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Feature article

Polyether 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 polyether 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 polyether-based amphiphilic architectures, some unresolved issues and challenges, along with the future perspective of polyether based nanocarriers for delivery of active components.

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 [2–5]. 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 [8–11]. 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

Abbreviations: ABCs, amphiphilic block copolymers; AFM, atomic force microscopy; *-b-*, block (copolymer); CAC, critical aggregation concentration; CMC, critical micelle concentration; CMS, core multi shell; *-co-*, (linear) copolymer; DDS, drug delivery system; DEX, dexamethasone; DLS, dynamic light scattering; $DM5NH_2IP$, dimethyl 5-amino isophthalate; DM5OHIP, dimethyl 5-hydroxy isophthalate; DNA, deoxyribonucleic acid; DOX, doxorubicin; DP, degree of polymerization; dPG, dendritic polyglycerol; EO, ethylene oxide; EPR, enhanced permeability and retention; FDA, food and drug administration; FITC, fluorescein isothiocyanate; FTIR, Fourier transform infrared spectrometer; HB, hyperbranched; HBP, hyperbranched polymer; *-hg-*, hyper(grafted); HPCMS, hyperbranched poly(-chloromethylstyrene); HPLC, high performance liquid chromatography; HUVECs, human umbilical vein endothelial cells; IC_{50}, inhibitory concentration; IP, isophthalate; LCST, lower critical solution temperature; LDBC, linear-dendritic block copolymers; M_n, number average molecular weight; mPEG, monomethoxy polyethylene glycol; MTD, maximum tolerated dose; M_w, weight average molecular weight; NIR, near Infra-red; p(Asp), poly(aspartate); o/w, oil-in-water; PAMAM, polyamidoamine; PDI, poly dispersity index; PEG, polyethylene glycol; PEO, polyethylene oxide; PG, polyglycerol; PLA, poly(lactic acid); PPI, poly(propylene imine); PPO, poly(propylene oxide); PTX, paclitaxel; RCM, ring-closing metathesis; R_h, hydrodynamic radius; SANS, small angle neutron scattering; SAXS, small angle X-ray scattering; SFM, scanning force microscopy; SLN, solid lipid nanoparticles; UV–Vis, ultraviolet–visible.

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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 macromolecules 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 prospective 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 macroglobulines, 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 prospective 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 has 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-