Prayogik Rasayan

Recent Developments in RAFT Derived Side-Chain Amino Acid-Based Polymers for Biological Applications

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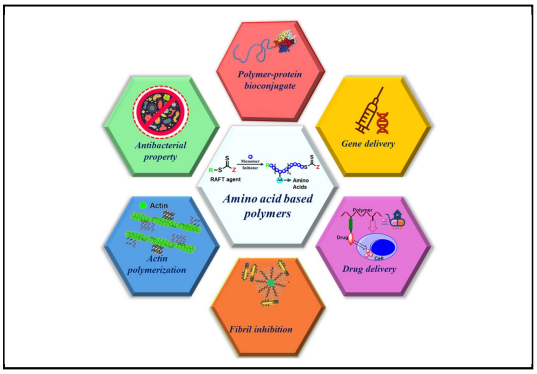
Abstract

Polymers with pendant amino acid moieties play a crucial role in shaping the properties of the resultant material, presenting captivating attributes like customizable amphiphilicity, chiral induction, organocatalytic capabilities, biocompatibility, aqueous solubility, and the ability to self-assemble into complex hierarchical structures. This review article aims to highlight the recent developments in the synthesis and utilization of these polymers, encompassing a range of current, high-demand applications such as drug and gene delivery, antibacterial activity, fibril inhibition, and biomimetic catalysts.



1. Introduction

Nature, as the best and most significant combinational library of natural compounds, often inspires enthusiasm toward mimicking biological processes or biomaterials in various domains due to its diverse desirability.[1] Natural amino acids serve as the fundamental building blocks of living systems and construct the protein.[2] In this context, amino acid-based polymers offer a unique chance to blend the advantages of synthetic polymers with natural biomolecules.[3] Various amino acids have been employed to modify a range of polymers, including homopolymers,[4] block copolymers,[5] random copolymers,[6] hyperbranched polymers,[7] and other polymeric structures,[8] thus developing smart materials. Kulkarni and Morawetz pioneered the concept of utilizing side-chain amino acid-containing polymers to explore the optical properties of polymers incorporating chiral monomers.[9] Subsequently, Sanda and Endo achieved significant progress in the 1990s by classifying amino acid-functionalized polymers into two groups: those with amino acid groups integrated into the backbone and those with amino acid functional groups attached to the side-chains.[10] Incorporating amino acid moieties into the polymer side-chain offers a significant advantage over main-chain amino acid-containing polymers, as it provides exceptional opportunities for modifying its functional groups.

Numerous innovative methods have been reported for the synthesis of side-chain amino acid-based polymers with amino acid-containing functionalized monomers. Polymers with amino acid pendants were prepared *via* free radical polymerization (FRP) or controlled radical polymerization (CRP) methods, e.g., nitroxide-mediated polymerization (NMP),[11] atom transfer radical polymerization (ATRP),[12] and reversible addition-fragmentation chain transfer (RAFT) polymerization.[13] Among other polymerization techniques, RAFT polymerization is very popular because it offers fine control over the molar mass with narrow dispersity (*Đ*) and precise chain end functionality.[14]

The amino acid-based vinyl monomer can be prepared *via* the *C*-terminus (-COOH group) or *N*-terminus (-NH_2 group) of the amino acid, or in certain instances through the attachment to the -*R* group.[15] These monomers can be polymerized *via* RAFT polymerization to prepare polymers with controlled chain length, structure, composition, and properties of the polymer.[16] In RAFT polymerization, the protection of amine groups in amino acids is vital, and their successive deprotection results in the formation of side-chain amino acid-based polymers with exposed pendant amine groups.[17]

Polymers containing pendant amino acids significantly influence the properties of the resulting polymer, offering intriguing features such as adjustable amphiphilicity, chiral induction, organocatalytic potential, biocompatibility, aqueous solubility, and the capacity to form self-assembled higher-order hierarchical structures.[16,18] Also, the incorporation of side-chain amino acid moieties into the polymeric backbone opens avenues for creating smart material with diverse applications.[19,20] This review article primarily explores the diverse applications of side-chain amino acid-containing polymers, encompassing drug and gene delivery, inhibition of amyloid fibril formation, biomimetic catalysis, antibacterial properties, and actin polymerization. Additionally, we provide brief insights into other potential applications such as cell membrane penetration, bioimaging, wound healing, tissue engineering, and self-healing. Despite significant advancements in this thriving field, there remains a lack of literature that provides comprehensive reports on side-chain amino acid functional polymeric scaffolds for promising bioapplications. Most of the reviews emphasized only the applications with a few case studies. Hence, it is crucial to generate a report that precisely outlines the advantageous impacts of RAFT-derived side-chain amino acid-based polymers in today's most demanding bioapplications. Herein, we offer a concise overview addressing the demand for

polymeric architectures featuring amino acid pendants in the side-chain, relevant to the advanced global challenges.

2. Applications

Stimuli-responsiveness, and biocompatible features of amino acid-based polymers make them promising therapeutic candidates. There has been a lot of focus on developing new self-assembling polymeric scaffolds based on side-chain amino acids for use in drug delivery, gene transport, fibril inhibition, antibacterial activity, biomimetic catalysis, and other applications. The following sections highlight research on the therapeutic applications of side-chain amino acid-derived polymeric nanostructures throughout the past few years.

1. *Drug delivery.* The controlled release profile and enhanced bioavailability of drugs have led to the development of numerous drug delivery systems (DDSs) based on self-aggregated amino acid polymers.[21] Site-specific targeting, prolonged release capabilities, reduced toxicity, and biocompatibility of self-aggregated amino acid-based polymeric materials make them an attractive option for drug delivery applications. Towards this particular concept, a series of precisely defined amino acid-based amphiphilic block copolymers were synthesized through photoinduced electron/energy transfer (PET)-RAFT polymerization by Feng and coworkers (Figure 1A).[22] Through hydrophobic and hydrogen interactions, the copolymers self-assembled into nanostructures of diverse morphologies, including spheres, rod-like structures, fibers, and lamellae, by modifying the block ratio and monomer types (Figure 1B). The drug loading efficiency of the nanoparticles (NPs) formed from the valine (Val) and aspartic acid (Asp) based amphiphilic block copolymers (poly(*N*-acryloyl-Val)-*b*-poly(*N*-acryloyl-Asp)) was favorable (21.8-32.6%) across a diverse array of drugs, including paclitaxel, doxorubicin, cisplatin, and others.

Formulation of efficient approaches is addressed to deal both bacterial infections and tumor progression *via* combinational therapy. Biswas *et al.* developed an integrative approach for antibacterial drug delivery using stimuli-responsive amino acid-based system, which was efficient against *Escherichia coli* (E. coli) and may release the anticancer medication doxorubicin in response to stimuli.[23] Utilizing RAFT polymerization, pH and temperature dual responsive diblock copolymers of tyrosine (Tyr) and poly(ethylene glycol methyl ether methacrylate) (PEGMA) have been produced. The amphiphilic block copolymer was tested for the delivery of the anticancer medication doxorubicin against a human hepatoma (HepG2) cell line. The self-assembled polymers became active against bacteria upon delivery in an acidic pH due to an increase in surface charge. Mori's group investigated how the release of metronidazole (MTZ) from synthetic proline-based polymers was affected by the polymer's molecular weight.[24] Interestingly, the rate of release study demonstrated that polymer-MTZ adducts with lower molecular weights released MTZ more quickly than those with higher molecular weights. A fall in drug release rate as the molecular weight increases can be attributed to the increased entanglement of polymer chains, which hinders the diffusion of drug molecules from the polymer matrix by trapping them in the more densely entangled matrix of polymer chains.

Although there have been advancements in drug delivery methods, finding a safe and efficient way to administer both anticancer medicines and therapeutic genes for cancer treatment is still challenging. In this context, Dutta *et al*. have successfully synthesized smart pH-responsive block copolymers comprising capric acid and tryptophan (Trp), with the dual purpose of functioning as a drug delivery agent and deoxyribonucleic acid (DNA) sensor.[25] The hydrophobic nature of the block copolymer was largely due to the assimilation of the long hydrophobic tail of the fatty acid segment and the hydrophilic nature of the amino acid segment with pendant amine moieties. Thus, the amphiphilic block copolymers were suitable for encapsulating doxorubicin to deliver it to cancerous tissues in a pH-responsive manner. The block copolymer's cationic character, inherited from Trp enabled DNA binding and detection. Recently, Patra *et a*l. used RAFT polymerization to fabricate a photoswitchable smart polymeric vehicle consisting of a photoswitchable spiropyran (SP) moiety and an amino-acid-based cationic monomer-containing block copolymer.[26] The primary objective of this system was to identify triple-negative breast cancer by administering anticancer drugs and DNA. The hydrophilic, colored merocyanine (MC) form was produced from the colorless, hydrophobic nonpolar SP form in the presence of ultraviolet radiation. With an extremely low limit of detection values, the MC form of this polymer exhibited metal ion selectivity towards Cu(II). The utilization of intracellular Cu(II) ion detection in highly aggressive triple-negative breast cancer cells offers an alternative diagnostic pathway.

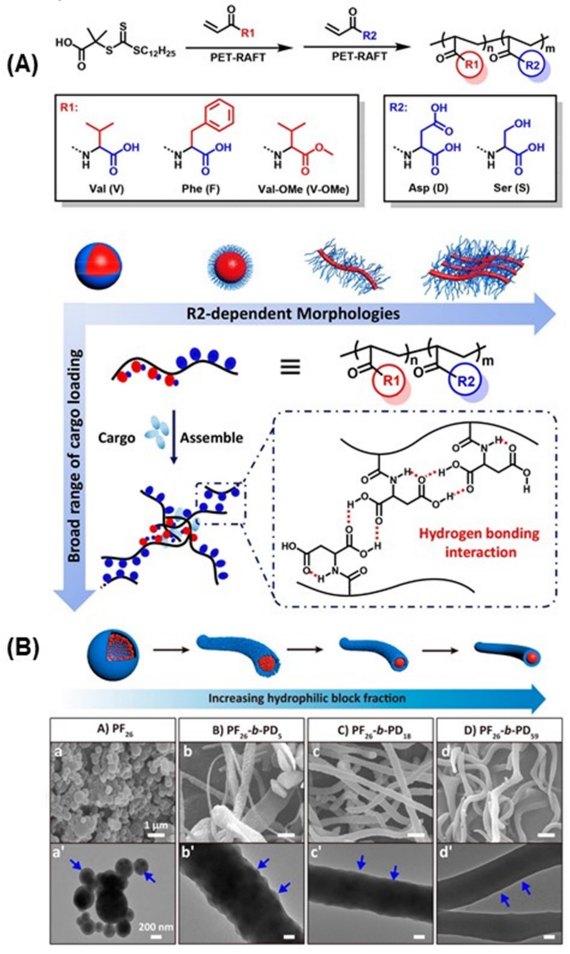


Figure 1. (A) PET-RAFT polymerization to synthesize homopolymers and diblock copolymers, their self-assembled morphologies and cargo loading ability based on strong hydrogen (*H*)-bonding interaction in hydrophilic fraction. (B) SEM images (a−d, scale bars = 1 μm) and TEM images (a′−d′, scale bars = 200 nm). Adapted with permission from

reference [22]. Copyright © 2021, American Chemical Society.

2. *Gene delivery.* Genetic elements are macromolecules with a negative charge that are susceptible to being degraded by enzymes in both *in vitro* and *in vivo* conditions. As a result, vectors are necessary to transfer genetic elements to target cells while keeping them safe. Cationic polymers are extensively used in this scenario due to their capacity to attach and protect genetic material.[27] It is noteworthy that the amino acid-based polymers exhibited a significantly reduced cytotoxicity in comparison to the linear polyethyleneimine (PEI).[28] In this context, three amino acid-based diblock copolymers consisting of glycine-phenylalanine (Gly-Phe), leucine-phenylalanine (Leu-Phe), and glycine-leucine (Gly-Leu) have been synthesized by Saha *et al.* [29] By agarose gel electrophoresis and particle size, the gene complexation capability of each polymer was verified. Further investigation was conducted to assess the stability of the polymer/pDNA complexes against enzymatic degradation to determine whether these vectors are suitable for *in vivo* applications.

It is beneficial to develop safe and efficient nanocarriers for multitype delivery systems to combine the carrier with multiple types of successful biomedical therapies. Therefore, we have successfully engineered hybrid block copolymers composed of biomolecules derived from chiral amino acid-containing (L-Phe and L-alanine (L-Ala)) vinyl monomers (Figure 2). These block copolymers exhibited great potential for both gene transfer and drug delivery.[30] The self-assembled micellar aggregation of these amphiphilic block copolymers was examined and a drug was encapsulated. Deprotection of side-chain *tert*-butoxycarbonyl (Boc) groups in amphiphilic block copolymers produced hydrophilic pH-responsive cationic block copolymers which were tested for DNA binding using agarose gel retardation assay. Sahoo *et al.* engineered a new DNA carrier by preparing a histidine (His) based star-shaped *β*-cyclodextrin (CD)-capped poly(*N*-methacryloyl-L-His methyl ester) using RAFT polymerization technique with the biocompatible *β*-CD host as a core.[31] Using a disulfide-containing cross-linker with two adamantane (Ad) groups at its two ends, a 2:1 inclusion complex (IC) was developed which exhibited a strong DNA-condensing capability to create polymer-DNA complexes (polyplexes) and an efficient redox-responsive release of the DNA payload. Using thiazole orange as an intercalating dye, the time-correlated single-photon counting approach was used to study the DNA condensation–decondensation in great detail.

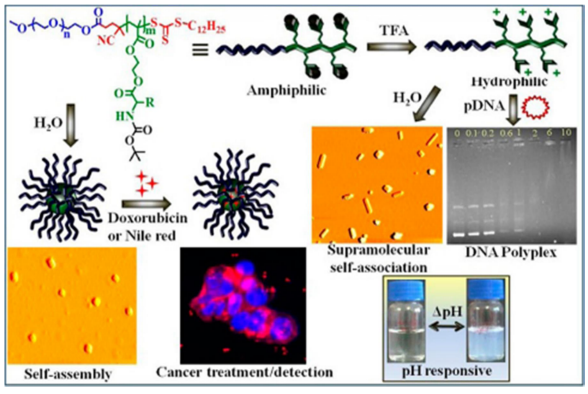


Figure 2. Schematic diagram of RAFT polymerization derived amino acid-based diblock cationic polymers for gene transfection. Adapted with permission from reference [30]. Copyright © 2013, American Chemical Society.

3. *Fibril inhibition.* Amyloid aggregation, misfolding of various proteins is an extreme trait observed in age-related diseases.[32,33] Designing suitable therapeutic agents capable of efficiently inhibiting the formation of amyloid fibrils poses significant challenges, including issues such as poor bioavailability across the blood-brain barrier, reduced biostability, low biocompatibility, and the need to avoid complicated synthetic routes. Recently, apart from several inhibitors, polymers, and polymer-based nanomaterials are the good choice for the retardation of amyloid aggregation as they have flexible molar mass, various architectures and functionality, suitable thermal properties, functional groups with hydrophobic and hydrophilic groups, the nature of charged groups (cationic, anionic, or zwitterionic), high biocompatibility and bioavailability, etc.[34] Amino acids like arginine (Arg) and proline (Pro) have previously showcased their therapeutic potential in inhibiting the protein aggregation process.[35,36] Therefore, a challenging endeavor will involve the design of novel side-chain amino acids or peptides comprising biologically pertinent macromolecules, aimed at investigating protein fibril inhibition. Numerous pieces of literature showcase the inhibitory activity of amino acid-based polymeric systems on amyloid fibril formation. Chaudhury *et al*. have reported that PEGylated block copolymers, derived from the side-chain tripeptide (Leu-Val-Phe), serve as polymeric inhibitors targeting the essential hydrophobic amino acid sequence 'Lys-Leu-Val-Phe-Phe-Ala' of the Aβ_{42} peptide. This polymeric inhibitor developed a new generation of Alzheimer's disease therapeutics targeting the inhibition of misfolded Aβ_{42} peptide fibrillization.[37]

Our group revealed the admirable *in vitro* insulin fibril inhibitory activities of side-chain proline-based homopolymers and block copolymers (Figure 3).[38] We demonstrated that along with hydrophobic interactions, polar interactions are the crucial factors for fibril inhibition. A polymeric micelle comprising of polyaspartic acid backbone with oleyl amine, ethylenediamine, and Arg functional groups was reported. These synthesized micelles effectively eliminate amyloid-aggregated species from cells by enhancing the cellular autophagy process.[39] Bera and coworkers have developed block copolymers with Boc-protected Leu and acetyl (Ac)-protected glucose pendant groups, respectively. The amphiphilic polymers, obtained through selective or dual deprotection of Boc and Ac groups from Leu and/or glucose moieties, exhibited self-assembly into nanoaggregates in aqueous medium, which inhibited the insulin fibril formation *via* the *H*-bonding and electrostatic interactions between insulin and polymers.[40] Bera *et a*l. synthesized three copolymers composed of poly(ethylene glycol) methyl ether methacrylate (PEGMA) and methacrylate monomers containing Boc-protected amino acids (Ala, Leu, and Phe). In successive deprotection of Boc groups, the copolymers were coated on silver nanoparticles used for inhibiting insulin fibril formation. The novel amino acid-based polymer coated silver nanoparticles (PC-AgNPs) effectively inhibited insulin fibril (77-96%) and also showed noticeable disaggregation.[41]

A newly developed biocompatible polymer poly(*N*-acryloyl-L-phenylalanyl-L-phenylalanine methyl ester) nanoparticle, incorporating hydrophobic dipeptides (L-phenylalanyl-L-phenylalanine) within the polymer side-chains, showed promise for inhibiting amyloid-*β* fibril formation.[42] The presence of polymeric nanoparticles was observed to significantly delay the direct secondary structure transition from random coil to *β*-sheets during Aβ_{40} fibril formation. This observation suggested that these nanoparticles notably prolonged the lag time, consequently impacting the kinetics of Aβ_{40} fibrillation.

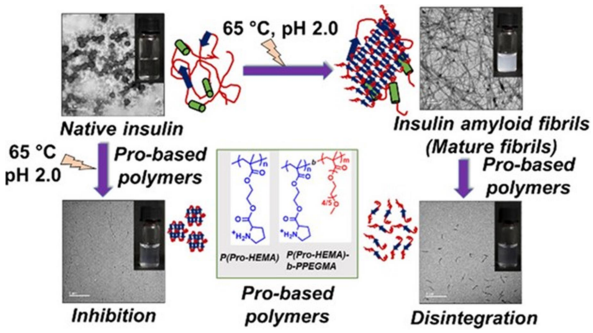


Figure 3. Schematic presentation of side-chain proline functional homopolymer and block copolymer induced inhibition of insulin amyloid fibril aggregation. Adapted with permission from reference [38]. Copyright © 2020, American Chemical Society.

Nevertheless, when exposed to poly(*N*-acryloyl-L-Ala-L-Ala methyl ester) nanoparticles, a contrary trend emerged, suggesting an acceleration in the kinetics of Aβ_{40} fibrillation. Palmal *et al*. investigated the amyloid fibril inhibitory activities of gold nanoparticles coated with His-based polymer.[43] Polymeric nanomaterials have demonstrated facile surface modifications, offering a diverse array of binding sites for interactions with proteins. Certain polymers stabilize native proteins by safeguarding their higher-order structures, facilitating protein refolding through interaction with the hydrophobic amino acid residues, thus impeding protein aggregation.

4. *Antibacterial properties.* Antibacterial coatings play a vital role in infection control, public health, and safety across various sectors. By preventing bacterial contamination and reducing the spread of infections, these coatings contribute to healthier environments, improved patient outcomes, and enhanced quality of life. In this regard, polymers with antibacterial activities are good choices compared to small molecules for potential improvements to medical devices. A lot of attention has been paid to cationic-charged amphiphilic polymers with antibacterial activities so far because of their lower toxicity, extended blood circulation duration, protease inactivity, and increased antibacterial efficacy.[44]
Influenced by the intriguing characteristics of cationic side-chain amino acid-containing polymers with antibacterial activity, various architectural structures, including linear, hyperbranched, and star-shaped polymers having cationic leucine moieties have been reported against the gram-negative bacterium E. coli, by using the zone of inhibition study, calculating minimum inhibitory concentration (MIC), and bacterial growth experiment.[7] Hyperbranched and star architectures showed the highest antibacterial activity based on the MIC values, attributed to the presence of a higher degree of cationic and hydrophobic functional groups in hyperbranched and star polymers which facilitated the cell wall penetrability is significantly enhanced in comparison to the linear polymer.

A range of side-chain amino acid-based antibacterial polymers, including Gly, Ala, Val, Leu, Ile, Phe, Tyr, Asp, and Glu, have been reported by Barman *et al*.[45] By changing the amino acid moieties in the polymers, it was discovered that the antibacterial and hemolytic activity differed (Figure 4). The most advantageous aspect of these polymers is their strong anti-acinetobacter baumannii (A. baumannii) activity, as this pathogen is thought to be the deadliest in the world. These polymers eliminated A. baumannii's metabolically dormant stationary phase in just two minutes. A lysine-attached styrenic monomer was copolymerized with maleimide-linked octanoic acid (**ACP2**) and maleimide-linked myristic acid (**ACP3**). The antibacterial activity of the cationic polymers **ACP2** and **ACP3** was evaluated using the broth microdilution method against B. subtilis and E. coli.[46] The B. subtilis development was inhibited more by the myristate-attached polymer (**ACP3**) than by the shorter chain fatty acid tethered polymer (**ACP2**), mainly because of different hydrophobicity in those two polymers. But in the case of E. coli inhibition, these polymers' hydrophobicity serves no additional benefit. Field emission scanning electron microscopy (FESEM) images revealed that after polymer treatment both of the bacterial cell membranes compromise membrane integrity and expose intracellular contents, ultimately leading to cell death.

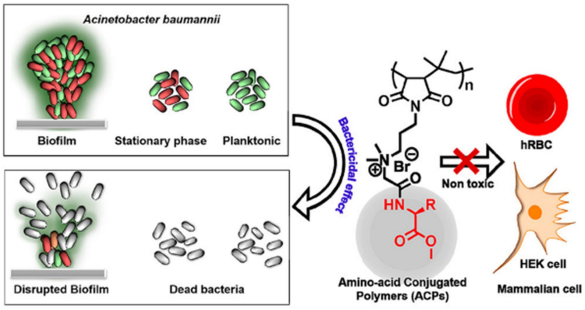


Figure 4. Schematic of amino acid-conjugated polymers having strong antibacterial activity and low mammalian cell toxicity. Adapted with permission from reference [45]. Copyright © 2019, American Chemical Society.

5. *Biomimetic catalysts.* A broad spectrum of biochemical reactions is facilitated by biocatalysts such as enzymes, which demonstrate remarkable selectivity and efficiency in promoting reaction rates even under mild reaction conditions.[47] In this regard, polymer-supported organocatalysts have been extensively used as biomimetic catalysts for various reactions. The polymer-supported organocatalysts immobilize active moieties within the polymeric matrix. This class of organocatalysts are designed with high stability and reusability, thus facilitate facile separation from the reaction mixture.[48]

L-proline mimics the same pathway of the aldolase enzymes in the asymmetric aldol process that facilitated the side-chain L-proline pendant polymers for catalyzing asymmetric aldol reaction. O'Reilly *et al*. demonstrated that the incorporation of hydrophilic amino acid L-proline into a hydrophobic polystyrene backbone produces a polymer exhibiting excellent catalytic activity in aldol reaction, achieving high yields and selectivity at room temperature for 24 h in *N,N*-dimethylformamide (DMF)/water (v/v) medium (Figure 5A).[49] The same research groups also synthesized two L-proline-based block copolymers, where the hydrophilic block contains poly(acrylic acid), and the hydrophobic blocks consist of styrene and methylmethacrylate.[50] These two amphiphilic block copolymers underwent self-assembly, forming polymeric nanoreactors. These nanoreactors enabled the efficient reactivity of hydrophobic starting materials in aqueous environments, eliminating the necessity for a solubilizing co-solvent. Moreover, they displayed superior catalytic properties in aqueous conditions for aldol reactions.

Zayas *et al*. designed and synthesized a thermoresponsive block copolymer with a hydrophilic block poly(dimethylacrylamide) and a thermoresponsive segment which above its lower critical solution temperature (LCST) became hydrophobic. This block copolymer efficiently

directed the asymmetric aldol reaction in water with excellent yields and enantioselectivity (Figure 5B).[51] At temperatures exceeding the LCST (ranging from 25 to 40 °C), micelles with sizes of ~15-20 nm were formed, encapsulating the catalytic L-proline moiety within the hydrophobic core. Upon cooling the reaction mixture below the LCST, the block copolymer achieved complete water solubility, facilitating the effortless separation of the catalyst from the water-insoluble aldol product. Gruttadauria *et al*. undertook an extensive exploration of the catalytic activities exhibited by proline amide derivatives immobilized on polystyrene support, resulting in notable outcomes of high yields and exceptional enantioselectivities.[52]

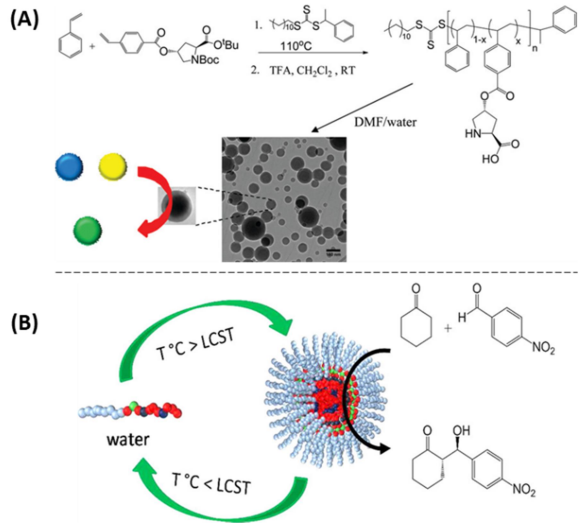


Figure 5. (A) Proline-based amphiphilic polymers showed organocatalysis behavior for the asymmetric aldol reaction in DMF/water (v/v) medium. Adapted with permission from reference [49]. Copyright © 2011, American Chemical Society. (B) A thermoresponsive block copolymer with proline pendants efficiently directed the asymmetric aldol reaction in water with excellent yields and enantioselectivity. Adapted with permission from reference [51]. Copyright © 2013, American Chemical Society.

6. *Actin polymerization.* The actin cytoskeleton is characterized by a network of microfilaments formed from the polymerization of G-actin monomers into filamentous actin (F-actin). The dynamic nature of the actin cytoskeleton is crucial for cellular processes such as exocytosis, endocytosis, cytokinesis, cell motility, phagocytosis, polarization, adhesion, as well as cell growth and development.[53] There are several actin binding proteins, which control the actin dynamics. The actin-binding proteins, effectively employed for actin nucleation and polymerization, also play crucial roles in stabilizing actin filaments, facilitating depolymerization, capping filaments, and crosslinking/bundling them.[54] Several positively charged compounds are reported to counterbalance the negative charge present on polyelectrolytes like actin filaments.[55] Polystyrene beads coated with polylysine, polyamines, positively charged liposomes, polypeptides, polycations, histones, and physiologically myristoylated Ala-rich C kinase substrate bind with actins through its cationic charge or electrostatic interactions.[56] Although these compounds offer new avenues for exploring the regulation of the actin cytoskeleton in motile and morphogenetic processes, the majority of the aforementioned actin-binding substrates have been identified as cytotoxic to cells. Therefore, biocompatible synthetic compounds containing a cationic charge are necessary for the actin nucleation process.

Amino acid-based polymers can influence actin polymerization through a variety of techniques, including mimicking structural properties, supplying binding sites, and modifying actin dynamics.[56] Side-chain amino acid-based polyelectrolytes, inherently biocompatible and possessing a cationic nature, hold promise in forming electrostatic complexes with negatively charged actin molecules. Maiti *et al.* synthesized poly(Boc-L-Ala methacryloyloxyethyl ester), followed by deprotection of the Boc group, resulting in the formation of a positively charged amine moiety within the side-chain amino acid-based polymer, poly(L-Ala methacryloyloxyethyl ester), which was used to investigate the impact of a side-chain Ala functionalized cationic polymer on actin polymerization. Their detailed study suggested that the polymer binds to multiple actin monomers, thereby promoting the formation of a stable actin nucleus/seed (Figure 6).[56] Sahoo and coworkers synthesized various cationic polymers derived from amino acids (Ala, Phe, and Leu), both with and without the addition of a chain-end cholic acid moiety (cholate) for the study of actin dynamics.[55] Additionally, they prepared cationic polymeric amphiphiles with varying cholate content in the side-chain. This investigation presented a potential prospect of the cholate based polymeric amphiphiles with amino acid pendants as actin-interacting material to regulate cellular function for biomedical purposes.

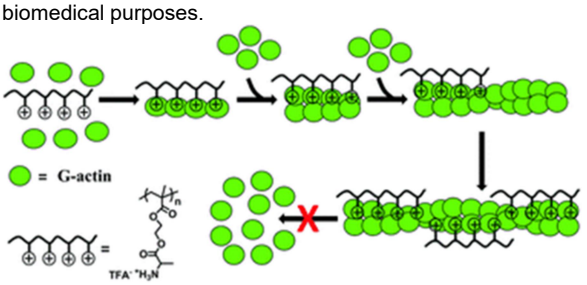


Figure 6. Application of side-chain alanine based cationic homopolymer during the polymerization of G-actin to F-actin. Adapted with permission from reference [56]. Copyright © 2017, Royal Society of Chemistry.

7. *Other applications.* Beyond the above-mentioned widespread applications, amino acid-based polymeric materials exhibit vast potential in various other biomedical contexts, a summary of some other applications is provided here.[57,58] Polymeric materials with amino acid pendants are widely employed in constructing efficient sensor platforms for detecting heavy and transition metal (HTM) ions, nitro aromatic compounds, picric acid, and other substances.[59] Choudhury *et al*. synthesized a fluorescent water-soluble copolymer with tryptophan moieties *via* RAFT polymerization, utilizing Boc-tryptophan methacryloyloxyethyl ester (BTE) and *N,N*-dimethylacrylamide (DMA).[60] Following the removal of the Boc-group and subsequent modification with 2-pyridinecarboxaldehyde, the resulting water-soluble copolymers exhibited efficient detection capabilities for both Cu^{2+} and Hg^{2+} ions in aqueous environments. Another report demonstrated the synthesis of a polymeric probe containing tryptophan-dithiocarbamate, which targets selective recognition and sensing of both cation and anion in aqueous

media.[61] This amino acid-derived polymeric probe demonstrated high efficiency in detecting Hg^{2+} ions at concentrations as low as 300 parts per trillion (ppt) and hydrogen sulfate anions (HSO^{4-}) at the parts per million (ppm) level among various ions in aqueous media, exhibiting a 94% removal capacity for Hg^{+2}. Kumar *et al*. developed a polymeric probe tagged with dansyl and alanine moieties, poly(MMA-*co*-Dansyl-Ala-HEMA) (DCP), to selectively detect conventional nitroaromatic explosives like 2,4,6-trinitrophenol (TNP), 2,4-dinitrotoluene (DNT) and 2,4,6-trinitrotoluene (TNT) with remarkable sensitivity.[62] Wang *et al*. disclosed a pH-responsive hyperbranched polymeric material derived from lysine, which emulates the endosomolytic properties of cell-penetrating peptides, showing promise as a vehicle for delivering therapeutic payloads into the cytoplasm.[63]

Smart polymers derived from amino acids have demonstrated considerable promise in the realm of tissue engineering as well as wound healing.[39,64] Juriga and coworkers innovatively designed a polymeric hydrogel using poly(aspartic acid) (PASP) crosslinked with cystamine (CYS) and lysine methyl ester (LYS) amino acids to utilize in tissue engineering.[65] Recently, there has been considerable interest in porous poly(lactide-*co*-glycolide) (PLGA)/hydroxyapatite (HA) scaffolds, which support cell attachment and growth while facilitating the transfer of waste products and nutrients from the cells through the pores. Here, Zheng *et al*. modified PLGA/HA scaffold with poly-L-Lysine to stimulate cell growth and osteogenic differentiation. Different studies like Alizarin red staining, alkaline phosphatase activity, mechanical strength, and cell culture demonstrated that the proliferation and osteogenic differentiation of cells were improved by an amino acid-coated scaffold.[66] Several polymeric substances fulfill the requirements for wound healing by exhibiting favorable biocompatibility, maintaining a localized humid environment, promoting the release of growth factors, and safeguarding the wound against bacterial infections.[39] Yang *et al*. reported several hydrogels derived from ε-poly(L-lysine)-modified poly(vinyl alcohol) (CPVA-g-EPL)/chitosan/Ag complexes, crosslinked with oxidised dextran.[67] This biocompatible materials demonstrated great injectability and wound healing characteristics in a mouse skin defect model.

Besides these applications of amino acid-based polymers, several different types of applications were observed by various groups of researchers. Armes group performed RAFT dispersion polymerization to synthesize a series of new diblock copolymer vesicles which reacted with an amino acid to form Schiff base linkage for a significant change of electrophoretic footprint of that vesicles under mild conditions.[68] In another report, the Arms group synthesized a novel zwitterionic poly(amino acid) brush to see the protein adherent capability of some new synthesized aldehyde-functionalized hydrophilic polymer brushes.[69] Recently, they have synthesized arginine functionalized block copolymer nanoparticles and studied their adsorption properties on a model planar substrate.[70]

The efficacy of using amino acid-based polymers in industrial-scale RAFT polymerization is demonstrated. This approach, feasible in various solvents (even water) and temperatures, exhibits high tolerance for functional groups and absence of metals.[71] Commercially, readily available and customizable chain transfer agents (CTAs) boost its viability. This availability allows tailoring polymer properties through CTA functionalization, expanding potential applications. The mild reaction conditions of the RAFT process may simplify industrial scale-up, reducing the need for complex or costly equipment setups.[71] The versatility and cost-effectiveness of RAFT polymerizations make it a potent method for making new materials, leading to its increasing presence in industrial applications.

3. Conclusions

In this article, we have summarized the intriguing features of side-chain amino acid-based biocompatible polymers for various bioapplications. Their customizable amphiphilicity helps them to self-assemble in aqueous solution, thus advantageous for the applications in the area of the biological field. Herein, we discussed applications of side-chain amino acid based polymers derived from RAFT polymerization in the area of drug and gene delivery, antibacterial materials, fibril inhibition, and biomimetic catalysis. However, leveraging these amino acid-derived biopolymers as structural and functional materials remains a significant challenge for researchers within their respective applications.

Continuous effort is needed for the development of amino-acid based polymeric materials addressing the critical challenge of targeting specific cells, tissues, and organs. Most of the reported studies should be extended to *in vivo* experiments in order to understand the efficiency of amino-acid based polymers. It is vital to note that an innovative design of polymer is required in each of these applications. This includes assuring the existence of an appropriate cationic charge for successful gene delivery and effective actin polymerization. Since the polymeric scaffolds containing proline moieties were responsible for effective catalysis during the aldol reaction, several other polymeric architectures such as hyperbranched, star, star block, etc. should be studied in detail. Although these amino acid based side-chain polymers have widespread bioapplications, there remains plenty of opportunity for enhancing the design and synthesis of amino acid-based polymeric materials to realize their full potential as effective platforms for various applications. A significant gap exists between *in vitro* and *in vivo* research findings that must be addressed to develop polymeric scaffolds effectively across animal and clinical trials. In addition, future studies will focus on commercializing these polymers for biomedical applications.

4. Acknowledgements

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