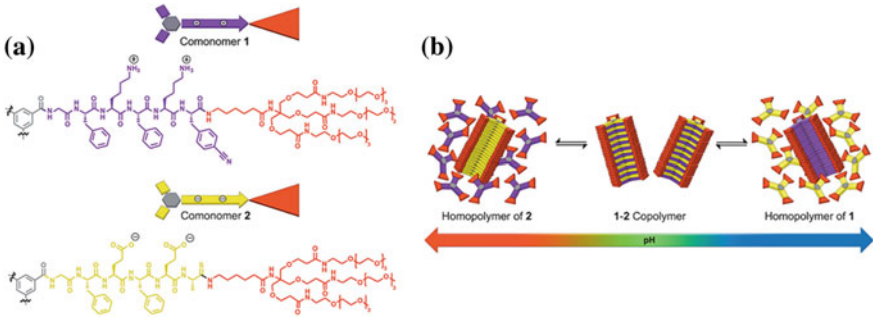

Fig. 8 **a** Chemical structures of the C_3-symmetric dendritic peptide comonomers 1 and 2; **b** their pH-regulated supramolecular polymerization into homopolymer of 1 and 2, at high and low pH, respectively, and 1–2 copolymer at neutral pH. Reprinted with permission from Ref. [76]. Copyright (2015) WILEY

SO_4^{2-} and two NH_3^+ groups of two neighboring polymers. Hence, the absence of specific binding capacity toward polycation by SO_4^{2-} unlike ClO_4^- dominantly regulates the mechanistic pathway.

The pH-induced conformational transition of an alternating amphiphilic peptide with an amino acid sequence Phe-$(Leu\text{-}Glu)_8$ can regulate the structural control of peptide-gold nanoparticles, where the surface of the nanoparticle is covered by the peptide chain [78]. The sequence defined alternating amphiphilic peptide surface adopts a α-helical conformation along with a substantial extent of a random coil and β-sheet arrangements under basic condition, whereas β-sheet structure was the dominant orientation for the peptide material under acidic environment. These conformational changes lead to morphological differentiation of the peptide coated gold nanoparticle assembly from globular to nanosheet structure by changing pH leading to intermolecular hydrogen bonding among the surface peptide (Fig. 9). The core gold nanoparticles could be fixed to the β-sheet assembly of the surface peptides, generating a useful system for new molecular tools with quantized properties.

Alanine and lysine containing sequence defined peptides $(AKA_3KA)_2$ (AK_2) produce an alternating architecture with flexible PEG moiety. Hence, a multiblock polymeric fusion material has been developed to imitate the molecular structure and design of natural elastin. The peptide $(AKA_3KA)_2$ (AK_2) is an essential structural component of the cross-linking structural biomolecules like proteins, e.g., mechanically active tissues to provide elastic property. Natural elastin-like mechanical strength could be introduced to a peptide-polymer hybrid hydrogel synthesized by covalently cross-linked alternating copolymers composed by hexamethylene diisocyanate and lysine side chains in the peptidic blocks (Fig. 10) [79]. Furthermore, PEG was substituted by an amphiphilic ABA block copolymer composed of PEG end blocks and a poly(propylene oxide) (PPO) center block, known as pluronics (F127). These types of copolymers can self-assemble into micelles leading to various conformational and assembly characteristics of AK_2 peptide under various environments (Fig. 11) [80]. Helical property and thermal stability of F127 micelles connected

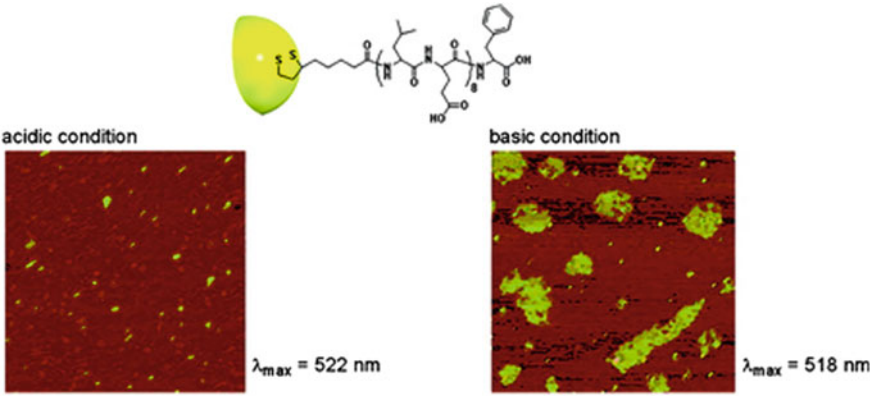

Fig. 9 Morphological changes of the alternating amphiphilic peptide, Phe-(Leu-Glu)$_8$ coated gold nanoparticle assembly from the globular to nanosheet structure by changing pH. Reprinted with permission from Ref. [78]. Copyright (2008) American Chemical Society

peptide materials are improved significantly as compared to the free peptide.

In contrast, amino acid-based alternating approach has opened a new dimension to develop a series of interesting, novel, biodegradable, and biocompatible materials called polyesteramides (PEAs) having potential applications in agricultural fields, drug delivery system, and tissue engineering scaffold. The potential thermal and mechanical properties of PEAs were introduced by the biodegradability of polyesters, substantial thermomechanical activities, and hydrogen bond-forming ability of polyamide functionality. The ring-opening bulk polymerization of morpholine-2,5-diones is an established technique for synthesizing alternating PEAs, called polydepsipeptides, which consist of alternating monomer units from α-amino acids like aspartic acid or lysine and α-hydroxy acids [81, 82]. Hence, a wide variety of polydepsipeptides could be prepared with different functionality and reactivity [83]. Copoly(L-lactide-depsipeptide)s [84] or poly(L-lactide)-polydepsipeptide block copolymers [85] are produced by the copolymerization of morpholine-2,5-diones with L-lactide which can be utilized for drug-loaded microspheres generation. This method has some limitations to the production of polyesteramides from α-amino acids and α-hydroxy acids as such cyclic compounds are difficult to synthesize from bulky monomers. A direct reaction between cyclic esters and amino acids can also generate PEAs. Melt polymerization of ε-caprolactone with 6-aminocaproic acid or 11-aminoundecanoic acid has been reported to prepare desired PEAs where the tensile strength is dictated by the amino acid portions in the primary mixture [86, 87]. Bulk copolymerization of ε-caprolactone and shorter amino acid, β-alanine, with extensive properties and biomedical applications are recently explored which is schematically represented in Fig. 12 [88].

Stereocomplexation can be achieved by using amino acid-based alternating strategies with potential applications in biomedical hydrogels and micelle or vesicle type microspheres for drug delivery systems [89, 90]. 12-mer sequence defined alternating

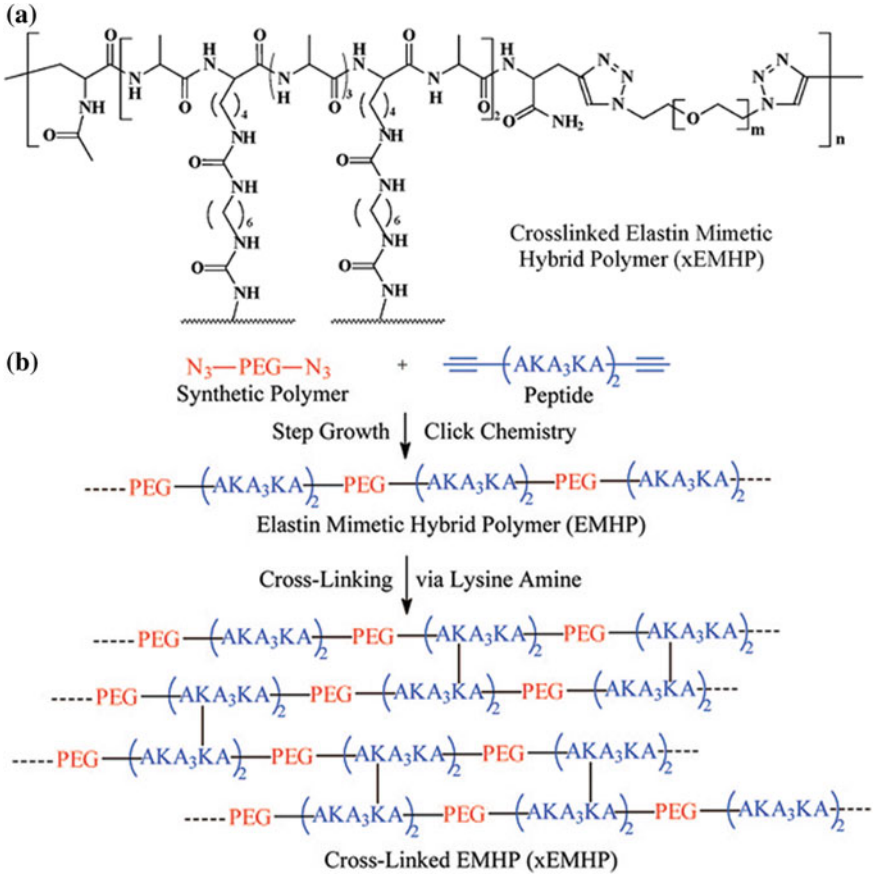

Fig. 10 **a** Chemical structure and **b** schematic representation of synthesis of covalently cross-linked elastin-mimetic hybrid polymer. Reprinted with permission from Ref. [79]. Copyright (2009) American Chemical Society

architecture composed of L-leucine (Leu) or D-leucine (leu) and 2-aminoisobutylic acid (Aib) produced a helical conformation of peptide chain and from the *N*-terminal residue, a poly(sarcosine) block was incorporated as expressed in Fig. 13 [91]. The molecular assembly from the mixtures of those block amphiphilic polypeptides transforming from planner sheet to vesicle upon heating is explained by stereocomplexation between right-handed and left-handed helical structure in hydrophobic core area of the sheet conformation [92, 93]. Right-handed helical amphiphilic peptide-based material was introduced to second-generation dendrimer at its eight terminal positions as a hydrophobic block, therefore leading to the supramolecular assembly as a consequence of stereocomplexation.

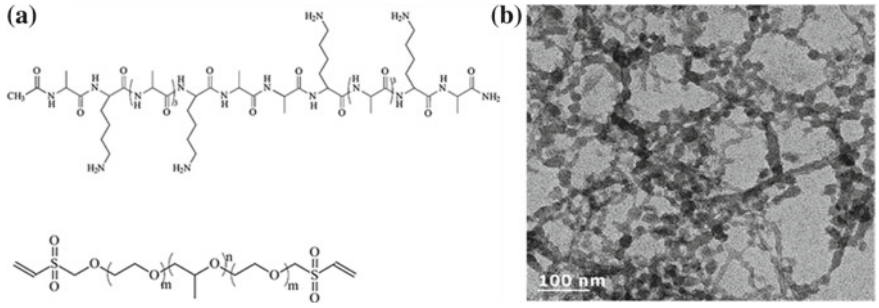

Fig. 11 **a** Chemical structure of alanine-rich, lysine-containing peptide with a sequence of Ac-$(AKA_3KA)_2$-NH_2 (AK_2, top) and vinylsulfone terminated pluronic F127, **b** transmission electron micrographs of peptide/F127 hybrid. Reprinted with permission from Ref. [80]. Copyright (2011) WILEY

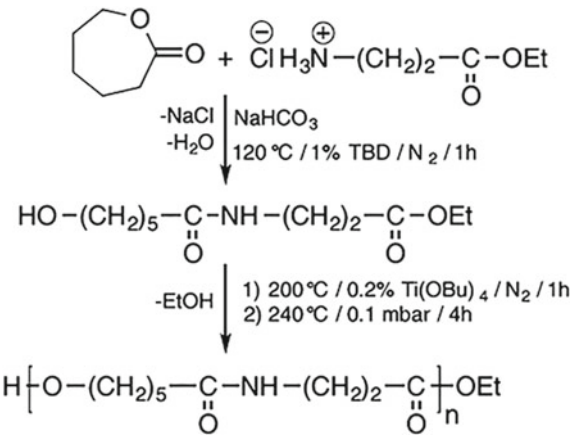

Fig. 12 Synthesis of alternating copolymer from ε-caprolactone and β-alanine. Reprinted with permission from Ref. [88]. Copyright (2014) Elsevier

Collective H-bonding and hydrophobic interactions lead to the generation of multiblock nanoparticle possessing elastin-mimetic property consisting an alternating sequence of poly(acrylic acid) (PAA) and alkyne-terminated, valine and glycine-rich peptide, $(VPGVG)_2$ (VG2) via the step-growth polymerization with potential application as pH-responsive drug delivery systems [94]. Biomedical applications of amino acid-based alternating polymers are further extended in several fields like bone repair, which is sluggish and complex physiological practice, biosensing applications [95], e.g., peptide-mimetic alternating copolymers (PMACs), synthesized by the copolymerization of ε-Z-lysine with hexamethylene diisocyanate (HDI), acted as an antibacterial delivery vehicle to transfer growth factors which were used to control bone repairing process [96].

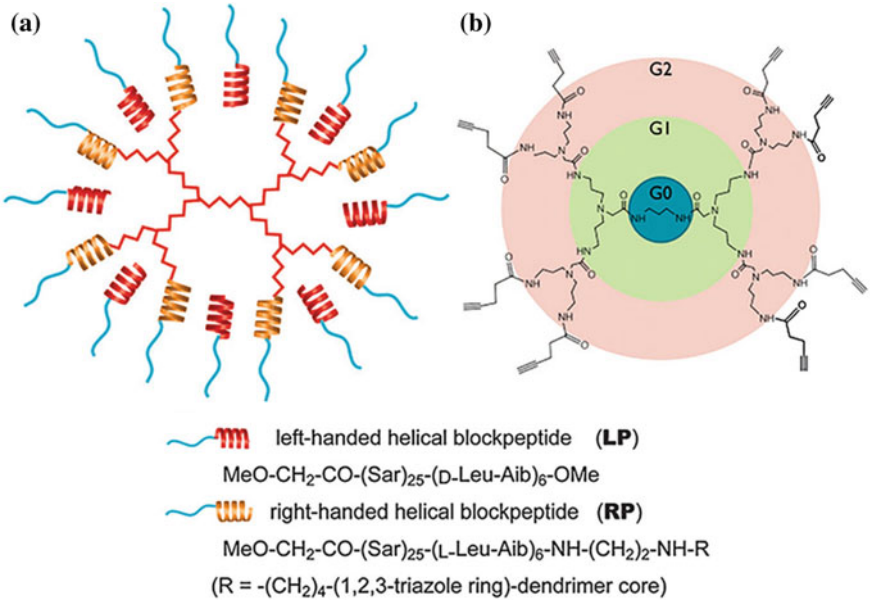

Fig. 13 The diagrams of molecular design: **a** the cartoon-like diagram of a co-assembling second-generation dendrimer template bearing amphiphilic right-handed block peptides (yellow helix) with amphiphilic left-handed block peptides (red helix), **b** the schematic diagram of the second-generation dendrimer core emphasized on the generation number. Reprinted with permission from Ref. [91]. Copyright (2012) The Royal Society of Chemistry

A novel and interesting traditional fluorophore-free water-soluble dual pH- and thermoresponsive fluorescent poly(styrene-*alt*-maleimide) skeleton-based copolymer was recently explored by our group through amino acid-based sequence-controlled copolymerization [43]. The thermoresponsive properties originated from the diethylene oxide side chain attached to maleimide moiety and the pH-responsiveness instigated from the deprotected leucine-appended styrene backbone. Thus, pH/thermoresponsive fluorescence activity in water was observed due to "through-space" π–π interaction between the benzene ring and the neighboring carbonyl group of the maleimide unit. This leucine containing alternating copolymer was further explored for speedy, selective, and sensitive detection of a well-known explosive nitro compound, picric acid (PA), in a 100% aqueous medium utilizing their nonfluorophore fluorescence property through determination of fluorescence quenching efficiency expressed in Fig. 14 [97].

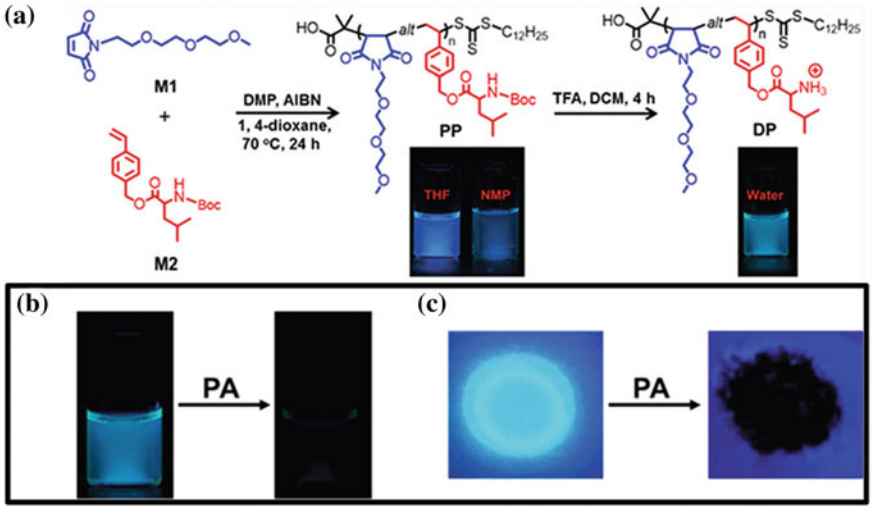

Fig. 14 **a** Synthesis of Boc-protected alternating copolymer (PP) and its subsequent deprotection under acidic conditions to afford the target macromolecular probe, deprotected polymer (DP). Fluorescence images of PP in tetrahydrofuran (THF) and *N*-methyl-2-pyrrolidone (NMP) and DP in water upon excitation with UV light at 366 nm. Naked-eye observation of fluorescence quenching under UV light: **b** in the solution state upon the addition of picric acid (PA) to the aqueous sensor solution, and **c** in the solid state upon adsorption of the PA solution on the sensor spot on a TLC plate. Reprinted with permission from Ref. [97]. Copyright (2017) The Royal Society of Chemistry

5 General Applications Originated from Alternating Architectures

Several applicative sides such as catalysis, molecular recognition, generation of biodegradable materials have been opened up from the alternating sequence-controlled polymeric architectures leading to the generation of microstructural periodicity, single-chain functional group distributions, and complicated macromolecular architectures [98]. Poly(styrene-*alt*-maleic anhydride) backbone supported copolymers displayed a selective detection for definite dialkylammonium ions or other size-specific complexations via inclusion complex formation where the crown ether moiety was formed by cyclo copolymerization [99]. Again, heterogeneous solid acid catalytic activity in organic transformation [100]; a new, recyclable, highly active Pd modified heterogeneous catalyst for Suzuki and Sonogashira cross-coupling reactions under "green" condition [101]; preparation of surfactant-free modified latexes [102]; fuel cell application [33]; drug release application [103]; fluorescence "OFF–ON" response to several selective metal ions and solution pH [42]; nanotube self-assembly behavior [104]; guest molecules entrapment, release properties along with multiple end group modified dendritic side chains [105]; generation of polyhedral oligomeric silsesquioxane (POSS)-based organic–inorganic hybrid materials having alternating architecture with enhanced thermal properties [106],

self-assembly behavior in aqueous solution [107], unusual fluorescence behavior in solid and solution state [34]; preparation of well-defined polyelectrolyte with complex microstructure [108] were explored from the same alternating skeleton with selective modification of side chain functionality attached to styrene or maleic anhydride/maleimide. Sequence control copolymer microstructure like their amorphous, crystalline or semicrystalline nature can finely tune the material properties with potential applications [109].

Synthesis of alternating copolymers with the cluster of bulky functional groups snatched a great attention as impenetrable well-designed clusters presenting in many biological organisms exhibited a crucial role in biological detection procedures susceptible of many applications [110]. Interactions with biomolecules can be exhibited by multivalent dendritic structures through introducing into the polymeric materials. Sterically crowded alternating polymer backbones based on functionalized stilbenes and maleic anhydride/functionalized maleimides lead to the generation of new anionic polyelectrolytes with tunable charge densities [111] with variable solution properties like dissociation or aggregation behavior [112]. A 2,3,4,5,6-pentafluorostyrene (PFS)-based alternating copolymer bearing $-NH_2$ and $-SO_3^-$ functional groups was originated as a capable organocatalyst for a Henry reaction between benzaldehyde and nitromethane [113]. Nanoporosity originates from the *tert*-butyl group deprotection of alternating copolymer containing *tert*-butyl carboxylate-functionalized stilbene or styrene and *N*-phenylmaleimide resulting in carbon dioxide capture properties [114]. Nitrogen adsorption/desorption applications can also be promoted by the hypercross-linked alternating sequence [115]. An interesting class of toothbrush like alternating graft copolymers with biocompatible PEG or polycaprolactone (PCL) can act as a potent drug career [116]. A novel approach, amphiphilic alternating copolymer brush (AACPB) opens a new dimension in applications like self-assembly [117], lithium salt-induced microphase separation, high-temperature ionic conductivity [118], and so on. The alternating copolymers consisting an anhydride functionality and a carbon-to-carbon double bond like twisted 1,3-butadiene in each replicate were conveniently applied for the polymer-surface alteration by several post-polymerization reactions, thermosetting and successive degradation process [119]. Low cytotoxicity and high serum compatibility of sugar responsive polymersomes with alternating architectures facilitated the application as elegant insulin delivery careers and the glucose level in the surroundings controlled the release properties [120]. Recently, a potential application for sterically stabilized nanoparticles in the area of foam stabilization was explored by styrene and *N*-phenylmaleimide-based alternating architectures [121].

Nowadays, amino acids or peptide functionalized alternating architectures have attained a significant interest as those units can self-assemble into ordered nanostructures like the assembly of diphenylalanine leads to the core detection motif of Alzheimer's β-amyloid [122]. Well-defined nanotube with potential self-assembly application is reported from peptide functionalized alternating copolymer of poly(2,3-dihydroxy butylene-*alt*-butylene di-thioether) (P(DHB-*a*-BDT)) [123]. The application of the peptide-based alternating polymers in various technological

utilizations, self-organization properties, piezoelectric devices, energy storage components, devices with light-emitting properties, superhydrophobic surfaces for self-cleaning, metal-organic frameworks, composite strengthening, ultra-sensitive sensing devices, 3D hydrogel scaffolds for inorganic ultra-structures, tissue engineering, and drug delivery purposes is investigated extensively [124].

6 Conclusions

The generation of huge and assorted collections of alternating copolymers has developed an exciting and creative area of progressive polymer sciences, where several novel functionalities could be oriented along the polymer backbone leading to an innovative functional polymer structure. In this chapter, we presented an overall discussion on different types of alternating copolymers, different synthetic strategies, mechanism, their interesting properties, and several applications along with the recent developments of amino acid and peptide-based alternating constructions. Peptide-based substances present an outstanding platform for the development of tissue engineering scaffold, targeted drug delivery systems, inclusion chemistry, molecular recognition and as substrates for regenerative medicine with the demand for several newly emergent technologies. Though a large number of synthetic strategies like solid-phase synthesis, ring-opening polymerization, NCA polymerization etc. are available for the production of these materials, defined regulation of the amino acid sequence in higher molecular weight peptides can only be generated by genetic engineering method. But several drawbacks associated with this method like lower yield, more laborious technique than others have led to additional, more fascinating approaches like side chain modifications of styrene and maliemide units through amino acids [43, 97]. Hence, several modified molecular tools involving amino acid sequence in the main chain and side chains are adopted for the creation of these alternating peptide-based compounds with potential applicative sides. However, the evolution and bridging between fundamental research and industry applications still remain elusive. Those peptide composed materials have the extensive and prospective viewpoints including self-assemblies that not only acquire unique chemical and physical properties, but also responsive nature, functional self-healing or wound-healing capacity, and catalytic activities. However, both the academic and industrial sector must realize and should construct an attempt to bridge the gap existing between fundamental research and industrial applications.

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