Polymer based amphiphiles for delivery of active components

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**ABSTRACT**

The bioavailability of hydrophobic drugs is critically dependent on the development of efficient and safe drug delivery vehicles. Nanoparticulate pharmaceutical carriers commonly used in delivery of active components are often non-ionic in nature. Among them polymer based amphiphiles have become increasingly relevant over the past decades. Polyether based amphiphiles exhibit good chemical stability, high water solubility, low toxicity, have decreased interaction with blood components, and are highly biocompatible; and thus have been applied in biomedical and pharmaceutical areas. The current review highlights the synthetic progression and biomedical applications of these non-ionic polymer-based amphiphilic architectures, some unresolved issues and challenges, along with the future perspective of polymer based nanocarriers for delivery of active components.

**Keywords:**
Polyethers
Non-ionic surfactants
Dendritic polymers
Drug delivery systems

1. Introduction

Today, the major problems with the vast majority of clinically used drugs are their short half-life in the bloodstream and high overall clearance rate. More than 80% of the drugs available in the market are small molecules; these drugs typically interact through multiple binding sites and diffuse rapidly all over the body without selectivity. As a consequence, a relatively small amount of the drug reaches the target site, while the non-selective distribution in the body leads to undesired side effects. The applied dose of the drug is reduced to avoid these side effects, thus the full therapeutic potential of the drug is not achieved. These disadvantages are especially pronounced with drugs that exhibit a narrow therapeutic index \([1]\) such as anti-cancer, anti-rheumatic, and immunosuppressive agents. Improving the therapeutic index of drugs is a major incentive for innovation in many therapeutic areas and the search for new drug-delivery concepts and new modes of action are the major driving force in polymer therapeutics \([2\text{–}5]\). Furthermore, many of the drugs are hydrophobic and have limited aqueous solubility. The current approach towards drug delivery also aims at solubility enhancement of poorly water soluble drugs. Clinically acceptable organic solvents, Cremophor EL, and certain surfactants are used in formulations for solubility enhancement \([6]\). However, they have certain shortcomings such as toxicity, undesirable side effects \([7]\), and hypersensitivity reactions \([8\text{–}11]\). To address such toxicity issues as well as to extend the systemic circulation time of the lipoplexes, polymeric architectures may provide a solution because of their resemblance to natural carriers like viruses and serum lipoproteins \([12]\).

Over the last few decades, research on nanoscale drug delivery vehicles has been largely concerned with an outright development of modern pharmaceutical technology. Polymeric nanoparticles are particularly interesting for drug delivery applications because of...
their several characteristic features. Their small size helps them penetrate smaller capillaries and be taken up by cells, which allows an efficient drug accumulation at the target sites. Also, biodegradable materials can be used in nanoparticle preparation, which allows sustained drug release within the target site over an extended period of time. Drug loaded polymeric nanocarriers passively accumulate in the large gaps between the adjacent endothelial cells in the tumor neovasculature, while the poor lymphatic drainage leads to enhanced retention of these macroscopic molecules within the tumors and enhances the drug delivery in the tumors sites [13,14] via a phenomenon termed “enhanced permeability and retention” (EPR) by Maeda and Matsumura [15,16]. So far, a number of macromolecular delivery systems are under investigation to bypass these boundaries and expand the perspective of the respective drug. Many different drug delivery vehicles such as block copolymer micelles [17], polymer grafted liposomes [18] or dendritic core-shell type architectures [19] have been realized in recent years.

Among the many nanoparticulate pharmaceutical carriers being studied for the delivery of extremely hydrophobic drugs, amphiphilic architectures are of particular interest and have significantly affected the drug delivery era. These amphiphilic nanocarriers can be ionic or non-ionic. Ionic amphiphiles, particularly the cationic one, have been developed as promising carriers for genetic materials and receptor targeted gene therapy [20,21]. Although cationic amphiphiles suffer from certain limitations, such as excess positive charge of the lipoplexes favor non-specific electrostatic interactions with negatively charged hydrophobic serum albuminate proteins, cellular components such as low density lipoproteins and macro-globulines, and myriads of other negatively charged systemic molecules [22–24]. Such non-specific interactions promote a promiscuous binding of the transfection complexes to biological surfaces and other systemic molecules at the cost of compromised targeted lipofection [21]. In order to address the previous concerns in addition to toxicity issues associated with the cationic amphiphiles, the search for alternative architectures for targeted drug delivery has brought non-ionic amphiphilic architectures into the lime light. Their advantages over ionic amphiphiles include their pH independence and the generation of non-toxic nanoparticulate aggregates, which provide a great benefit for drug delivery.

The research in the field of non-ionic amphiphiles is growing rapidly and the applications include solubility enhancement for nanodevices [25–28], template synthesis [29–31], and delivery of various drugs [32–35] including low molecular weight anti-cancer drugs, contrast/imaging agents, proteins, plasmid DNA etc. [36–40]. Polyether based non-ionic self-assembled architectures have attracted considerable attention due to their resemblance with natural carriers. Advances have been made from conventional amphiphiles to Pluronics (triblock PEO–PPO–PEO copolymers), PEGylated amphiphiles to dendritic structures, and hyperbranched amphiphilic polymers to core multi-shell architectures. These special architectures of amphiphilic molecules can result in aggregate morphologies at interfaces and different self-assembly behavior in solutions. Currently, several promising candidates are in clinical trials and have paved the way towards the development of nano-DDS [36].

Polyether based hydrophilic polymers have been extensively used to enhance the pharmacokinetic properties of drug carriers because of their high biocompatibility. PEG is considered as a gold standard in the field of drug delivery and has FDA approval for different drugs. Due to its specific properties, such as water solubility, non-toxicity, ion-transporting ability, decreased interaction with blood components, high chemical stability, and biocompatibility, it has found potential applications in biomedical and pharmaceutical areas [41,42]. As a potential alternative to PEG e.g., poly(glycerols) [41] and aliphatic dendritic polyethers, polyols, which have a biocompatible polyether scaffold, high-end group functionality, and a compact, well-defined dendrimer-like architecture, have also become important. These characteristics of dendritic polyether scaffolds are been currently used to generate new material properties for biomedical applications. Such materials have the potential to create extremely high local concentrations of drugs, molecular labels, or probe moieties and to modulate therapeutic efficacy of the active molecules [43].

Considering the importance of non-ionic amphiphiles in drug delivery and taking into account the numerous useful properties of polyether based scaffolds, our focus here will be on the polyether based non-ionic amphiphiles, in particular, the recent synthetic progression in the development of amphiphilic nanocarriers from PEG based block copolymers, to PEGylated comb-like architectures, and to dendritic, hyperbranched and core multi-shell architectures along with their biomedical applications. The conceptual progression has occurred taking into account the drawbacks of linear polymers and to improve upon the nanocarrier architecture for drug delivery. Although, linear PEG based polymers have been successfully implicated for the delivery of bioactive components through the systemic circulation, still they have certain limitations, such as dissociation under high dilution conditions and thus lack of long term stability, accumulation in the body above an uncertain excretion limit and immunological responses. Advanced polymeric materials such as dendritic, hyperbranched and core multi-shell architectures have now been introduced, which avoid the problems of dissociation and are stable in high dilution conditions, have reproducible pharmacokinetic behavior, and are now being evaluated for their safety and ability to deliver therapeutic agents [44,45]. The synthetic progression of these non-ionic polyether-based amphiphiles (Fig. 1) will be discussed in this review.

2. Non-ionic amphiphilic nanocarriers based on PEG

A number of macromolecular delivery systems are under investigation to bypass the boundaries of clinical drugs and expand the perspective of the respective drug. Further, a high solubilizing capacity and a good physical stability are two critical factors for ideal drug delivery systems, which can be achieved by micelles possessing several characteristics, such as low CMC, suitable size of 100–200 nm, sufficient half-life in the body, non-toxic degraded components, and ease of excretion [46,47]. PEG based ABCs have gained a worldwide interest as one of the versatile classes of biomaterials in DDS [46]. PEG is most commonly used as the hydrophilic segment of these copolymers, because of its unique physicochemical characteristics (high water solubility, high flexibility, and large exclusion volume) provide good “stealth” properties [48–50]. PEG’s hydrophilic surface allows prolonged circulation of polymeric micelles in the bloodstream. This is because the hydrophilic shell of PEG acts as a dense brush of highly hydrated chains that rapidly sweep out a large exclusion volume. The barrier formed by the PEG chains around the hydrophobic core of the micelle serves to minimize interactions with proteins, enzymes, and cells [51] and provides the stability to micelles. Furthermore, the micelles of ABCs have a remarkably low CMC (10^-5–10^-7 M) as compared to that of surfactant molecules, and their slow kinetic dissociation makes them more suitable for drug delivery [38].

2.1. Block copolymeric amphiphiles and Pluronics®

The medicinal applications of ABCs have been well recognized, one of the widely researched area is to use them as pharmaceutical carriers in drug delivery. Herein our focus is on studying the self-
assembly properties of ABCs in aqueous solution, and to enhance the solubility of hydrophobic drugs for drug delivery. Although many other methods such as adjustment in pH, cosolvents, cyclodextrins, surfactants, etc. have been used to improve the water solubility of drugs, each of them has their inherited problems and is unable to achieve an adequate drug dose for therapy [52]. In order to overcome these limitations and to enhance the water solubility of drugs, studies have largely been confined to two different areas. One utilizes the development of ABCs in which the drug is physically adsorbed or entrapped within an insoluble polymer matrix, the second includes soluble prodrugs or drug carriers where the drug is either chemically bound to the backbone of block copolymer or is part of the backbone itself [53,54]. A large variety of such copolymers have been studied: dexamethasone (DEX) conjugated to poly(caprolactone) unit of PEG-PCL copolymer via hydrazine linker [57] and poly(-aspartic acid) with chemically conjugated DOX (pAsp(DOX)) [58]. These systems have also been tested for drug release at different pH due to acid cleavable linkages used for drug conjugation. There are more such examples e.g. poly(propylene glycol) (PPO Pluronics) [59], PEG-poly(b-benzyl-l-aspartate) (PBLA) [60] and poly(ester)s such as PEG-poly(lactic acid) (PLA) [61,62], and PEG-PCL [63,64] that have been widely used for physical entrapment of drugs. Currently, several such examples have progressed into clinical trials, e.g., [DOX-encapsulated PEG-(PPO)-PEG] micelle (SP1049C) in phase III [36], [PTX-encapsulated PEG-Asp] block copolymer (NK015) in phase II [65,66], [PTX-encapsulated PEG-PLA block copolymer] micelle (Genexol-PM) in phase II [67], [SN-38 (the active form of irinotecan hydrochloride) encapsulated PEG-poly(glutamate)block copolymer] micelle (NK012) in phase II [36,68,69], and cisplatin-incorporated PEG-poly(glutamate) block

### Non-ionic polyether-based amphiphilic architectures

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**Fig. 1.** Synthetic progression of non-ionic polyether based amphiphilic architectures.
Pluronics block copolymers have also been widely studied for drug solubilization. Pluronics, i.e., (PEOₙ-PPOₘ-PEOₙ) is an amphiphilic copolymer whose hydrophilicity (PEO unit) and hydrophobicity (PPO unit) can be varied by changes in the molecular weight of its units. The use of pluronic micelles in drug delivery has been extensively reviewed by Kabanov et al. [71,72]. Mei et al. reported a docetaxel loaded PCL-pluronic F68 system which gives 200 nm spherical shape nanoparticles. The cytotoxicity of these particles was found to be comparative to commercial Taxotere in the MCF-7 TAK30 cell line [73]. Sun et al. coupled stearic acid (SA) to a free hydroxyl group of PEO blocks of pluronic F127 which lowers the CMC of pluronic F127 and provides more stable micelles which were used for DOX encapsulation. This formulation enhanced in vitro cytotoxicity against MCF-7 cell lines as compared to free DOX [74]. Physical mixing of two types of pluronics L81 and P123 has also been done to produce more stable micelles by lowering the CMC which showed high solubilization potential for hydrophobic drugs [75].

PLA is a synthetic biodegradable polymer, thus PEG-PLA copolymers have been widely used in drug delivery. The recent advances of these copolymers have been reviewed by Zeng et al. [76]. These studies have proven the practical utility of polymer self-assemblies as injectable nano-drug delivery systems through both experimental and clinical results, which has generated much interest because they provide a strong foundation for further development in the nano-DDS field. There has also been progress in improving the pharmacokinetics and pharmacodynamics of existing drugs. Lang et al. majorly contributed to [PEG-b-PCL]-based amphiphilic block copolymers for achieving a better micellar drug delivery system with improved solubilization and delivery of DOX with thermo and pH responsive release mechanisms [77–79]. The high loading efficiency and in vivo stability of PTX was achieved with hydrolytic block copolymer micelles of PEG-poly(4-(2-vinylbenzylxylo-N-picolinicotinamide)), i.e., PEG-p(VBOPNA) [80] and PEG-poly(2-(4-vinylbenzylxylo)-N,N-diethylaminocetamide), i.e., PEG-p(VBODENA) [81]. The more relevant results for improving the loading efficiency of drugs are summarized by Cheng et al. [82].

Recently, Gao et al. synthesized multifunctional polymeric micelles that incorporate therapeutic agents, molecular targeting, and diagnostic imaging capabilities to improve the therapeutic outcome of drug therapy [74]. This was achieved by amphiphilic block copolymers of maleimide-terminated PEG-b-poly(ε-lactide) (MAL-PEG-PLA), and methoxy-terminated PEG-b-poly(ε-lactide) copolymer (MPEGPLA). The targeting ligand, i.e, RGD was attached to the micelle surface through a covalent thiol-maleimide linkage (0–16%). These micelles were used to incorporate DOX and a cluster of super paramagnetic iron oxide (SPION) nanoparticles inside the micelle core by a solvent-evaporation method at 6.7 and 2.7 w/w%, respectively. This system enables the selective targeting as well as detection of micelles at nanomolar concentration and an active pH-triggered release of encapsulated DOX. Lavasanifar et al. reported a DOX delivery system based on DOX-conjugated (PEO-b-PCL) block copolymers and also PEO-b-PCL micelles bearing benzyl, carboxyl, or DOX groups in the core for the physical encapsulation of DOX, where a maximum level of drug-loading and control over the rate of DOX release was achieved by polymeric micelles containing benzyl groups in the core [83]. These ABCs were also successfully demonstrated for active cancer targeting by using tri-peptide RGD ligand conjugated to PEO-b-PCL copolymers [57].

More details on ABCs in drug delivery, such as engineering of micelle core and shell to achieve stable micelles with high loading capacity and control over drug release along with active targeting, are summarized by Lavasanifar et al. in a recent review article [84].

2.2. Comb-like polymeric amphiphiles

Watterson et al. generated amphiphilic PEGylated block copolymers by polymerizing dimethyl isophthalates, having alkoy group at the C-5 position with the PEG diol in the presence of organometallic catalyst (Scheme 1) [85]. This methodology required harsh reaction conditions and the quality of synthesized amphiphiles was not very suitable for biomedical studies due to metallic contamination. In order to overcome these limitations, they developed a greener chemo-enzymatic approach to carry condensation polymerization of dimethyl-5-hydroxy-isophthalate with PEG diol (Mₙ 600–1500 Da). Polymerization occurred in a chemo-selective manner leaving the phenolic hydroxyl groups intact (Scheme 1) which were then utilized for post-polymerization modification by attachment of different substituents to tailor the properties of resulting copolymers [86].

The amphiphilic polymers obtained by the attachment of hydrophobic side chains exhibit comb like structures as shown in Scheme 1. The process of micellization of the amphiphilic copolymers (IP-PEG-O-C₉-R) studied by ¹H NMR longitudinal relaxation

![Scheme 1. Synthesis of amphiphiles (IP-PEG-X-C₉-R).](image-url)
time ($T_i$) [86] indicated that, in water, the hydrophobic segments have a strong tendency to aggregate and generate the core of the micelle that is covered by linkers and an external corona of PEG loops as illustrated in Fig. 2.

Light scattering techniques were used to gather additional self-assembly parameters i.e CMC (0.03–0.05) mM, the radius of gyration ($R_g$) ~ 12–21 nm, hydrodynamic radius ($R_h$) ~ (6–13) nm, and shape of micelles. The ratio of $R_g/R_h$ suggests that the micelles have a shape between a hollow sphere and a star-like sphere [87]. A cartoon model of amphiphilic polymer developed by molecular modeling study suggested aromatic units and alkyl chains to be in close proximity and form an inner hydrophobic core. In this process, the phenyl rings tend to stabilize the system by orienting themselves in nearly parallel positions so as to maximize the $\pi-\pi$ interactions. The alkyl chains tend to line up in a nearly parallel fashion as shown in Fig. 3 [88].

Clearly the amphiphilic polymer system developed by Watter-son et al. are not only effective for avoiding rapid renal exclusion, but are also small enough to avoid undesirable uptake by the reticulo endothelial system. Because of these micellar optimal properties for drug delivery, they were evaluated for encapsulation of two drugs molecules naproxen and aspirin [86]. The electronic properties for drug delivery, they were evaluated for encapsulation commercially available naproxen sodium (34%) and aspirin (32%) compared to the same aqueous dose (800 fl) prepared from commercially available naproxen sodium (34%) and aspirin (32%) (Fig. 4). The nanosphere-mediated delivery increased the efficacy by 1.8–2.0 fold. The encapsulation of aspirin was also evaluated in amphiphiles where alkyl chain was linked with ether (IP-PEG-O-C10), ester (IP-PEG-O-OC8), amide (IP-PEG-NHCO-C8), and maximum loading was observed with amide linked systems (up to 26%) [89].

IP-PEG copolymers with phenolic hydroxyl at C-5 of isophthalate, were found to be interesting for selective metal ion interactions. The interaction of metal ions with organic ligands is of special interest to understand various biochemical processes [90–95]. The interaction of IP-PEG block copolymers with various metal cations (NaCl, KCl, CaCl2, AlCl3, BaCl2, MgCl2, and LiCl) was studied by UV spectroscopy [96]. The interaction was selectively observed with CaCl2. Furthermore, calcium bromide and calcium iodide also interacted with the IP-PEG copolymers in an identical manner indicating that the effect is a result of a cationic interaction and is not significantly influenced by the anion. The possibility of interactions due to the effect of pH was excluded by performing some control experiments. These results should be of relevance for biological systems and may find applications in the field of material science and biology.

Watterson et al. also synthesized photo-responsive amphiphilic polymers (IP-PEG-O-diaz) by attaching diazo alkyl chain (Scheme 1), which reduces the CMC tremendously, compared with amphiphiles (IP-PEG-O-C9-R) carrying alkyl chains. An efficient photo-isomerization (trans – cis/cis – trans) was observed in organic solvents chloroform and methanol, however this phenomenon was not observed in aqueous solution. As a result, these amphiphiles could not be explored for drug encapsulation and release studies [97].

Polymers made of naturally occurring building blocks are preferred for biomedical applications because their degradation products are non-toxic and can be easily metabolized by living tissues. Encouraged by the development of novel chemo-enzymatic approach, the efforts were made to synthesize various water soluble PEGylated copolymers by using biologically important non-toxic linker molecules such as coumarin, curcumin, glycerol, amino acids, and sugar molecules (Fig. 5). Each of these block copolymers have been explored for various biomedical applications. For example, PEG-coumarin copolymers were evaluated for their anti-inflammatory activity and have shown an enhanced and improved ability to inhibit the TNF-α induced ICAM-1 (intercellular cell adhesion molecule 1) expression on human endothelial cells compared to the coumarin linker itself [98]. PEG-curcumin block copolymers enhanced the water solubility of curcumin due to which the copolymers act as a potent Nrf2 activator which is a central transcriptional factor for the regulation of the anti-oxidant defense system and is considered a modifier for several inflammatory diseases [99]. Amino acids, glycerol, and sugar containing amphiphiles were evaluated for their self-assembly and drug encapsulation studies.

PEG-amino acid [100,101] and PEG-glycerol copolymers after post alkylation (Fig. 6) yield amphiphiles which self-assemble in aqueous solution and form micelles.

![Fig. 2. Structure of PEGylated amphiphile and its self-assembly in aqueous solution.](image-url)
Watterson et al. have developed an efficient single step biocatalytic approach wherein a series of three amino acid diesters, i.e., diethylamino malonate, dimethyl aspartate, and diethyl glutamate carrying a free amino group, were copolymerized with PEG [98]. The chemical method to obtain such copolymers is not only tedious but also often involves organometallic catalysts and requires additional processing to remove the trace amounts of organometallic catalyst which are often difficult to remove completely [102]. The free amino groups of the copolymers were used to attach alkyl chains and the resulting amphiphiles (Fig. 7) were studied for their self-assembly behavior in aqueous solution and found to be optimal with amphiphile A2-PEG-C9. This has CMC of $2.2 \times 10^{-4}$ mmol, $R_g$ 18 nm, and aggregation number 15. These physical properties are comparable to that of IP-PEG-O-C_y amphiphiles as shown in Scheme 1.

Sharma et al. have synthesized lipase catalyzed chemo-selective glycerol containing block copolymers by copolymerization of glycerol with PEG-600 dimethyl ester. PEG diester was synthesized by esterification of the commercially available PEG-600 diacid. The copolymers carried a free pendant secondary hydroxyl group which was acylated with (C_5/C_7/C_9) acid chlorides [103]. The resultant amphiphiles (Fig. 8) self-assembled at a concentration of $10^{-3}$ M. Vitamin E encapsulation was evaluated in all the three amphiphiles with C_5/C_7/C_9 alkyl chain, and maximum loading (22%) was found for the amphiphile carrying C_9 chain.

Haag et al. have synthesized carbohydrate containing amphiphiles [104]. Suitable carbohydrate monomers carrying diol functionality were obtained by the multistep synthesis starting from diacetone-$\alpha$-glucose and copolymerized with PEG-600 dimethyl ester. Aggregation studies of the resulting copolymers PEG-S1/S2/S3, (Fig. 9) revealed that they self-assembled in aqueous solution.

The polymeric aggregates were further explored for their drug encapsulation properties in buffered aqueous solution of pH 7.4 (37°C) using nile red as a hydrophobic model compound by means of UV–Vis and fluorescence spectroscopy. The drug loading capacity of polymeric aggregates of copolymer (PEG-S2) bearing the hydrophobic five carbon alkyl chain was found to be significantly higher than that of the polymer bearing the benzylidene moiety (PEG-S3). There was no significant encapsulation in copolymer (PEG-S1) which lacks hydrophobic content in comparison to PEG-S2 and PEG-S3 copolymers. The nile red release study was performed at pH 5.0 and 7.4 using fluorescence spectroscopy. The release of nile red from the copolymers (PEG-S3) and (PEG-S2) was observed with a half-life of 3.4 and 2.0 h, respectively, at pH 5.0, while no release was found at physiological pH 7.4 (37°C).

Watterson et al. modified IP-PEG copolymers as shown in Scheme 1 for the transportation of vitamin E with high loading capacity. For this purpose, polymeric nanocarriers containing the covalently bound vitamin E have been designed and synthesized using a chemo-enzymatic method (Scheme 2). The synthesized nanocarriers can further be utilized to encapsulate vitamin E through non-covalent interactions [105]. It was observed that the covalent attachment of vitamin E to the polymer backbone enhances the capacity of the polymer to encapsulate vitamin E, i.e., it increased from 17% (with fully functionalized alkyl chain) to 26% (with 30% covalently attached vitamin E, and 70% alkyl chain functionalization).

It was also found that the amphiphiles (fully functionalized with alkyl chains) increased the efficacy of the encapsulated vitamin E against amyloid-$\beta$ induced reactive oxygen species [106]. The vitamin E containing nanocarriers are highly soluble in both water and oil, making them suitable for both aqueous and non-aqueous preparations. This approach allows a better control of the release and bioavailability of vitamin E and can be used in combination with other bioactive agents in various formulations for cosmetic and pharmaceutical applications.

Advanced nanocarriers have also been produced by Watterson et al. that may fulfill the parameters required for efficient drug delivery for an early detection of tumors by in vivo imaging [107,108], and for a selective targeting of the therapeutics to the cancer cells (Fig. 10). The design allows the customization of each region of its micelle components, i.e. its surface, shell, and core for...
generation of biomaterials, to make it suitable for imaging and targeting the cancer disease in advanced stages.

For MRI and specific tumor targeting purposes amphiphiles were synthesized by copolymerization of two linkers, i.e. DM5O-HIP (95%) and DM5NH2IP (5%), with equivalent moles of PEG diol [108,109] as a hydrophilic component. In the resulting copolymer, the amino groups were used for the covalent attachment of FITC dye, and the phenolic hydroxyl groups were used for attachment of peptide that carried a PEG spacer and, perfluoro alkyl chains. The self-assembly of the resulting material contained perfluoro alkyl chains in the core. The perfluoro moiety enabled their usage as a potential nano-probe for 19F-MRI and the availability of peptide on the outer surface of micelles could facilitate their selective binding with tumor cell receptors and internalization in the tumor cells by a receptor mediated endocytosis process (Fig. 11).

These fluoro amphiphiles (Fig. 10) have shown the capability to encapsulate cargo 1H,1H,2H,2H-perfluorodecanol and enhance the fluorine signal in 19F-NMR up to 30% and 57% with ether linked and amide linked perfluoro chains, respectively. The enhancement in 19F content makes these amphiphiles more suitable for MRI and allows retention of the antitumor drug (Fig. 12) curcumin up to 14%.

Initial in vitro studies examining the cellular uptake of these nanocarriers by radioactive labeling and analysis have shown that these particles target cancer cells more selectively than the normal cells. This selectivity has been further demonstrated in the area of drug delivery through increased cell death of targeted cancer cells versus non-targeted cells when incubated with nanocarriers containing the chemotherapeutic agent DOX.

Overall, based on the literature discussed herein, PEG containing block copolymers point to the suitability of prepared polymeric micelles as delivery vehicles compared to conventional drug formulations for the efficient administration of a range of therapeutic compounds. However, comb like architectures developed by chemo-enzymatic method may find application in the development of new DDS for efficient cell targeting and disease control. The synthesized biodegradable polymers by this approach however need further evaluation in vitro and in vivo.

The PEG containing block copolymeric micelles lack the availability of free functional groups on the outer surface of micelles due to limited functional groups of PEG. This limits the post-modification of micelles. To overcome this problem and for the availability of multivalent functional groups on the outer surface of the micelles, the chemo-enzymatic approach could be useful for their construction. Further there are some pros and cons of PEG discussed by Schubert et al. in a recent review article [41] which need to be considered for new PEG containing micellar drug carrier systems.

![Fig. 5. Lipase catalyzed condensation polymerization of linkers with PEG.](image)

![Fig. 6. Post modification of copolymers.](image)
3. Non-ionic amphiphilic nanocarriers based on dendritic polyglycerols

Dendritic polymers, including perfect dendrimers and HBPs with remarkable physical and chemical properties and unique topological structures, are of immense importance for materials science, catalysis, and biomedical research [110–115]. The unique properties of dendrimers, such as their high degree of branching, multivalency, globular architecture, well-defined molecular weight, large number of tunable surface groups, and an interior that provides space as well as microenvironment for host–guest chemistry, makes them promising scaffolds for drug delivery. So far, only two types of dendritic polymers, namely, polyamidoamine (PAMAM) and poly(propylene imine) (PPI), have been commercialized.

The synthesis and self-assembly of hyperbranched PGs [116–118] are currently attracting considerable interest for application in drug solubilization and delivery [43]. dPGs are structurally defined, consist of an aliphatic polyether backbone, and possess multiple functional end groups [43,119,120]. Their size can be precisely defined between 5–20 nm [19,121]. PG-based architectures demonstrate optimal biocompatibility on the cellular and systemic levels. They have similar toxicological properties as PEG which is classified as highly non-toxic for in vivo applications [43]. Thus, the development of new generation PG architectures with an improved biocompatibility and designed drug release profile will further enhance our fundamental understanding of such systems and could potentially lead to new DDS [122]. In recent years much attention has been given to versatile architectures, most of which are based on dendritic polyglycerol and classified according to the chemical nature of the building units. The following section reviews the recent progress in synthesis and application of non-ionic dendritic polyglycerol based amphiphiles and dendritic core multi-shell architectures.

3.1. Linear-dendritic block copolymeric (LDBC) amphiphiles

Perfectly branched and highly symmetrical dendrimers have a well-defined number of end groups, and can be functionally modified for controlling solubility, surface and interfacial properties, and encapsulation behavior [123–125]. Dendrimers have been extensively studied for biomedical application in diagnostics and therapy [126,127]. They have been employed for the synthesis of LDBC amphiphiles and used in DDS.

Frechet et al. described the first synthesis of LDBCs in 1992 [128]. They reported the convergent synthesis of both AB diblock as well as ABA triblock type structures with poly(benzyl ether) dendrons of generation [G3] and [G4] and poly(ethylene oxide) (PEO) (Mn in the range of 500–20,000 g/mol) as the linear polymer segment. Nguyen and Hammond studied the properties of linear (PPO)-dendritic (PAMAM) triblock copolymer (PAMAM–PPO–PAMAM) as drug carriers [129]. The solution phase behavior of these block copolymers was studied as a function of the generation of the dendritic block, ionic strength, and solution pH. The trilobal self-assemblies in aqueous media to form stable micelles with CMC values ranging from $10^{-6}$–$10^{-5}$ M and particle size ranging from 9 to 18 nm in diameter, with smaller diameters exhibited at higher generations. These block copolymers encapsulated hydrophobic drugs with high efficiency and showed sustained release of the drug. Although it was shown that there was no pH dependence at generation [G3] for drug release, but it was assumed that pH dependence could be observed for higher generations.

Kanani et al. and Shukla et al. used linear-dendritic macromolecules containing PEG and dendrimer block for transport of small guest molecules such as 5,7-dibromo-8-hydoxy quinoline, ibuprofen, Congo red, and rose Bengal [130,131]. The linear-dendritic copolymers/guest molecule complexes were stable at room temperature for about 10 months and did not release the encapsulated guest molecules. The controlled release of guest molecules from linear-dendritic copolymers/guest molecule complexes in vitro conditions was also investigated. It was found that higher generations exhibited enhanced transport capacity, but the drug release was also faster in comparison with lower dendrimer generations. Furthermore, Shukla et al. also reported the modification of these LDBCs with benzyl alcohol and the pH-dependent cleavage of the ester bonds over time [131]. Recently, Zhou et al. studied the guest uptake into micelles formed of LDBCs based on poly(butenylene oxide)-b-PEO as the linear part that is connected to different generations of dend-PAMAM [132]. Light scattering results indicated the formation of “flower like” micelles composed of a hydrophobic oxybutylene core and dendrimer periphery in aqueous buffer solution. Drug solubilization in micellar solutions of the conjugates was mainly done by the incorporation of drug molecules in micelle cores, with a marginal enhancement of solubility that was attributable to encapsulation in the dendritic micelle coronas. The solubility of hydrophobic drugs in 1 wt% micellar solutions increased up to 6-fold.

Haag et al. reported a modular approach for the synthesis of well-defined micellar constructs of non-ionic dendritic glycerol based amphiphiles via click chemistry (Scheme 3) [133]. All the amphiphiles featured a construction with dendronized hydrophilic head groups [G1-G3] connected to hydrophobic segment of aliphatic units via mono- or biaromatic spacers.

It was shown that the dendritic head group strongly influenced the self-assembly as well as the aggregation number which led to structurally persistent and highly defined spherical micelles for [G2] and [G3] dendrons. Due to the packing parameter, [G1] amphiphiles preferably formed cylindrical micelles (Fig. 13) with CMCs lying in the micro molar concentration range. The micelles were tested as potential nanocarriers for hydrophobic compounds and were shown to entrap the solvatochromic dyes Nile red and pyrene. Additionally, it was shown that the aromatic spacer group in the hydrophobic part plays an important role for the binding and transport of aromatic guest molecules. Besides the hydrophobic effect, CH–π and π–π interactions of arenes with other aromatic units of the guest molecules seem to be particularly important for solubilizing hydrophobic (aromatic) compounds [133].
The potential application of micellar assemblies as drug delivery vehicles is the solubilization of hydrophobic drugs for which it is necessary to investigate the effect of different core structures with respect to solubilization, micelle (formulation) stability, and cytotoxicity. Haag’s group further extended the study of non-ionic dendritic glycerol based amphiphiles composed of different hydrophobic modifications: PG[G2]-DiAr-C18, PG[G2]-(C18)2, PG[G2]-C18-BiP, and PG[G2]-C18-Naph and investigated them with respect to solubilization and micelle stability using sagopilone, an anti-cancer drug with low aqueous solubility (12 mg/L) [134]. The cytotoxicity using HUVECs was also investigated and compared to standard excipients. With regard to the clinical application of sagopilone as an anti-cancer therapeutic, a final formulation concentration of at least 1 g/L was required. The amphiphiles formed spherical (7–10 nm), monodisperse (PDI 0.04–0.20) micelles in buffered aqueous solution with the exception of the double-chained amphiphile PG[G2]-(C18)2. All the micelles solubilized sagopilone and showed a superior solubilization behavior compared to standard excipients used in parenteral formulations. The amphiphiles revealed a 2–3 fold higher solubilization of sagopilone than Cremophor® ELP and polysorbate 80 independent of the core structure. Sagopilone was best solubilized in the presence of amphiphile with a diaromatic spacer (PG[G2]-DiAr-C18) (Fig. 14) among all the dendritic amphiphiles tested. Cytotoxicity studies with various functionalized amphiphiles showed a clear structure-response relationship with the structure comprising a naphthyl end group being the least cytotoxic. Its actual cytotoxicity values were comparable to the standard excipient Cremophor® ELP and polysorbate 80 [134].

In addition to better solubility of the hydrophobic compounds, a triggered release of guest molecules is highly desirable for increasing pharmaceutical potential of the drugs and to reduce their side effects. Attempts have been made to disrupt micellar structures with different external stimuli like temperature [135].
pH [136], and redox processes [137]. Most of these methods involve the degradation of the amphiphilic molecule, which is irreversible or can lead to other undesired effects. Another promising approach is the light-induced isomerization of azobenzenes [138]. Haag et al. recently developed a new non-ionic photo-switchable delivery system and investigated it with regard to transport and release of guest molecules [139]. The photo-responsive amphiphiles were synthesized starting from 4-aminophenol under standard diazotization conditions and then reacted with phenol. The hydrophobic building block was attached to the azobenzene by etherification with the chosen aliphatic chain (C11 and C16). The attachment of glycerol dendrons to the azo switch was carried out by etherification using mesylated acetal-protected glycerol dendrons under basic conditions. Subsequent removal of the acetal protecting groups resulted in the azobenzene-containing amphiphiles.

All four PG-based amphiphiles (G2azoC11, G3azoC11, G2azoC16, and G3azoC16) formed monodisperse (PDI 0.02–0.2), well-defined spherical (7–10 nm) micelles and offered a higher ability to undergo trans–cis photoisomerization in comparison to a corresponding linear mPEG amphiphile, which formed rather large ill-defined aggregates (205 nm, PDI 0.28). It was observed that the size of the micelles influenced the photo-stationary state: the smaller the micelles, the higher the photo-stationary state. These findings were based on the larger empty space between the molecules in smaller micelles formed from [G3] amphiphiles which improved the photo response better than the densely packed larger

Fig. 10. Amphiphile for MRI and targeting. Adapted from Refs. [107,108].

Fig. 11. Cartoon representation for micelles with ligands and their specific internalization in tumor cells. Adapted from Ref. [108].
aggregates of [G2] amphiphiles. Because the CMC was effectively altered by light, these amphiphiles can be used for controlling the solubilization and encapsulation of a guest molecule (Fig. 15). It was demonstrated that light attenuated uptake of nile red occurred effectively by these photo-switchable amphiphiles. The effectiveness of the switching in modulating the aggregation behavior of the amphiphiles is highly influenced by the photo-stationary state. A high photo-stationary state led to a larger change in the CAC and a larger overall effect on the solution behavior [139].

The use of PG dendrons allows a great diversity of architectures by the convergent synthetic approach (Fig. 16). Haag et al. reported the synthesis of a library of core-shell architectures, based on a variety of aromatic cores attached to different generations of PG dendrons (Fig. 16) [140,141]. The synthetic protocol included the linking of the dendrons through amidation [140] or click coupling [141]. Nile red was used as the model drug for evaluating the encapsulation efficiency of these architectures. No correlation between encapsulation and dendron generation was found for PG dendrons coupled to a biphenyl core via amide bonds. It was shown that the amount of encapsulated nile red unexpectedly decreased with higher dendron generations. However, because the complexes formed between nile red and the dendritic PG derivatives were lower than 1:1 compositions in all cases, larger aggregates were more likely to occur. On the other hand, in the core-shell architectures obtained by the ‘click’ approach, UV–Vis absorption spectra revealed a strong red shift of the absorption band of nile red with a [G1] dendron complex which suggests the presence of nile red in a very polar environment, e.g. when it is surrounded by glycerol units. The hydrophobic cores probably coupled with the smallest dendron [G1] to form aggregates by π−π interactions; therefore the dye was not accommodated into the core. In higher generations, where the maximum absorption shifted to lower wavelengths, nile red was usually located in the hydrophobic core. The transport capacity of the dye was significantly improved by expanding the core size which indicates that an extended aromatic core is necessary for efficient encapsulation and transport of hydrophobic compounds. The encapsulation of nile red was significantly improved by a factor of ~200 by enlarging both core and dendrimer size.

3.2. Linear-hyperbranched block copolymeric (LHBC) amphiphiles and dendronized polymers

HBPs have gained importance in recent years because they only require a single polymerization step [142]. In contrast to perfectly branched and monodisperse dendrimers, hyperbranched architectures exhibit large polydispersity in molecular weight and structure due to the random branching process. They lead to compact, globular shaped macromolecules because of spatial restrictions of the branched topology and they are unlikely to form entanglements, which is a well known feature for high molecular weight linear copolymers [143]. These HBPs have been employed for the synthesis of linear-hyperbranched amphiphiles by a few research groups.

Frey et al. reported the preparation of a new type of linear-hyperbranched surfactant consisting of a linear polymer chain and a hPG segment [144]. These well defined amphiphilic block copolymers were prepared by anionic ring-opening multibranching polymerization of glycidol onto an end-functional poly(propylene oxide) (PPO) macroinitiator (Scheme 4). Molecular weights of the non-ionic amphiphiles obtained were all monomodal, with moderate polydispersities of around 1.5. These hPG homopolymers were investigated with respect to amphiphilic properties. On comparison, these hPG homopolymers were closest in chemical nature to Pluronics, although the structures do not match completely, since Pluronics possess a symmetric triblock structure with an interior PPO-segment. Based on an equal molar mass range, the CMC values for the Pluronics are approximately ten

Scheme 3. Synthesis of glycerol based non-ionic amphiphiles via click chemistry approach.
times larger than for these systems [145]. The CMC of non-ionic poly(propylene oxide)-hb-poly(glycerol) was investigated via a fluorescence-probe method using diphenyl hexatriene as probe molecule. For these linear-hyperbranched block copolymers the CMC increases with the molecular weight of the hyperbranched block. Since this system possesses amine functionality as the linkage between the linear PPO and hPG block, the pH dependence of the CMC was also studied. The CMC constantly increased over the whole range of the hydrophobic/hydrophilic ratio. Due to the proven biocompatibility of PGs [146,147], the synthesized polymers are of considerable interest for biomedical applications. It was observed that the polymers render multi-drug resistant (MDR) to cells sensitive to drug, decreasing the resistance factor [148]. The linear-branched surfactants have been shown to influence the transport of doxorubicin through biomembranes and into cells, offering interesting possibilities for the chemotherapy of cancer [148].

Dendronized polymers which combine the two concepts of dendrimers and polymers, are a promising approach for generation of smart materials. They can be prepared by four ways: direct polymerization of dendron monomer (the macromonomer approach), grafting dendrons to a linear polymer (attach-to approach), divergent step-growth from a core of linear polymer (divergent approach), and their combinations [149–151]. Amphiphilic dendronized polymers have unique structural motifs [152]. In nature they can be found in some ion channel membrane proteins, which means that amphiphilically dendronized polymers are of interest as models for such proteins [126,153–155]. They may also serve as novel and giant constituents of self-aggregated assemblies and show interesting behavior at interfaces. A good candidate is a dendronized polymer whose repeating units are equipped with two sterically demanding substituents, one hydrophobic and the other hydrophilic.

Mery et al. synthesized a series of dendronized polymers carrying oligo-(ethyleneoxy) peripheral branches by post polymerization functionalization of multiallylic dendronized polymers using a radical addition of mercaptans, namely, 2-methoxy(ethoxy)ethanethiol and (2-(2 methoxyethoxy) ethoxy) ethanethiol (Fig. 17) [156]. According to the hydrophilic and hydrophobic balance, some polymers exhibited a thermoresponsive behavior in water solution, which is characterized by a sharp LCST transition and a small hysteresis. The LCST was found to increase with increasing DP. This uncommon behavior was explained by two concomitant factors: a polymer dilution effect and an increase of the apparent hydrophilicity of the polymers due to a densification of the EO coverage.

Fig. 13. Schematic representation of micellization of various types of non-ionic dendritic glycerol based amphiphiles in water. Due to the packing parameter [G1] amphiphiles preferably form cylindrical micelles. Reproduced with permission from Ref. [133]. Copyright 2010 American Chemical Society.

The structural properties of the polymers in solution have been investigated by SAXS and SANS. By SAXS investigations and using a spherocylinder shape model, the polymers in solution (below the LCST) have been satisfactorily described. By increasing the DP, the shape of the macromolecule was found to evolve from a spherical to a spherocylinder shape with a constant cross section of ca. 40 Å.

Fig. 14. Structural formula of the dendritic amphiphile used for the solubilization of sagopilone in buffered aqueous solution. The amphiphile revealed a 2–3 fold higher solubilization of the drug than Cremophor® ELP and polysorbate 80 independent of the core structure. Reproduced with permission from Ref. [134]. Copyright 2010 Elsevier.
In the same area Mandal et al. have synthesized a new family of dendronized polymers by functionalizing ethylene oxide–epichlorohydrin copolymer with aromatic ether dendrons based on 3,5-dibenzyl ether (Fig. 18) [157]. The polymers were characterized by FTIR spectroscopy and tested for possible application as an electrolyte for lithium-ion batteries. The polymer with increased dendritic residue exhibited improved ionic conductivity and excellent thermal stability. Thermogravimetric analysis and differential scanning calorimetry were performed to determine the thermal stability and crystallinity of the polymeric material. Incorporation of bulky dendritic pendent moieties into the polymer backbone effectively broke down the crystallinity of these polymers.

Dendronized polymers are currently under intense investigation with respect to various applications, including the synthesis of hierarchically structured materials, catalysis, applications in the biosciences, such as ion channel mimics and DNA compactization, as well as optoelectronic applications [149].

3.3. Hyperbranched core-shell architectures

Physical aggregates of amphiphilic molecules, such as micellar structures, are frequently proposed as drug-delivery systems because of their non-covalent assembly [37]. However, these aggregates can be unstable under shear force and other kinds of environmental effects as a result of their weak assembly. They are also not very suitable for the active release of the encapsulated species through the application of an external trigger, such as pH...
change. Although the encapsulation and the transport of guest molecules into these dendritic architectures have been studied by several research groups [158–169] relatively little is known about the active release of the encapsulated guest molecules by pH-triggered cleavage of the shell in the physiological pH range (Fig. 19). An alternate approach is the covalent modification of dendritic macromolecules with an appropriate shell that results in stable micelle-type structures, which are suitable for the non-covalent encapsulation of guest molecules (Fig. 19) [170]. The size of these dendritic nanocarriers can be exactly defined in the range of 5–20 nm. The encapsulation of guest molecules by these dendritic nanocarriers is driven by non-covalent interactions (ionic, H-bonding, and van der Waals interactions) and can be tailored for various drugs at the same time and thus have an advantage over polymer-drug conjugates, which have to be synthesized individually in an extensive multi-step synthesis.

Dendritic polymers with their regular and well-defined unimolecular architecture can be chemically modified either at the core (to increase hydrophobicity) or at the shell (to increase hydrophilicity) thereby tailoring the solubility profile of such nanotransport systems. Among the various polymeric drug carriers known today [115,121,171], dendritic polymers based on PG and with defined core-shell type architectures have shown good transport capacities for several poorly water-soluble bioactive molecules. Several investigations covered the influence of post-modification of the PG scaffold in an attempt to increase transport capacity and/or efficiency, decrease inherent toxicity, tune structural topology, and impart targeting modalities. Micelles as well as inverted micellar structures have been constructed and their carrier properties investigated for several bioactive molecules.

PEGylation of hPG is a promising method for rendering aqueous solubility, minimizing immunogenicity, and increasing the blood circulation half-life of the resulting nanocarriers, as well as mimicking the structure of so-called “stealth” liposomes [172]. Brooks et al recently reported an efficient synthesis of hydrophobically modified as well as PEG-grafted hyperbranched PGs using 1,2-epoxyoctadecane and α-epoxy, ω-methoxy PEG 350 (MPEG-epoxide) as the monomer, respectively [173,174]. Initially hyperbranched PG of molecular weight 7 kDa was prepared by anionic ROMBP of glycidol. An equivalent of 2–5% of the OH groups were derivatized with C18 alkyl chains and 20–40% of the OH groups were modified with mPEG 350 chains by sequential addition of the corresponding epoxides. The obtained structures carried alkyl chains at the core and PEG moieties grafted on the shell (Fig. 20).

The unimolecular micellar nature of the molecules with different alkyl chains/PEG composition was probed by multiangle laser light scattering (MALLS). Due to low intrinsic viscosity, these scaffolds were extremely promising candidate for human serum albumin (HSA) substitutes [173]. The encapsulation efficiency was evaluated using paclitaxel and pyrene as model compounds. Fluorescence studies revealed that the hydrophobic molecules are most likely to be located in the hydrophobic pockets of the unimolecular structures [175]. The solubility of paclitaxel in water was increased from 0.3–1 μg/mL up to 2 mg/mL after encapsulation in the nanocarriers, without any considerable effect on the size of the unimolecular micelles. The release profile was characterized by a burst release phase followed by a slower sustained-release phase [175].

These structures presented mucoadhesive properties. Paclitaxel was incorporated into these mucoadhesive nanoparticles and was evaluated as an intravesical agent against non-muscle-invasive bladder cancer [176]. Though the encapsulated paclitaxel was slightly less potent than the free drug in vitro, the in vivo studies showed that the mucoadhesive formulation of paclitaxel was significantly more effective in reducing orthotopic bladder tumor growth than the standard Cremophor-EL formulation of paclitaxel (Fig. 21). Relative tumor growth with paclitaxel complex was reduced to 15% of the control compared to 66% for the free paclitaxel group. The complex was well tolerated in mice and the resulting stabilized level of hematuria and body weight with zero mortality indicated no sign of systemic toxicity. These amphiphilic systems were reported to adsorb onto the
human RBCs in vitro [177], and they have shown very promising sustained drug release characteristics in vitro using the drug paclitaxel [175].

Furthermore, Frey et al. [178] have described the synthesis of \( \alpha, \omega \)-linear-hyperbranched PEG-PG heterotelechelics with a single amino moiety in the \( \alpha \)-position and subsequent attachment of biotin in this position. They have used this material subsequently for non-covalent bioconjugation, which can be achieved with or without a linear PEG-spacer. Paleos et al. [179] prepared functional HBPs based on a commercially available polyether polyol that bear PEG chains with folate targeting ligands on their end. They found that PEG chains, in addition to their well-established function as protective coating for drugs and their carriers, enhanced the encapsulation efficiency and controlled the release of fluorescent probes, pyrene, and anti-cancer drug tamoxifen. DLS revealed unimicellar encapsulation of the guest molecules within the PG-PEG structure. A salt-triggered release was observed upon addition of sodium chloride and was enhanced as the concentration of salt in the medium increases. The cationization of the poly(ethylene glycol) moieties of the carriers by the sodium ions leads to the formation of complexes. This may lead to the replacement of solubilized drug by the metal ions and, therefore, release of the drug can occur.

Frey et al. described the use of hPGs for the preparation of amphiphilic molecular nanocapsules for hydrophilic guests [164].

Construction of molecular nanocapsules was demonstrated using narrow poly-dispersion PGs and simple esterification of only a certain fraction of hydroxyl groups (43–93%) with hydrophobic fatty acid chains (Scheme 5), thereby leaving residual hydroxyl moieties and hence, the inner sphere of the molecule remained highly hydrophilic (Fig. 22).

The considerable flexibility of the polyether structure permits the hydroxyl groups to arrange in a manner that represents a solvating environment for polar guest molecules in apolar solvents. These hyperbranched molecular nanocapsules were thus able to solubilize a distinct average number of polar molecules in their interior, depending on the core size and substituents. This encapsulation which is based only on a hydrophobically shielded, hydrophilic solvating microenvironment represents a different principle in comparison to the topological entrapment observed for some dendrimer-based structures. From light scattering measurements it was tentatively concluded that the solvating species are present in an unimolecular form in organic solvents, thus, representing “inverted unimolecular micelles”. Release of the encapsulated dyes was achieved by cleaving the ester bond, thus, removing the hydrophobic molecular shield of the nanocapsules.

The polyfunctional polyol architecture of dPG polymers makes them suitable for multiple functionalization. They hold considerable promise as binding agents for drug delivery due to their three-dimensional shapes and availability of a large number of functional
groups for suitable modifications [180–183]. The presence of primary and secondary alcoholic groups provides a platform for the selective modification and tuning of the physio-chemical properties so that these architectures can be further used as potential drug carriers. Haag and Sharma et al. reported for the first time chemoenzymatic regioselective modification of the dPG with PEG chains via the primary hydroxyl groups and further alkylation of the remaining hydroxyl groups to generate well-defined architectures with an easily hydrolyzable ester linkage [184]. The dPG was first PEGylated in a regioselective manner using the PEG carboxylic acid (Mn ~ 1 kDa) and Novozyme-435 as a biocatalyst. The esterification reaction primarily occurred through the primary hydroxyl groups of PG leaving the secondary hydroxyl groups intact. PEGylated PG was then acylated through its remaining hydroxyl groups to generate well-defined architectures [Scheme 6].

The solubilization behavior of these polymeric architectures was studied by means of UV–Vis spectroscopy using nile red as hydrophobic model compound [Fig. 23]. It was observed that the amount of dye solubilized by the polymer increased with the polymer concentration which suggests that these systems exist as aggregates at low concentrations (<0.1 g/L). The degree of solubilization was also influenced by the increase in size of the alkyl chain. The polymer with undecenoyl chain showed better transport behavior than other polymers, which may be due to the more hydrophobic contribution of the alkyl chain and the possibility of π–π interactions between the terminal olefinic bond and aromatic ring system of nile red that resulted in more compact aggregates and thus led to a decrease in particle size with improved polydispersity index values. These systems were found capable of releasing the encapsulated nile red at pH 5.0 (e.g. endosomal pH), while no release was observed at pH 7.4 (physiological pH). Furthermore, cell viability studies of these polymers showed that they are relatively non-toxic. These successful efforts in tuning the synthesis and physio-chemical properties of dPG based amphiphilic polymeric architectures as novel DDSs are currently being explored as biodegradable dendritic nanocarriers for biomedical applications [184].

The architecture of hyperbranched dPG consists of two types of hydroxyl functionalities, arising from linear glycerol units in proximity to the core and from the terminal glycerol units in the periphery of the macromolecule [Fig. 24b] and has no distinguishable interior or periphery like the perfect dendrimers. An effective and highly reproducible “chemical differentiation” strategy to generate core-shell architectures has been reported by the Haag group, where these two types of hydroxyl groups can be chemically differentiated to generate core-shell type architecture within the hyperbranched PG scaffold [185]. The 1,2-diols of the terminal glycerol units were selectively converted to the corresponding acetals or ketal s in order to distinguish between the interior (close to the focal unit) and periphery (distant from the focal unit) of the macromolecule, which was possible because the remaining linear glycerol units remained unaffected by this transformation. A subsequent reaction of the linear units with alkyl halides, such as allyl or benzyl chloride, under phase transfer condition yielded the corresponding polyether polyketal s. Selective deprotection of 1,2-ketals was achieved with an acidic ion-exchange resin to give “core” functionalized PGs.

This “chemical differentiation” strategy allowed a selective tailoring of the PG scaffold to contain a hydrophobic interior or a hydrophobic periphery, thereby modulating the distribution coefficients of the generated structure between organic and aqueous phases. Such selective ketal functionalized hyperbranched PGs were found to be effective for the encapsulation and transport of polar guests (e.g. dyes or drugs) and the creation of special micro-environments as demonstrated by the shaded area in Fig. 24 [186]. The extensive branch-on-branch topology of these polymers leads to typical properties associated with core-shell architectures, i.e., nanosegregation depending on the polarity of the “core” and the “shell”.

Haag’s group has also investigated the effect of a specific core modification of the hydroxyl groups of linear glycerol units with hydrophobic biphenyl moieties on encapsulation and transport capacities [Fig. 25] [187]. Amphiphilic nanocarriers containing unsubstituted and donor-/acceptor-substituted biphenyl groups in the core were synthesized in an effective three- to four-step procedure by employing etherification and Suzuki-coupling reactions. The generated amphiphiles were then employed to solubilize

![Fig. 21. In vivo evaluation of hydrophobic PG-paclitaxel complex against orthotopic bladder tumor. Reproduced with permission from Ref. [176]. Copyright 2008 Wiley.](image)
pyrene and the commercial drug nimodipine, a calcium antagonist used for the treatment of heart diseases and neurological disorders.

A major advantage of these amphiphilic PGs is that a hydrophobic core could be designed to tailor certain polymer–drug interactions. Consequently, it was possible to design dendritic architectures with a specific interaction profile for functional drug molecules. As example, the core-shell PG derivative with 3',4'-dimethoxybiphenyl-4-methyl ether groups in the core showed specific π–π interactions as detected by UV spectroscopy in the case of nimodipine complexation, in addition to non-specific hydrophobic host–guest interactions (Fig. 25). These observations indicated the formation of aggregates. The modified dendritic polymers were found to self-assemble around the drug molecules in a controlled manner, as revealed by DLS and AFM analysis (Fig. 26) [188]. CAC measurements revealed that these flexible, amphiphilic macromolecules self-assemble to extremely defined supramolecular structures with diameters of around 10 nm in the presence of the drug at very low concentrations (CAC typically ca. 10^{-6} M).

In addition to the transport of different drug molecules, these structures exhibited a substantial release of nimodipine in SEC column filtration where highly dilute conditions could be mimicked.

Haag’s group further modified the core of the dPGs with biphenyl groups and perfluorinated chains [188]. Due to the increased hydrophobicity of the core the newly developed systems were used to selectively solubilize hydrophobic (aromatic) dyes and drug molecules such as pyrene, nile red, and nimodipine. The encapsulation of the guest molecules was driven by weak non-covalent interactions such as hydrophobic, van der Waals interactions, and π–π stacking. The transport capacity increased 450-fold for nile red, 47-fold for nimodipine, and 37-fold for pyrene at a polymer concentration of only 0.1 wt.%. The aggregation properties were studied by surface tension
measurements and scanning force microscopy (SFM). The diameter of the formed supramolecular aggregates was 20 nm and CAC was observed to be $2 \times 10^{-6}$ M. Encapsulation experiments in water revealed that cores functionalized with 45% of biphenyl groups showed better transport capacity than those with a lower degree of functionalization (27%). However, the polymer became insoluble in water if the degree of functionalization exceeded 50%. Polymers with a perfluorinated core were substantially hydrophobic in nature and showed better transport capacity [188]. This phenomenon has particularly been observed with Nile Red encapsulation.

The selective and reversible shell functionalization of dPG scaffolds (Fig. 24c) allows preparation of core-shell structures with reverse micellar character. The self-association of amphiphilic polymers in non-aqueous solvents should thus yield nanostuctures with a polar core surrounded by a hydrophobic shell. This type of inverted micellar systems has been extensively investigated in encapsulation of oligonucleotides, metal complexes, and several water-soluble dyes and drugs [189]. The potential use of such systems in pharmaceutical applications is highly promising since they can be used in oleaginous formulations thereby providing better stability against enzymatic degradation and facilitating absorption through biological barriers such as the intestinal membrane. In addition, these systems could allow the controlled delivery of active compounds by subcutaneous administration. The hydrophobic character of the shell also makes these architectures attractive candidates for use in hydrophobic devices like teflon-based bone replacement materials and transdermal patches [43].

Haag et al. developed a way to synthesize such amphiphilic dendritic architectures for potential application in pH-dependent delivery of the encapsulated guest by using acid-sensitive linkages (acetals/ketals) for the PG shell [170]. The synthetic route involved a selective condensation reaction of the 1,2-diol units by a one-pot pathway, based on two consecutive transketalization reactions (Fig. 24c). The selective core-shell architectures obtained were highly amphiphilic with a hydrophobic shell and hydrophilic interior due to the remaining, unreacted hydroxyl groups. Such ‘molecular nanocarriers’ do not exhibit aggregation in dilute solution, as demonstrated by DLS, and thus represent inverse unimolecular micelles.

The transport capacity of these systems was governed by core-molecular weight, alkyl-chain length, and degree of functionalization. A minimum core size of 3 kDa and a highly branched architecture are required for successful encapsulation of the guest molecules [170], while the degree of alkylation should be around 50% and the alkyl chains should have a minimum length of 10 carbons for efficient transport of guest molecules.

**Fig. 23.** Model for drug solubilization and release. Reproduced with permission from Ref. [184]. Copyright 2011 Wichtig.

**Fig. 24.** Selective functionalization of hPG scaffold. (a) hydrophilic outer shell, (b) hPG, and (c) hydrophobic outer shell. Reproduced with permission from Ref. [43]. Copyright 2010 Wiley.
The transport capacities of these molecular nanocarriers were evaluated using congo red as an easily detectable polar model compound and it was observed that the transport capacity of these nanocarriers critically depends on the packing density of the shell. It was found that acetal functionalization of PG core with C\textsubscript{16} aldehyde containing one alkyl chain per diol unit resulted in an effective degree of alkyl functionalization of 25% and a poor transport capacity (0.15 congo red molecules). The ketal functionalized nanocarrier with two alkyl chains per diol unit and 45% effective alkyl functionalization, however, can transport up to 13 congo red molecules indicating an optimal core-shell functionalization, as a higher degree of ketal functionalization (55%), could transport only two dye molecules and the encapsulation process was very slow. The transport properties of these nanocarriers were then studied with different guest molecules containing polar or ionic organic groups as model systems. Many organic dyes, such as bromophenol blue, congo red, methyl orange, methyl red, and fluorescein, all of which contain polar anionic sulfonate or carboxylate groups and sodium counterions, were readily encapsulated and transported by these nanocarriers. A controlled release of encapsulated congo red from such a system was achieved in the aqueous phase (Fig. 27) [170].

The near-infrared absorption by red blood cells and water thus allowing the light to pass through the body of the mouse to the depth of several centimeters. Increased levels of tissue fluorescence suggested that the nanocarrier altered the biodistribution of the free dye which led to higher concentrations in the nanocarrier format. The designed structures were able to encapsulate the anticancer agent DOX and a near-infrared imaging dye, indotricarbocyanine for optical imaging. It was found that nanocarriers with the shortest PEG chain (n = 4) and a denser shell showed the best encapsulation efficiency (up to 5 molecules of DOX or NIR dye) PEGylated PG. The pH-dependent release of the DOX-nanocarrier was investigated by incubation at pH 4.0 or 7.4 (37 °C) and by dialyzing the sample over time and determining the amount of released DOX in the ultrafiltrate using HPLC. It was observed that a certain fraction of DOX (~20%) can be released in a pH-dependent manner, but the major amount of the drug remained associated with the nanocarrier (plateau level reached after 4 h) under the chosen experimental conditions. In an early study with nude mice, the DOX nanocarrier could be dosed up to 24 mg/kg free DOX equivalents intravenously which was a significant increase in the MTD compared to free DOX MTD [191]. Cytotoxicity experiments with the nanocarriers revealed higher IC\textsubscript{50} values for three cancer cell lines (3.3–31 μM) than for free DOX (0.02–0.39 μM), suggesting that the DOX loaded nanocarriers exhibited much lower antiproliferative activity than the free drug which may be due to an insufficient release of DOX from the complex.

The ability of the nanocarriers to localize in tumors in vivo was demonstrated by fluorescence imaging of tumor-bearing mice (Fig. 29) with the indotricarbocyanine–nanocarrier complex [190]. The near-infrared fluorescence imaging allowed an easy visualization of the tumor-accumulation of the dye-PG complexes since the near-infrared and far-red light (650–900 nm) can avoid strong absorption by red blood cells and water thus allowing the light to pass through the body of the mouse to the depth of several centimeters. Increased levels of tissue fluorescence suggested that the nanocarrier altered the biodistribution of the free dye which led to higher concentrations in the nanocarrier format. Haag et al. recently developed water-soluble core-shell unimolecular transporters by tandem coordination-ring opening hyperbranched polymerization [45]. A late transition metal-catalyzed chain walking polymerization (CWP) was employed to generate a highly nonpolar dendritic polyethylene (PE) core, followed by anionic ring-opening polymerization of glycidol to graft a hydrophilic hyperbranched polyglycerol shell (Fig. 30). This amphiphilic core-shell architecture was then investigated for its capability as molecular nanotransporters for hydrophobic compounds pyrene and Nile red. Evidence from fluorescence spectroscopy, light scattering, and electron microscopy, supported the unimolecular transport mechanism by the core-shell copolymer.
The applicability of the PE-PG core-shell copolymer was further demonstrated by the unimolecular transport of hydrophobic dye nile red into living cells under extremely high and biologically relevant dilute conditions. The results clearly indicated the successful uptake of nile red into the A549 lung tumor cells incubated with dilute solution of the PE-PG copolymer, which was in sharp contrast to a small molecule amphiphile (Fig. 30), which showed only a weak nile red fluorescence. The results suggest potential applicability of such core-shell molecular transporters in the administration of poorly water-soluble drugs [45].

Fine tuning the hyperbranched polymeric architecture in a predictable fashion is of significant interest for various applications [110,111]. Zimmerman et al. reported the covalent linking of the allyl and homoallyl ether end groups of dendrimers using ring-closing metathesis (RCM) reaction [192,193]. In addition to creating molecularly imprinted dendrimers [194–196] and organic nanotubes [197], cross-linking of the end groups was shown to produce a significant decrease in the size of the dendrimer [198]. These organic nanoparticles also became more rigid. The extent of cross-linking could be controlled, thus allowing the dendrimer size and rigidity to be finely and independently modulated. Haag group designed and investigated a series of smart systems with PG scaffolds that have a cross-linked outer shell and cleavable or tunable moieties at the core-shell. The RCM of the allyl groups located on the PG surface generated the cross-linked dendritic architectures with a covalently closed dense shell system (Fig. 31) [199,200]. The complete hydrogenation of the alkene groups on the shell led to fully water soluble polymers. They displayed a crown ether-type binding of picrate ions in organic phases, with ion affinity and selectivity comparable to several crown ethers. Investigations to assess the capacity of these architectures to effectively host organic dyes like rose Bengal, thymol blue, and Congo red demonstrated that a larger loop size in the shell exhibited better complexation properties while smaller cavities within the PG scaffold assured a higher stability of the host–guest complexes [201].

To investigate the host–guest stability, the polymer-dye solutions were extracted for a few minutes with water. After phase separation, the UV absorption of the organic phase was measured again (Fig. 32) and a clear difference between allylated and RCM cross-linked HPGs was observed. Whereas the hydrophilic rose Bengal and thymol blue sodium salt were extracted to the water layer from its organic soluble complex with allylated hPG, the dye complex with RCM cross-linked hPG was sufficiently stable and the dye remained in the chloroform layer. Indeed, the cross-linked host 2 did not liberate the dye even after 12 h of shaking with water and the use of sonication.
To further achieve a controlled release of the guest molecules, Haag’s group developed photo-responsive cross-linked systems by the introduction of o-nitrobenzyl groups within the shell (Fig. 33) [201]. The photolytic degradation of the polymer was then studied with UV–Vis spectroscopy. The photodegradable nanocapsules retained the capacity and selectivity for encapsulating bioactive molecules, while modification of the building blocks allowed substantial control over host–guest stability.

The photo initiated guest release of rose bengal was studied from these nanocarriers. The light-triggered release of the dye from the dye complex in chloroform was confirmed by irradiation of the solution at 350 nm monochromatic light. Fig. 34 shows the controlled release of the dye as a function of UV irradiation time.

It was demonstrated that these systems show high capacity and selectivity in guest encapsulation. The modification of the building blocks, in particular the outer shell, allows control of the host–guest complex stability. The presence of the hexa(ethylene glycol) outer-shell instead of the hexene shell increased the stability of the formed host–guest complexes but led to difficulties in guest release. However, the introduction of the hexene shell assured a high release of guest molecules from the nanocapsules (up to 80%).

3.4. Hyperbranched core multi-shell architectures

The fundamental problem of most carrier systems is their limited matrix compatibility. They generally transport nonpolar molecules into an aqueous environment [158,202] or polar molecules into a hydrophobic environment such as an organic medium, in the case of an inverted micellar architecture [159,160,170]. Therefore, the generation of nanocompartments that are compatible with various environments should solve many solubility and stability problems of active agents. Haag et al. developed a novel kind of CMS architecture for a more universal transport behavior that was inspired by the molecular mimicry of a liposome based on a hyperbranched PG core surrounded by double-layered shells [203,204]. The synthesis of such dendritic multi-shell architectures was performed by coupling alkyl chain to monomethylated PEGs which were in turn coupled to hyperbranched PG amine as shown in Fig. 35. The multi-shell nanocarriers self-assemble into supramolecular aggregates above a well-defined threshold concentration (CAC). Single nanocarriers with a size range of 8–9 nm coexisted with their larger aggregates with diameters of 20–50 nm. These multi-shell nanocarrier aggregates not only accommodated polar and nonpolar guest molecules but also adapted to various environmental polarity conditions ranging from toluene to water. In contrast to already existing micelle-analog systems, this new architecture mimics the structure of a liposome on an unimolecular basis.

The therapeutic potential of the synthesized CMS architectures was evaluated for their skin penetration properties and compared to those of solid lipid nanoparticles (SLN) and oil-in-water (o/w) cream. Nile red was used as a probe molecule and it was found that CMS systems significantly enhanced the skin penetration of the dye [205].

The encapsulation of nile red in the CMS architectures was time and concentration dependant. With increasing nile red concentration, the surface was assumed to be totally clad with the dye molecules. From this concentration on, corresponding to a diffusion time of 10–20 min, nile red diffused into the agglomerate of the particles sitting first at the inter-particular spaces and, with still increasing diffusion time, within the matrix of individual particles.
It was observed that the concentration of Nile red, physically encapsulated into a stable dendritic CMS system, increased 8-fold in the stratum corneum and 13-fold in the epidermis as opposed to when loaded in o/w cream. Despite the degradation at the stratum corneum surface, SLN enhanced skin penetration less efficiently (3.8 and 6.3-fold) than CMS nanoparticles. Viable human keratinocytes showed an internalization of both nanocarriers within 30 min of incubation.

These CMS systems were further studied for the topical treatment of skin diseases as they facilitate the skin penetration of the loaded hydrophilic agents, which was demonstrated using the dye rhodamine B as a model compound [203,205]. The cutaneous uptake of rhodamin B loaded onto SLN, CMS nanotransporters, and a conventional cream was studied, respectively. Representative fluorescence staining (Fig. 36) indicated an enhanced dye penetration of the CMS architectures loaded into the viable epidermis and dermis after application of the nanoparticulate carrier systems compared to the cream. The penetration of rhodamin B into the viable epidermis increased up to 11.5-fold following the application of CMS nanotransporters, which shows the potential of such structures as topical DDSs.

A new CMS architecture was developed in the Haag group in an attempt to obtain core double-shell architectures with different densities and flexibility (Fig. 37) [206]. These new architectures were synthesized from simple and non-toxic building blocks by applying straightforward and heavy metal-free synthesis. The periphery of the hPG was modified with different lengths of aliphatic chains which were further decorated with monoamino HPGs (HPG-NH₂). The synthesized multi-shell polymers possessed low polydispersities which is an important issue for many potential applications, especially for biomedical purposes. Another important characteristic of the synthesized CMS architectures was the hydrodynamic radius ($R_h$), which was found to be $\sim 1.5$ nm for 3 kDa hPG core. The $R_h$ of the synthesized architectures increased up to 5.2 nm for a 10-carbon aliphatic inner shell with 1100 Da hPG outer shell. These observations indicate that a 10-fold increase in the molecular weight leads to a dramatic increase in the molecules size. The effect of the individual building blocks on guest encapsulation was studied by varying the hydrophobic and hydrophilic domain of the polymers.

The universal nanotransport character of the obtained CMS was confirmed by encapsulation of polar guest molecules as rose bengal.

![Fig. 31. Schematic representation of allylated (1), RCM cross-linked (2), dihydroxylated (3), and RCM cross-linked and dihydroxylated hPG (4). Adapted from Ref. [200].](image1)

![Fig. 32. Photographs of encapsulated rose bengal sodium salt in polymers 1 and 2 before (left) and after 5 min extraction with water (right). Reproduced with permission from Ref. [200]. Copyright 2009 American Chemical Society.](image2)

![Fig. 33. Formation of light-responsive nanotransporters with o-nitrobenzyl groups in the outer shell obtained by intramolecular ring-closing metathesis. Reproduced with permission from Ref. [201]. Copyright 2009 Wiley.](image3)

![Fig. 34. Release of rose bengal from photo-responsive cross-linked systems by UV irradiation ($\lambda = 350$ nm). Reproduced with permission from Ref. [201]. Copyright 2009 Wiley.](image4)
and congo red, and water insoluble compounds, as nimodipine, nile red, and pyrene. Moreover, this new type of CMS system, in contrast to the previously reported one, acts as unimolecular nanocarrier system for nonpolar guest molecules, with transport capacities of 1.5 guest molecules per nanocarrier. However, for polar guest molecules, the formation of uniform aggregates with a diameter of 70 nm and with transport capacities of up to 10 guests per nanocarrier was detected. This may be due to the fact that the dye molecules are preferentially located on the outer shell of the polymer and therefore may be acting as non-covalent linkers between molecules.

4. Conclusions

Polyether based amphiphilic nanocarriers have evolved rapidly over the last decade circumventing the limitations of conventional surfactants such as toxicity, undesirable side effects, and hypersensitivity reactions; and thus have led to an ease in delivery of active components. The gold standard—PEG is currently the most used polyether polymer for therapeutic applications with a safety profile, non-toxicity, high biocompatibility, and decreased interaction with the blood components. The low CMCs of these nanocarriers enable the delivery of active components even at high dilution in the blood stream. Although these PEG-based amphiphilic nanocarriers demonstrate optimal biocompatibility over cellular and systemic levels, they have possible drawbacks such as degradation under stress, accumulation in the body above an uncertain excretion limit and interaction with the immune system generating various immune responses. Furthermore, limited end group functionality of PEG leads to intrinsically low modification potential at the polyether backbone.

As potential alternative to PEG, polyglycerol (PG) based perfect dendrons and well-defined hyperbranched amphiphilic
architectures are potential polyether scaffolds, which are under current investigations. The biocompatibility and toxicity profile of PG runs parallel to PEG, and has been classified as highly biocompatible and non-toxic for in vivo applications. The topological 3D dendritic architecture and tunable polyol end groups of PG allow multiple modifications and make it a versatile candidate for supramolecular self-assembly and biomedical applications when compared to linear PEG based amphiphiles. However, the biodegradability of the PG core is still an unresolved issue when used at high molecular weights (>100 kDa).

Although it is still at an early stage of research, polyglycerol based amphiphilic architectures have shown great potential as a versatile material for supramolecular self-assembly and delivery of active components. Strong efforts are still needed to overcome the limitations of these existing amphiphilic nanocarriers and to investigate the translation of these nanocarriers into the clinics. Also, new chemo-enzymatic approaches to biodegradable polyether architectures need to be addressed in the future. Further advances in the field may open new arenas to enhance the versatility of polyether based amphiphilic scaffolds and will present a novel platform for the next generation of drug delivery systems.

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References

[1] The therapeutic index of a drug is defined as the ratio of the toxic dose to the therapeutic dose.
[2] The term “polymer therapeutics” was coined by Helmut Ringsdorf and Ruth Duncan. Other research groups use the more general term “nanomedicine.”
[5] “Polymer therapeutics” was coined by Helmut Ringsdorf and Ruth Duncan.
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