Chapter 5
Latest Biomedical Applications of Hyperbranched Polymers: Part 1: As Delivery Vehicle

5.1 Introduction to the Concept of Targeted Delivery

Alike dendrimers, hyperbranched polymers also play a significant role in various biomedical applications. An ideal delivery vehicle in biological applications should possess the following characteristics: excellent biocompatibility and biodegradability, it must have the ability to form a stable complex with the external agent, transport the external agent into the specified targeting site, and then release them in a controlled manner, while the physiological properties of the agent is kept intact. Polymer-based biomaterials are thus quite preferred as delivery vehicles over other small molecules as it meets all the above mentioned criteria. Again among all the polymers, hyperbranched polymers are considered as an ideal matrix for drug and gene delivery vehicles because of its tailorable architecture and availability of plenty of functional groups. Along with that, the typical characteristics of hyperbranched polymers like low (melt) viscosity and compact structure also contributes towards the more demand for hyperbranched polymers in the biological field. An additional promising feature is their void structure which has the ability to act as a host for smaller molecules in various ways. The main biomedical fields in which hyperbranched polymers are likely to find applications are gene delivery, drug delivery, protein delivery, as biodegradable materials, modification of surfaces (biocompatibilization, antifouling, etc.) and bulk materials, as bioimaging agent and applications related to biointeractions. With the passing years, researchers are trying to explore the use of hyperbranched polymers as drug carriers for the efficient and controlled delivery of drugs to the specified targeted sites. Although similar applications have been suggested and explored for dendrimers, their high cost and tedious synthetic procedure will favors the application of hyperbranched polymers over their symmetrical analogs. Many of the suggested potential applications, however, are still left to be explored till date [1, 2]. The encapsulation studies for both hydrophilic and hydrophobic guest molecules using hyperbranched polymers such as hyperbranched polyesters, polyglycerols, polyesteramides, and

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polyethylenimines has been extensively explored by the researchers in the past few years as already discussed in the previous chapters [3–5].

5.2 Encapsulation Ability of Hyperbranched Polymers

The primary feature that enables hyperbranched polymer to be used as delivery vehicle is its excellent encapsulating capability. The hydrophilic and hydrophobic guest molecules get entry within the hyperbranched polymers via two processes. First, the drug gets encapsulated within the cavities present within the hyperbranched structure via simple physical interactions [5]. Second, drugs can get entrapped within the unimolecular micelle formed by the self assembling of the hyperbranched polymers. It has been already stated that the unimolecular micelle formed by the hyperbranched polymers display better stability than multimolecular micelles formed from the conventional amphiphilic copolymers under similar standard conditions [6].

Haag and coworkers tried to get a comparison of encapsulating ability between hyperbranched and linear polymers. Hyperbranched PEI was modified with different functional fatty acids (C18, C16, C11, C6) and the resulting modified polymers were ampiphillic in nature. The structures were based on core–shell architectures which was capable of entrapping anionic guest molecules such as suitable caboxylate, sulfonate, phosphate, and acidic OH groups (Fig. 5.1). They observed that the fatty acid modified PEI exhibited much higher encapsulating capacity than their linear analogs [7].

Yan and coworkers have prepared a phospholipid mimicking material based on HPEEP [8]. Self condensing ring opening polymerization of hydroxyl functionalized cyclic phosphates and then the polymer was further modified with palmitoyl chloride which leads to a ampiphillic polymer with a hydrophilic HPHEEP head and plenty hydrophilic alkyl tails. These amphiphilic hyperbranched polymers had the capability of self-assembling in aqueous media. The micelles were in nano-range of size and thus can easily get entry into the living cells. An in vitro investigation was done using a hydrophobic anticancer drug, chlorambucil, loaded within the hyperbranched polymer, MCF-7 breast cancer cells. The results showed that there was a restriction in the rapid growth of the cancer cells (Fig. 5.2).

However, the main drawback with the unimolecular micelles of hyperbranched polymers is that due to its restricted extent of interior cavities, it is allows only a small amount of guest molecules to be entrapped within the matrix. Therefore multimolecular micelles from hyperbranched polymers with larger hydrophobic cores, higher encapsulating capacity and better controlled mechanism for drug delivery, are gaining more attention recently. Cheng and coworkers studied the drug loading capacity of a multimolecular micelle formed from the hyperbranched copolymer, H40-*star*-(PCL-*b*-PEG), attached with folate moieties used as the targeting ligands. Two antineoplastic drugs, 5-fluorouracil and paclitaxel were used in the study. In multimolecular micelles, the drugs got enfolded within the matrix

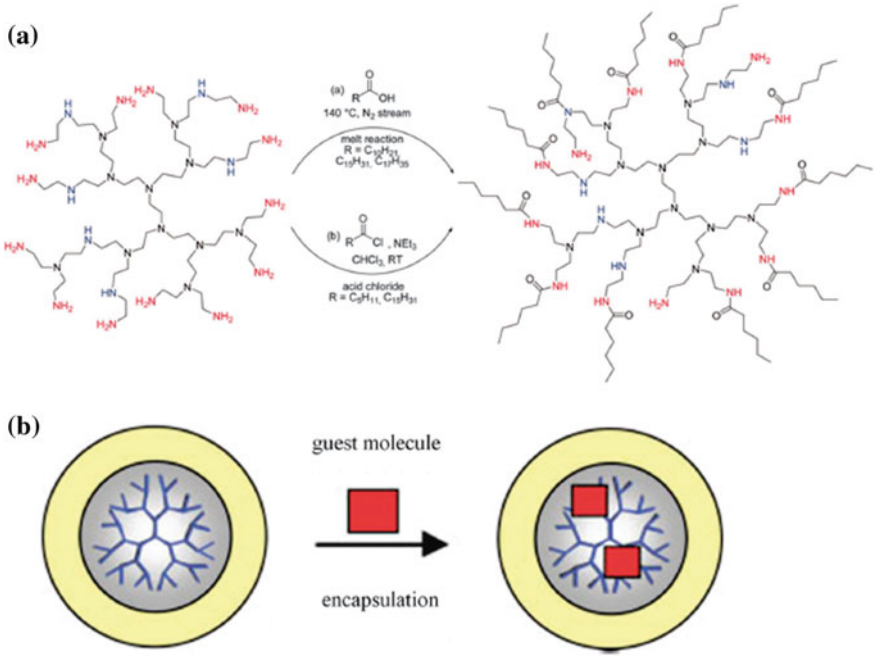

Fig. 5.1 **a** Modification of hyperbranched PEIs with different fatty acids leading to a ampiphillic copolymer. **b** Schematic representation of the core shell structure formed from the hydrophilic PEI and hydrophobic fatty acids which is capable of encapsulating polar guest molecules. Reprinted with permission from Ref. [7]. Copyright (2007) Wiley

through the non-covalent interactions. The results of the studies showed that the drug loaded micelle were very good biocompatible and is capable of restricting the abnormal growth of tumor cells [9].

Gao and coworkers studied about the multiple guest molecule encapsulation by hyperbranched polymers [10]. They observed that the loading capacity of one kind of guest molecule is enhanced in presence of other guest molecules within the amphiphilic hyperbranched polymers in the process of double-dye host–guest encapsulation. Thus it was concluded that hyperbranched polymers are also capable of multiple guest encapsulation instead of just one.

All the above-discussed topics demonstrate that the three-dimensional architecture of hyperbranched polymers plays a critical role in their encapsulation capacity but there are still some limitations which restrict the methodical and systematic drug encapsulation and controlled release phenomenon. The main disadvantage is due to non-covalent interaction, there is rapid and uncontrolled drug release from the hyperbranched core where as the covalently bound HB–drug conjugates exhibits better stability in both water and buffered solutions and the linker group used for the conjugates significantly affects the drug release

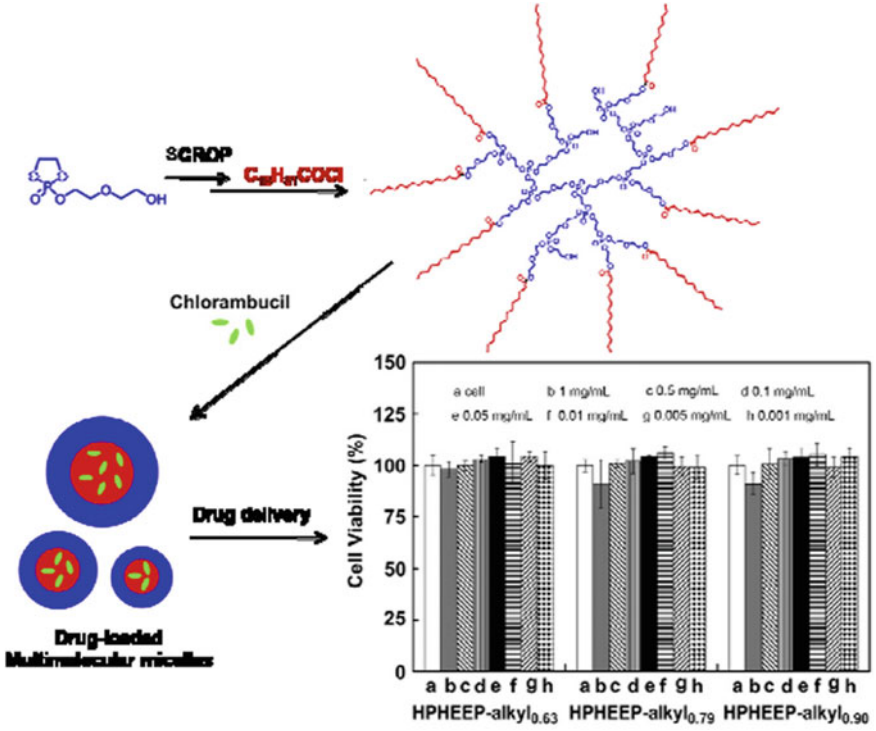

Fig. 5.2 A graphical representation of synthesis of phospholipid mimicking HPHEEP-alkyls and its self assembling capability. Reprinted with permission from Ref. [8]. Copyright (2010) Elsevier

kinetic [11]. The linker groups generally used for HB-drug conjugates must be easily biodegradable such as ester groups, acylhydrazone groups, or disulfide groups [12, 13].

5.3 Hyperbranched Polymers in Controlled Drug Delivery

The efficiency of the delivery vehicle is very much dependent on the release kinetics as demonstrated by the delivery system in the body. The release kinetics of drugs is of primary significance in a functional drug delivery system because it allows the vehicle to retain the drug content until the target site is reached and then goes for sustain release of the drugs for more effective action. Hyperbranched polymers exhibits high stability as drug carriers as it forms unimolecular micelles or self-assemble into multimolecular micelles. Moreover, hyperbranched polymers have many terminal functional groups, an alterable substitutional groups, and adjustable degree of branching to allow more regulated drug release.

Burt and coworkers worked on two commercially available hyperbranched polymers (HPG and H40) and modified them with carboxylic acid. These modified hyperbranched polymers were used as vehicle for the controlled release of anticancer drug cisplatin [14]. The drug delivery efficiency of both the polymers was examined thoroughly. It was observed that in physiological condition, the modified HPG formed strongly bound complexes with the drug; therefore there was a sustained release of the entire cisplastin drug over 7 days. But in case of H40 it was found that there was a rapid release of the drug which implied that the matrix formed higher proportion of weakly bound complexes with cisplatin. Though, after 5 days it was found that only 60% of the drug has released from the polymer matrix implying that the rest of 40% of the drug is strongly bounded with H40. Thus from the results it can be concluded that the complexes of HPG and cisplatin can be considered as promising delivery systems.

Further scientists have been trying to develop stimuli responsive hyperbranched for better controlled release applications. The polymer matrix is designed in such a manner that a slight change in pH, temperature, light, or redox conditions, greatly affects the sustained release of the drug at the target site.

Gong and coworkers constructed a biocompatible and biodegradable hyperbranched copolymer, H40-star-(PLA-*b*-PEG), as a vehicle for tumor-targeting drug (Fig. 5.3a) [15]. Folic acid was attached as targeting moieties. The anticancer drug DOX (Doxorubicin) got attached with the hydrophobic PLA blocks by pH-sensitive hydrazone linkages and thus in acidic medium, due to cleavage of hydrazone linkages, the rate of drug release significantly increased (Fig. 5.3b).

Ji and coworkers have tried to develop photoresponsive hyperbranched polymer. They modified the biocompatible and biodegradable HPHEEP with a photoresponsive segment (Fig. 5.4), hydrophobic 2-diazo-1,2-naphthoquinone-5-sulfonyl chloride (DNQ) [16]. The resultant terminal-modified HPHEEP is capable of forming micelle in water and have excellent biocompatibility. Under UV irradiation, the DNQ moieties disintegrates and the micelle gets destabilized for triggered drug release.

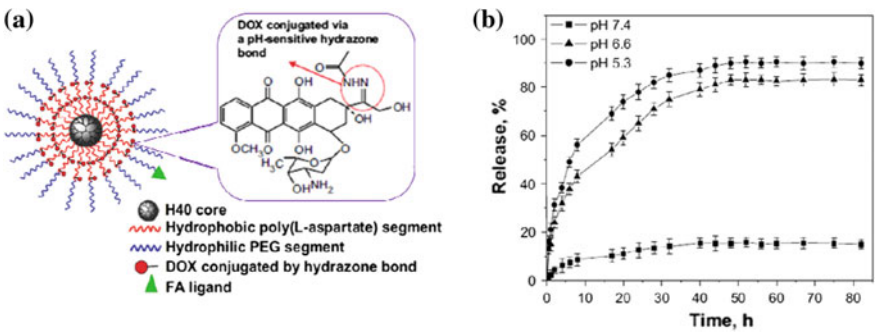

Fig. 5.3 **a** Schematic representation of the H40-*star*-(PLA-DOX)-*b*-PEG-OH/FA copolymer. **b** Release profiles of DOX from the H40-*star*-(PLA-DOX)-*b*-PEG-OH/FA micelles at 37 °C. Reprinted with permission from Ref. [15]. Copyright (2009) Elsevier

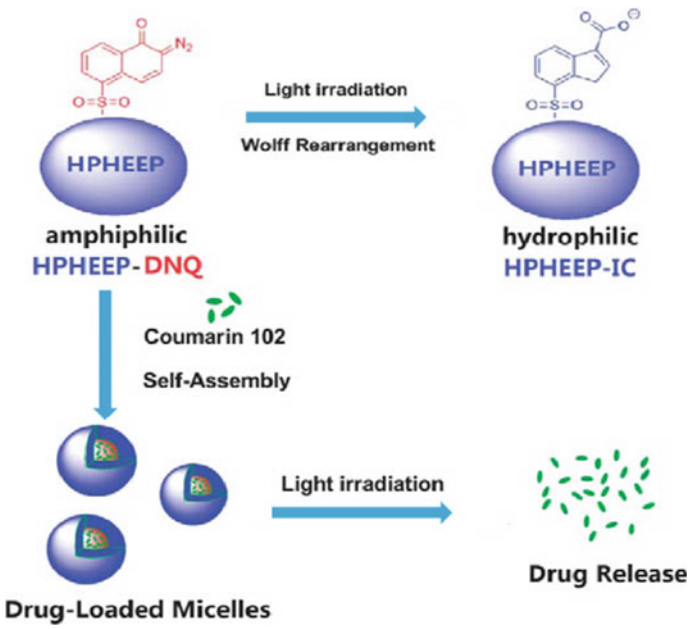

Fig. 5.4 Illustration of the self-assembly and photoresponsive behavior of HPHEEP-DNQ Reprinted with permission from Ref. [16]. Copyright (2011) Royal Society of Chemistry

Wang and his coworkers synthesized thermoresponsive PEG based hyperbranched copolymers using high concentration of ethylene glycol dimethacrylate as the branching agent via atom transfer radical polymerization (ATRP). These copolymers exhibited lower critical solution temperature (LCST) close to human body temperature [17].

Zhu and his coworkers have synthesized hyperbranched poly-((S-(4-vinyl) benzyl S0-propyltrithiocarbonate)-co-(poly(ethyleneglycol)methacrylate)) (poly (VBPT-co-PEGMA)) with multiple thiol groups through controlled reversible addition-fragmentation chain transfer (RAFT) mechanism. These hyperbranched copolymers were designed in such a manner that it was able to covalently attach thiol-containing drugs via disulphide linkages and displayed redox-responsive nature [13]. In tumor tissues, the concentration of Glutathione (GSH) is much higher than that in normal tissues, therefore the redox-responsive HB–drug conjugates exhibited better targeting capability for the tumor cells and release the drug at the specified sites, thus exhibiting a high anticancer efficiency (Fig. 5.5). This redox-responsive HB-drug conjugate behaves as an ideal delivery vehicle for the controlled release of thiol-containing drugs or biological molecules.

Thus it can be concluded that stimuli-responsive hyperbranched polymers need to be explored further for controlled drug delivery applications.

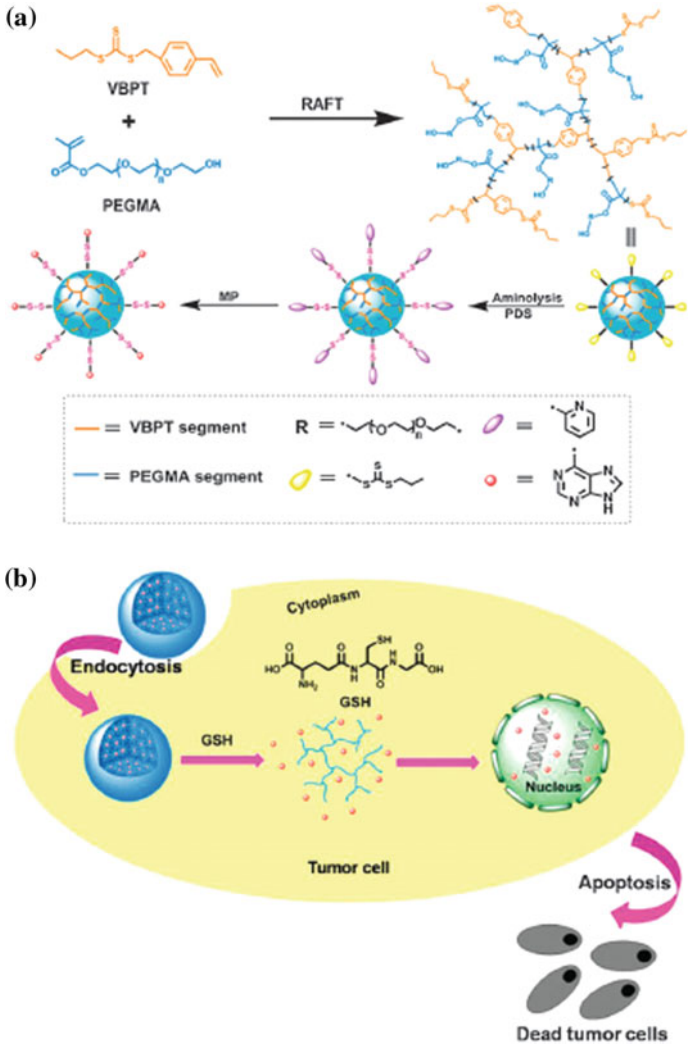

Fig. 5.5 Schematic illustration of **a** Synthesis of poly(VBPT-co-PEGMA)-S-S-MP; **b** redox-responsive behavior of poly(VBPT-co-PEGMA)-S-S-MP micelles for sustained drug release. Reprinted with permission from Ref. [13]. Copyright (2014) American Chemical Society

5.4 Hyperbranched Polymers in Protein Delivery

In the recent years, biologists have been trying to treat deep rooted clinincal disorders such as cancer, anemia and other metabolic diseases, by transferring active peptides and proteins in the targeted site [18]. But the hydrolytic instability and low bioavailability of the proteins is restricting the application. They can easily

disintegrate by physical, chemical or enzymatic disruption during the process of peptide storage or delivery [19]. To improve on these researchers have been trying to develop new and unique systems for protein delivery. Polymeric systems have showed great potential as protein delivery vehicle as they enhance the stability, improves absorption across the biological boundaries, and also enhances the protein residence in the bloodstream. Furthermore, some polymers have also been found to improve the protein incorporation mechanism within the cells and thus increases its potential to recover from the diseases. Hyperbranched polymers, with better stability and solubility, tunable surface functionality and the presence of a large number of functional end-groups, have proved to be a good vehicle for protein transfer in the specified region in comparison with its linear grade.

Wu and coworkers synthesized hyperbranched poly[(ester-amine)-co-(D, L-lactide)] (HPEA-co-PLA) copolymers. They were capable of forming self-assembly and the micelle was used as protein carriers for BSA delivery [20]. The BSA-encapsulated micelles displayed excellent delivery mechanism while retaining the properties of BSA during the process.

Frey and coworkers utilized the excellent solubility and stability of biocompatible hyperbranched polyglycerols to study its protein transmission efficiency. They synthesized hyperbranched-*b*-linear (HPG-*b*-PEG) heterotelechelics consisting of a linear PEG block attached with a HPG block along with biotin. Biotin binding protein, avidin, formed a stable conjugated complex with the polymer and further the results have proved that HPG can be used as protein delivery vehicle [21].

Zhang and coworkers studied on polylactic acid functionalized HPG (HPG-star-PLA) as delivery vehicle for bovine serum albumin (BSA) protein [22]. The copolymer formed self-assembly in nanoparticle range and holds a great potential as delivery vehicle. The results revealed that the loading capacity of HPG-star-PLA were up to 23% where as the association efficiency was up to 86%, and the protein release kinetics was highly dependent on the architecture of the hyperbranched polymers. Another important feature observed was that the physicochemical properties of released BSA were well stabilized for over 4 days. The same group also tried to transport insulin by using HPG-g-CD [23]. The polymer could efficiently load the insulin within its matrix and released at the specific site which was evident from the decreased glucose level in the specimen.

As hyperbranched polymers exhibit an easy strategy for introduction of different terminal functional groups, it has the capability of covalently conjugating a variety of proteins and peptides. Klok and coworkers tried to study on this property further and thus they attached both BSA and lysozyme into the HPG and hyperbranched-linear polymer HPG-PEG with the squaric acid mediated coupling strategy, and subsequently used for protein delivery.

5.5 Hyperbranched Polymers in Gene Delivery

Gene therapy is used to treat previously incurable diseases with genetic disorders and is considered much better than the conventional treatment procedures. It involves transference of exogenous nucleic acids into the nucleus of the specific cells of the human body [24]. An effective gene delivery vehicle is required for proper transfer of genetic materials as they are easily degraded by serum nucleases in the blood when injected intravenously.

Nonviral polycationic vehicles are regarded as ideal gene delivery systems, because of its improved stability, enhanced biocompatibility and biodegradability, high flexibility of trans-gene size, low cost of synthesis, and easy scale-up procedure. The electrostatic interaction between the cationic polymeric vectors and the negatively charged DNA improves cellular uptake efficiency and transfection efficiency of DNA or RNA. With the advantage of its architecture, cationic hyperbranched polymers have gained attention as gene transfer vehicle. Polyamines like hyperbranched polyethylenimine (HPEI) and hyperbranched polypropylenimine (HPPI) have proved to be an efficient gene transfection agent. The availability of plenty of terminal amino groups with flexible molecular architecture increases the efficiency of these hyperbranched polyamines for more effective and specific gene transfer. HPEI displays several attractive features that makes it superior transfection agent in various cell lines and tissues. The presence of numerous terminal primary amines helps them to form nanosized compact structure by condensing nucleic acids within its matrix and transferring it to the specified cell and also resists the degradation of the DNA complexes during the transfer process. But the main drawback with HPEI is its high cytotoxicity and lack of cell specificity which limits further applications. Therefore researchers tried to modify HPEI to reduce cytotoxicity in the vehicle as well as increase the gene delivery efficiency. The modification of the surface of HPEI with functional small molecules, hydrophilic or biodegradable polymers, such as PEG, natural glucose polymers, proteins, peptides, etc., is done to improve the efficiency of the polymer. It was observed that the modified hyperbranched polyamines showed improved transfection efficiency than the unmodified polyamines. The transfer phenomenon and the cell specificity of the vehicle greatly depend on the functional group attached and also on the degree of substitution. For instance, peptide-modified HPEIs show better prosperity as gene transfer vehicle as they improve the biocompatibility and are easily metabolized [25].

Wu and coworkers modified HPEI (25 kDa) with histidine based peptide for gene transfection studies [26]. The polymer matrix showed improved transfection efficiency and enhanced cell survival to the human embryonic kidney cell line (HEK 293FT). Along with that, these modified HPEI could also act as a gene delivery vehicle for highly resistant cells such as human adipose stromal cells (ASCs), dermal fibroblasts, and cardiac progenitor cells (CPCs).

To reduce the cytotoxicity and also to improve the controlled release of the nucleic acids, the backbone of hyperbranched polyamines are generally modified by linking with biodegradable linkages such as disulfide bonds or ester groups [27].

Wang and coworkers chemically crosslinked low molecular weight HPEI by 30-dithiobispropanoic acid (DTPA) to prepare bioreducible HPEI (SS-HPEI) [26, 28]. It is stated that low molecular weight HPEI crosslinked with disulfide containing agents have enhanced transmission efficiency than the original low molecular weight HPEI [29]. The SS-PEI complexes were used for the transfer of human telomerase reverse transcriptase (hTERT) siRNA. The in vitro and in vivo results revealed that the complexes of SS-PEI/siRNA were formed by condensation of the siRNA by the polymer matrix and was able to transfect HepG2 cells efficiently by condensing the siRNA into compact complexes. It also displayed low cytotoxicity due to the easy bond cleavage of SS-HPEI (Fig. 5.6). The results also showed that the complexes of SS-PEI/siRNA obstructs the growth of HepG2 tumor with no unfavorable effect on liver or kidney in a xenograft mouse model.

Hyperbranched poly(ester-amine)s (HPEAs) have been considered as a substitute for hyperbranched polyamines. It exhibits low cytotoxicity with efficient gene transfection at the specified site. They contain hydrolytically degradable ester groups in the structure which makes it readily biodegradable materials. HPEAs

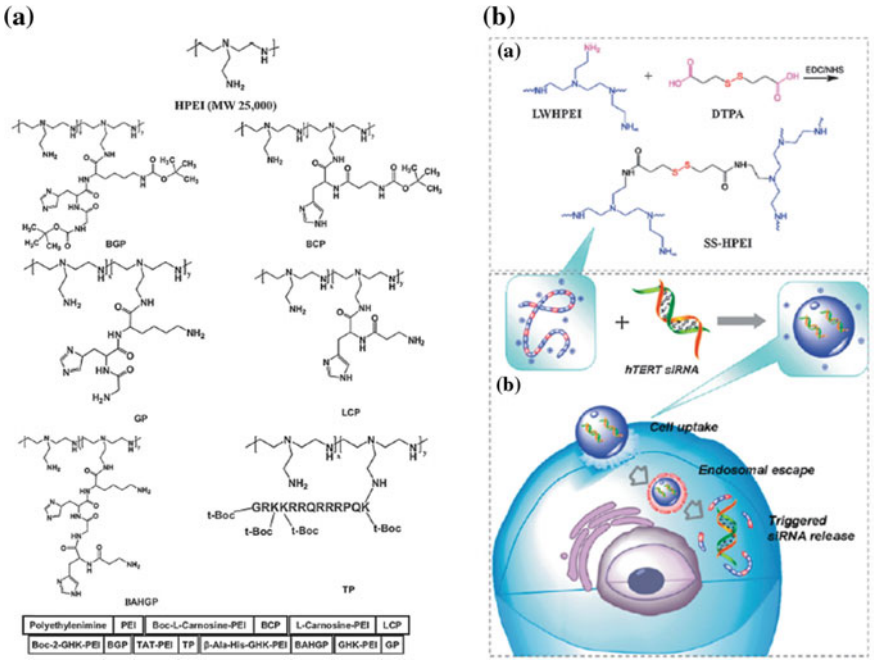

Fig. 5.6 **a** Graphical representation of HPEI; **b** schematic representation of a synthesis strategy of bioreducible SS-HPEI, b siRNA delivery by SS-HPEI. Reprinted with permission from Refs. [26, 28]. Copyright (2011, 2012) Elsevier

possess the characteristics similar to polyamines due to the presence high density of primary amines at the terminal ends, along with that they exhibit excellent biodegradability. Thus, HPEAs are considered as a promising gene delivery vehicle because of their controlled release capability and minimal cytotoxicity, along with a significant structural diverseness.

Different groups have tried to study about the transfection efficiency of HPEA by using different kinds of amine in the structure. For example, Liu and coworkers polymerized trifunctional amine monomers 1-(2-aminoethyl)piperazine with 1,4-butanediol diacrylate via Michael addition polymerization. The biodegradable HPEA prepared thus possessed primary, secondary and tertiary amines simultaneously [30]. The different types of amine groups affected the condensation of DNA as well as increased the ability to promote escape of vectors from lysosomes by enhancing the pH-buffering capacity. Even with high polymer/DNA weight ratio (approx 30:1), the HPEA vehicle exhibited negligible cytotoxicity and high transference ability.

Similarly, Park and coworkers reported synthesis of cationic HPEA with a hybrid structure of biodegradable ester backbone, primary amine present at the periphery, and tertiary amine groups present in the interior [31]. This biodegradable cationic polymer showed minimum toxicity and could condense negatively charged DNA.

Further Mikos and coworkers prepared a series of HPEAs keeping the amine monomer, 1-(2-aminoethyl)piperazine, same in each case and modified the structures by using different types of triacrylate monomers as spacer between the polymeric chains. They varied the structure of the spacer as they tried to analyze the relation between hydrophilic spacer lengths and HPEA properties related to the gene transference process [32]. The results revealed that in the presence of hydrophilic spacers in the structure of HPEAs the cytotoxicity of the resultant polymer decreased along with the increment in hydrolytic degradation rate. In addition to that the variation in the spacer structure also decreased the reduced charge density of HPEAs, which in turn influenced the end properties of the polymer such as polymer stability, DNA condensation, and enhanced endosomal escape.

Feijen and coworkers tried to develop a water-soluble, degradable gene carriers with very low cytotoxicity. They designed a HPEAs-based gene delivery vehicle consisting of primary, secondary and tertiary amino groups in the structure. The resultant HPEAs were capable of condensing plasmid DNA into nanostructured positively charged complexes [33]. From the results it was concluded that these water-soluble HPEAs had much better transfection efficiency than that of PEI and PDMAEMA.

As a substitute for polyamines, various hyperbranched poly (amidoamine) (HPAMAM)-based hyperbranched polymers have been considered for gene transfer. Though it has similar structure to that of HPEI, but it has more advantages such as peptide-mimicking properties, reduced haemolytic activity, excellent biocompatibility/biodegradability, and low toxicity. Generally three kinds of parameter is considered to study the efficiency of HPAMAM-based gene delivery

vehicles. First parameter is the branching architecture of the hyperbranched polymer. Increasing branches in the structure greatly makes the polymer more compact with high density of terminal functional groups. Thus the gene transfection capability also gets affected by the increasing degree of branching [34]. This concept was studied by Zhu and his coworkers. They synthesized a series of cationic HPAMAMs through surface grafting polymerization of *N*,*N*-methylenebisacrylamide and 1-(2-aminoethyl)piperazine monomers. Though they had similar compositions and molecular weights, but a variation of degree of branching was done to generate different set of copolymers [35]. It was found that with increasing DB, the DNA condensation capability of HPAMAM was improved significantly along with decreased cytotoxicity (Fig. 5.7). The observation could be explained on the basis that with increasing branching, the structure became more compact and there was more availability of primary and tertiary amino groups. Consequently, the efficiency of gene transfection was enhanced on a large scale.

Secondly, the gene transfection activity of HPAMAM can be altered by introducing various functionalities at the periphery of the polymer. The alteration of terminal groups and its direct effect on transfection efficiency has been examined by Gao and coworkers [36]. They modified HPAMAM by attaching phenylalanine to the terminal amine groups of the polymer and was able to improve the bioactivity of the polymer. Third, another method to enhance transfection ability and reduce cytotoxicity in HPAMAM is to attaché biodegradable linkages introduction of

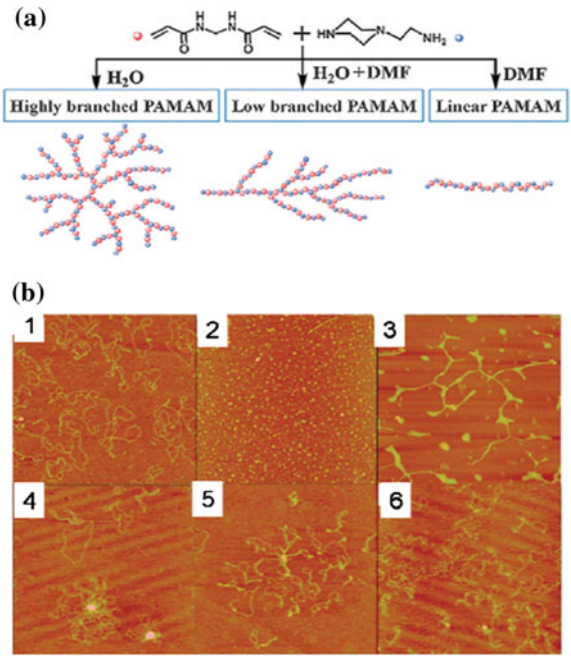

Fig. 5.7 **a** Schematic route for the synthesis of different structural PAMAMs (from highly branched to linear), **b** AFM images of DNA condensation by various branched PAMAMs with varying DB (0.44, 0.31, 0.21, 0.11, and 0.04, respectively). Reprinted with permission from Ref. [35]. Copyright (2010) American Chemical Society

biodegradable linkages (such as reducible disulfide bonds or ester groups) in the backbone of the base polymer.

Zhou and coworkers prepared a series of amphiphilic hyperbranched copolymer with a hydrophobic PEHO (poly (3-ethyl-3-(hydroxymethyl)-oxetane) cores and PDMAEMA arms with variable length for gene transfection [37]. The PEHO core had variable degree of branching. They wanted to study structure property relationship with the gene transfection efficiency. The results revealed that this copolymer, PEHO-g-PDMAEMAs, much better transfection efficiency than HPEI and PDMAEMA homopolymers and the efficiency was enhanced with the increasing branching in PEHO cores (Fig. 5.8). The HBs has very low cytotoxicity also which makes them a potential gene delivery vehicle.

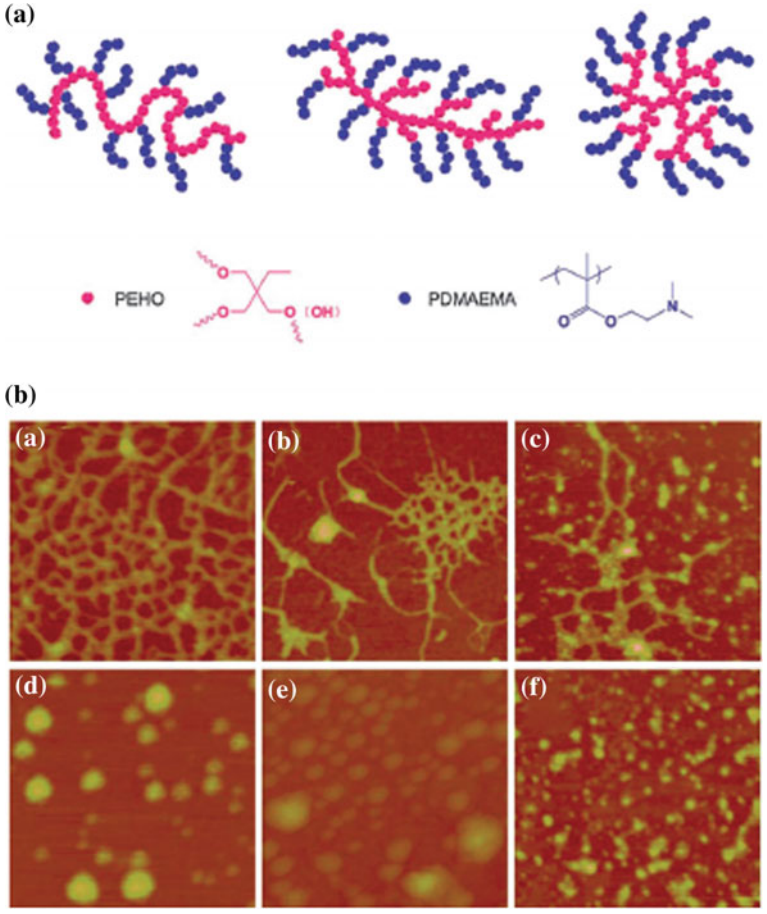

Fig. 5.8 **a** Schematic illustration of different architectures of PEHO-g PDMAEMA copolymers with varying DB. **b** AFM images of copolymer—pDNA complexes Reprinted with permission from Ref. [37]. Copyright (2012) Royal Society of Chemistry

Zhu and coworkers studied about the primary- or tertiary amine-modified β-CD derivatives and an AD-modified HPG for gene delivery (Fig. 5.9). The amine-modified β-CD compromised of per-6-amino-β-CD with seven primary amines and per-6-dimethylaminoethyl-β-CD with seven tertiary amines. The gene transfection efficiency of these charge-tunable supramolecules was based on the conventional host–guest interactions. The surface charge density of the resultant HPEAs was controlled by manipulating the molar ratios of the two cationic β-CD derivatives. These poly(etheramine)s can be considered as an efficient gene delivery vehicle with very low cytotoxicity and enhanced transfection efficiency than the standard HPEI [38].

Lee and coworkers reported poly(etheramine)s based on hyperbranched polysiloxysilane (HBS) and studied its gene transfection ability [39]. The HBS contained terminal carboxylic acid and quaternary amino groups. From test results it was confirmed that these cationic HBS nanoparticles were capable of forming stable complexes with pDNA, and this ability was directly proportional to the presence of quaternary amine groups at the periphery. Thus HBS can be designed to form very efficient gene delivery vehicle.

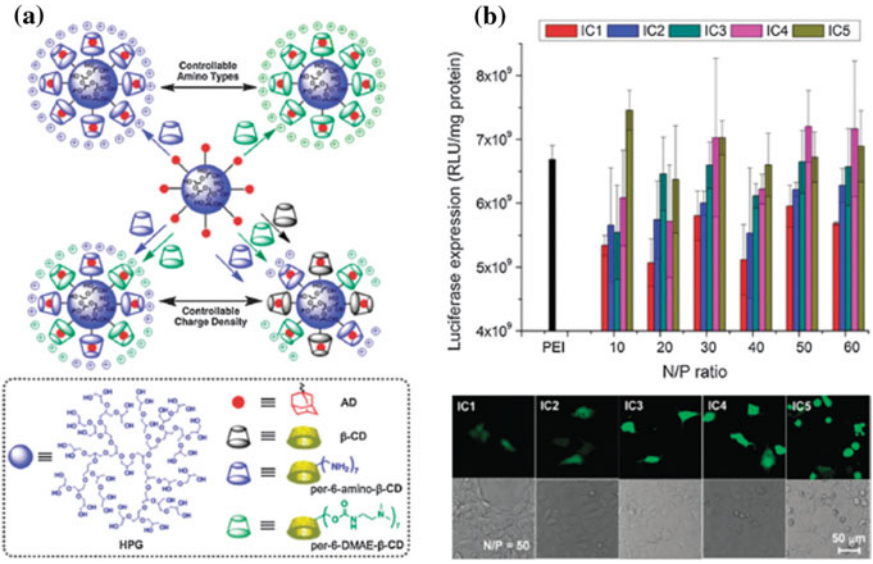

Fig. 5.9 **a** Schematic illustration of the synthesis of the charge-tunable HPEAs **b** Luciferase expression (*top*) and *green* fluorescent protein expression (*bottom*) of HPEAs in COS-7 cells. Reprinted with permission from Ref. [38]. Copyright (2011) Royal Society of Chemistry (color figure online)

5.6 Conclusion

In the last few years, a significant progress in the field of biocompatible or biodegradable hyperbranched polymers has been observed, an important subclass of architectural macromolecules. They can be easily modified to achieved tailor-made properties for specialized purposes. Due to their unique topological structures, abundant functional groups, low toxicity, non-immunogenicity, hyperbranched polymers prove to be of great potential for controlled release of therapeutic agents. Biocompatible or biodegradable assemblies formed by the hyperbranched polymers exhibits excellent delivery efficiency. This field needs to be further researched for more better and specific targeting as well as for more better control over the release kinetics by the hyperbranched vehicles.

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