Functional polymer nanoassemblies with various morphologies (e.g., micelles, vesicles, rods, disks, etc.) showed great potential in therapeutics delivery, bioimaging, biosensors, bioactuators, bioelectronics, food packaging and nanodevices. However, majority of the polymer nanoassemblies were formed via non-covalent driven forces, which offers them dynamic features and results in low stability under the conditions such as dilution, change of pH value and ionic strength, thermal and specific chemical stimulators, largely limiting their biomedical applications. To develop stabilized polymer nanoassemblies, crosslinking technique, a covalent approach, was rapidly developed and utilized to prepare chemically fixed, stabilized and functionalized polymer nanoassemblies/architectures by reinforcing the interactions between the polymer chains. Up to date, a number of crosslinked polymers and crosslinking methods have been developed for the construction of crosslinked nanoassemblies. In this field, rational utilization of high efficient, economical, biocompatible, controllable and quantitative crosslinkers and related crosslinking strategies, scale-up production of the crosslinked polymer assemblies with good reproducibility still remain challenging. Deciphering of the correlation between the structure/architecture of crosslinked polymer nanoassemblies and their physico-chemical, environmental and biomedical properties is also important. Many works have been performed to explore the above challenging topics and try to overcome the technical bottlenecks and shortcomings. To date, shell-crosslinked, core-crosslinked and interface-crosslinked nanoassemblies had been developed as stabilized nanocarriers, mainly for drug delivery. Among them, shell-crosslinked nanoassemblies take the advantages of: (1) comparatively large and flexible hydrophobic core which could enhance drug loading capacity, (2) hydrophilic polymer shell that could be functionalized by stimuli-responsive crosslinkers and make the nanoassemblies “smart”. Acetal-crosslinker-containing shell-crosslinked PEG-PAsp-PPhe nanomicelles showed high DOX-loading capacity, good stability under the existence of sodium dodecyl sulfate (SDS), and pH-responsive DOX release. Cystamine could be used as a crosslinker to react with N-acryloylsuccinimid (NAS)-containing polymer to prepare Shell-crosslinked PEO-b-P(DMA-stat-NAS)-b-PNIPAM micelles with high solution stability and the micelles showed bioreduction-responsive properties. By visible light-induced diselenide metathesis, CPT and DOX co-loaded shell crosslinked micelles were prepared and they demonstrated controllable CPT/DOX dual drug release manners in tumor microenvironments. Apart from these pH, redox and photo-responsive systems, ROS responsive protease and hyaluronidase responsive shell-crosslinked nanoassemblies were also developed. Towards the application of nanoassemblies under multiple stimulants, some shell-crosslinked dual responsive nanoassemblies were developed. Redox/pH dual responsive PCL-b-P(OEGMA-co-MAEA) and folic acid-modified micelles were prepared for camptothecin (CPT) delivery by using disulfide-bond and hydrazone linkage as the crosslinker, the loaded CPT micelles exhibited accelerated CPT release under low pH value and/or redox agent diithiothreitol (DTT). Our group recently developed a series of in-situ shell-crosslinked PDPA-b-P(NMS-co-OEG) diblock terpolymer micelles with pH-sensitive disopropylamine and cystamine crosslinker, the micelles demonstrated remarkable pH/redox dual-responsive manners for Camptothecin (CPT) delivery application. Although these progresses had been achieved, rationally in-situ incorporate crosslinkers into nanoassemblies to achieve low cytotoxicity, high drug loading efficiency, as well as dual, triple or multiple-stimuli responsive delivery manners is still a big challenge. Moreover, the structural characterization for the shell-crosslinked multi-stimuli responsive micelles needs to be further investigated. The construction of various functional shell-crosslinked polymer nanoassemblies is illustrated in Scheme 1.

Regarding the future innovation of crosslinked polymers, there are several issues to be extensively studied: (1) developing green, efficient, controllable and modular methods to prepare novel crosslinkable functional polymers with sustainability, (2) controlled release properties under physico-chemical stimuli-factors (thermal, light, mechanical, magnetic, etc.).

**Crosslinked Polymer Nanoassemblies and Their Delivery Applications**

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**Abstract** Chemical crosslinking technology was rapidly developed and utilized to prepare structurally fixed, stabilized and functionalized polymer nanoassemblies and nanoarchitectures by covalently reinforcing the interactions between the polymer chains. This perspective reviewed recent advances on the crosslinked polymer nanoassemblies and their applications, mainly in drug delivery. Moreover, possible future research outlooks in the field of Shell-crosslinked polymer nanoassemblies were also stated and discussed.

**Keywords** crosslinked polymers, crosslinker, nanoassemblies, controllable, applications
electrically and radiation, molecular/biomolecular),\(^{(16)}\) (2) expanding the structure/function diversity of the “smart” (reversible, stimuli-responsive, multifunction-integrated, biotargeting, etc.) organic crosslinker molecules, and macromolecular/dendrimer crosslinkers via clickable, controllable technique,\(^{(19)}\) (3) elucidating the structure-function relationship (SFR), especially the correlation between crosslinkers and nanoassemblies’ particle size and morphology, solution stability, stimuli-responsive feature, cytotoxicity, cellular uptake, intracellular behaviors, as well as therapeutic effects; (4) Based on the evaluation data, combining with artificial intelligence (AI) and machine learning (ML) to optimize the crosslinked nanobiomaterials to reach the desired performance by adaptive and modular-based design; (5) expanding the practical applications of crosslinked polymer nanoassemblies in the realms such as drug/gene/biomolecules delivery, agrochemicals/fragrant/nutraceutical encapsulation, nanomaterial-assisted tissue engineering and in vivo delivery, as well as bioelectronic devices-based smart delivery. The above-mentioned areas need to be systematically addressed (Scheme 2).

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Conflict of Interest

The authors declare no conflict of interest.

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