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Expert Review

Micellar Nanocarriers: Pharmaceutical Perspectives

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Abstract. Micelles, self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell are currently successfully used as pharmaceutical carriers for water-insoluble drugs and demonstrate a series of attractive properties as drug carriers. Among the micelle-forming compounds, amphiphilic copolymers, i.e., polymers consisting of hydrophobic block and hydrophilic block, are gaining an increasing attention. Polymeric micelles possess high stability both *in vitro* and *in vivo* and good biocompatibility, and can solubilize a broad variety of poorly soluble pharmaceuticals many of these drug-loaded micelles are currently at different stages of preclinical and clinical trials. Among polymeric micelles, a special group is formed by lipid-core micelles, i.e., micelles formed by conjugates of soluble copolymers with lipids (such as polyethylene glycol–phosphatidyl ethanolamine conjugate, PEG–PE). Polymeric micelles, including lipid-core micelles, carrying various reporter (contrast) groups may become the imaging agents of choice in different imaging modalities. All these micelles can also be used as targeted drug delivery systems. The targeting can be achieved via the enhanced permeability and retention (EPR) effect (into the areas with the compromised vasculature), by making micelles of stimuli-responsive amphiphilic block-copolymers, or by attaching specific targeting ligand molecules to the micelle surface. Immunomicelles prepared by coupling monoclonal antibody molecules to *p*-nitrophenylcarbonyl groups on the water-exposed termini of the micelle corona-forming blocks demonstrate high binding specificity and targetability. This review will discuss some recent trends in using micelles as pharmaceutical carriers.

KEY WORDS: anti-cancer drugs; diagnostic agents; drug-carriers; micelles; polymeric micelles; poorly soluble drugs.

INTRODUCTION

To minimize premature drug degradation upon administration; prevent undesirable side effects exersized onto normal cells, organs and tissues by cytotoxic drugs; and increase drug bioavailability and the fraction of the drug accumulated in the pathological area, various drug delivery and drug targeting systems, such as synthetic polymers, microcapsules, cell ghosts, lipoproteins, liposomes, micelles, niosomes, lipid particles and many others (1,2), are currently applied or under development. To still further their performance, all these drug carriers can be made slowly biodegradable, stimuli-reactive (pH- or temperature-sensitive), and targeted (by conjugating them with ligands specific towards certain characteristic components of the pathological area). In addition, drug carriers should stay in the blood long enough (3,4), since prolonged circulation allows for maintaining the required therapeutic level of pharmaceuticals in the blood for extended time intervals. In addition to that, long-circulating high-molecular-weight drugs or drug-containing microparticulates can also slowly accumulate in pathological sites with affected and leaky vasculature (such as tumors, inflammations, and infarcted areas) via the enhanced permeability and retention (EPR) effect and enhance drug delivery in these areas (5,6). The prolonged circulation allows also for achieving a better targeting effect for specific ligand-modified drugs and drug carriers since it increases the total quantity of targeted drug/carrier passing through the target, and the number of interactions between targeted drugs and their targets, which is especially important for the successful targeting of pathological areas with diminished blood supply and/or with low concentration of targeted component (7).

The development of biocompatible and biodegradable drug carriers possessing small particle size, high loading capacity, extended circulation time, and ability to accumulate in required pathological sites in the body, for the delivery of poorly soluble pharmaceuticals still has many unresolved issues. The availability of such carriers is especially important since the therapeutic application of hydrophobic, poorly water-soluble agents is associated with some serious problems. First, low water-solubility results in poor absorption and low bioavailability, especially upon the oral administration (8). Second, the aggregation of poorly soluble drugs upon intravenous administration might lead to various complications including embolism resulting in side effects as severe as respiratory system failure (9,10), and can also lead to high local drug concentrations at the sites of aggregate deposition, which could be associated with local toxic effects

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of the drug and its diminished systemic bioavailability (11). As a result, about a half of potentially valuable drug candidates identified by high throughput screening technologies including those with the highest activities demonstrate poor solubility in water and, for this reason, never enter further development including a formulation development stage (8,12). On the other hand, the hydrophobicity and low solubility in water seem to be intrinsic properties of many drugs (including anticancer agents, many of which are bulky polycyclic compounds, such as camptothecin, paclitaxel, or tamoxifen) (13), since it helps a drug molecule to penetrate a cell membrane and reach important intracellular targets (14,15). It was also observed that a drug or, in a more general case, a biologically active molecule may need a lipophilic group to acquire a sufficient affinity towards the appropriate target receptor (8,12). Still, poor aqueous solubility poses such a serious problem that some leading pharmaceutical companies make efforts to exclude poorly soluble compounds very early in their screening process regardless how active these compounds are toward their molecular targets (12). By some estimation, as much as 40% of potentially valuable drug candidates identified by high throughput screening are rejected and never enter a formulation development stage due to their poor water solubility (16).

To overcome the poor solubility of some drugs certain clinically acceptable organic solvents, Cremophor EL (polyethoxylated castor oil), and/or certain surfactants are used in formulations (11). The formation of salts or pH adjustment in some cases facilitate the dissolution of poorly soluble drugs if they contain ionizable groups (17). More recent approaches include the use of liposomes (18), microemulsions (19) and cyclodextrins (16) to increase the bioavailability of poorly soluble drugs. However, the administration of many co-solvents or surfactants causes toxicity or other undesirable side effects (20). Another shortcoming of co-solvents and surfactants is the danger of drug precipitation upon the dilution of the solubilized drug preparations with aqueous solutions (such as physiological fluids upon a parenteral administration), since surfactants cannot retain solubilized material at concentrations lower than their critical micelle concentration (CMC) value, which is typically rather high in the cases of conventional low molecular weight surfactants (21). Possible precipitation upon the dilution of drug solutions in water/organic solvent mixtures depends on a variety of factors and must be investigated for each excipient/drug combination of interest (11). The use of liposomes and cyclodextrins, on the other hand, although have brought some promising results with certain poorly soluble drugs, is limited by the low capacity of the liposomal membrane or cyclodextrin inner cavity for water-insoluble molecules. In addition, the solubilization capacity of these carriers varies for different drugs in rather broad limits. A sound alternative is the use of certain micelle-forming amphiphilic compounds in formulations of sparingly soluble pharmaceuticals (11).

MICELLES AND SOLUBILIZATION OF POORLY SOLUBLE DRUGS

Micelles represent colloidal dispersions (with particle size normally within 5 to 100 nm range) belonging to a large family of dispersed systems consisting of particulate matter (termed dispersed phase), distributed within a continuous phase (termed dispersion medium). They belong to a group of association or amphiphilic colloids, which form spontaneously under certain concentration and temperature from amphiphilic or surface-active agents (surfactants), molecules of which consist of two clearly distinct regions with opposite affinities towards a given solvent (22). At low concentrations in an aqueous medium, such amphiphilic molecules exist separately, however, as their concentration is increased, aggregation takes place within a rather narrow concentration interval. The concentration of a monomeric amphiphile at which micelles appear is called the critical micelle concentration (CMC), while the temperature, below which amphiphilic molecules exist as unimers and above—as aggregates, is called the critical micellization temperature (CMT). The formation of micelles is driven by the decrease of free energy in the system because of the removal of hydrophobic fragments from the aqueous environment and the re-establishing of hydrogen bond network in water. Additional energy gain results from formation of Van der Waals bonds between hydrophobic blocks in the core of the formed micelles (23,24). Hydrophobic fragments of amphiphilic molecules form the core of a micelle, while hydrophilic fragments form the micelle's shell (25–27). When used as drug carriers in aqueous media, micelles solubilize molecules of poorly soluble nonpolar pharmaceuticals within the micelle core (while polar molecules could be adsorbed on the micelle surface, and substances with intermediate polarity distributed along surfactant molecules in intermediate positions). This solubilization phenomenon was extensively investigated and reviewed in many publications (see, for example 27). Figure 1 shows a principal scheme of micelle formation from an amphiphilic molecule, its loading with a poor soluble drug, and some possible ways to further modify the micelle to improve its performance as a pharmaceutical carrier.

An optimal self-assembling drug delivery system (28) should spontaneously form from the mixture of drug molecules and carrier components. They should have a size of 10–20 nm in order to provide them the ability to penetrate various tissues, for example, by extravasation, be stable *in vivo* for a sufficiently long time and cause no biological side effects, and their carrier components should easily leave the body when the therapeutic function is completed. They are also expected to release a free drug upon the contact with pathological tissues. Micelles as drug carriers provide a set of clear advantages (29–31). The solubilization of drugs using micelle-forming surfactants results in an increased water solubility of sparingly soluble drug and its improved bioavailability, reduction of toxicity and other adverse effects, enhanced permeability across the physiological barriers, and substantial and favorable changes in drug biodistribution. The use of certain special amphiphilic molecules can also introduce the property of micelle extended blood half-life (31). Because of their small size, micelles demonstrate a spontaneous penetration into the interstitium in the body compartments with the leaky vasculature (tumors and infarcts) by the enhanced permeability and retention (EPR) effect; a form of selective targeted delivery termed as "passive targeting" (5,6,32). It has been repeatedly shown that micelle-incorporated anticancer drugs, such as adriamy-

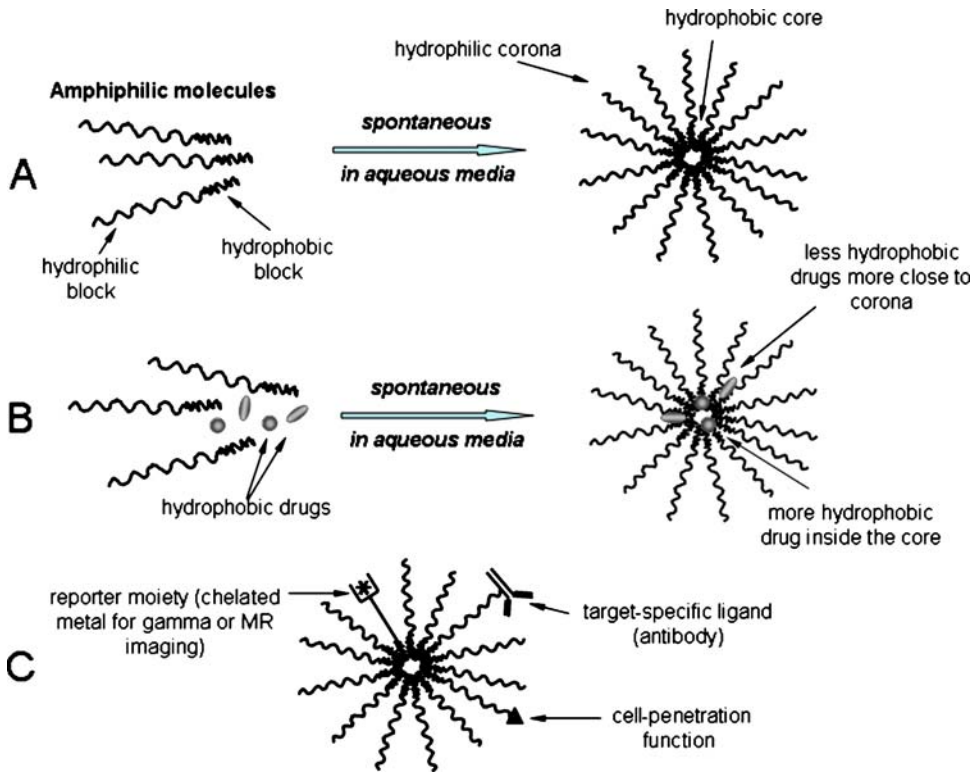

Fig. 1. Pharmaceutical micelles. (A) Spontaneous micelle formation from amphiphilic molecules in aqueous media; (B) Micelle loading with hydrophobic drugs; (C) Multifunctional pharmaceutical micelle.

cin (see, for example 33) better accumulate in tumors than in non-target tissues, thus minimizing the undesired drug toxicity towards normal tissue. Diffusion and accumulation parameters for drug carriers in tumors have recently been shown to be strongly dependent on the cutoff size of tumor blood vessel wall, and the cutoff size varies for different tumors (34,35). Exemplifying the greater permeability of micelles within such biological constraints is the superior delivery of a model protein drugs into low permeable murine tumor (Lewis lung carcinoma) by the PEG–PE micelles compared to other particulate carriers (36). In addition, micelles may be made targeted by chemical attachment of target-specific molecules to their surface. In the latter case, the local release of free drug from the micelles in the target organ should lead to the drug's increased efficacy. On the other hand, being in a micellar form, the drug is well protected from possible inactivation under the effect of biological surroundings, and does not provoke undesirable side effects on non-target organs and tissues. According to the available literature, the usual size of a pharmaceutical micelle is between 10 and 80 nm, its CMC value is expected to be in a low millimolar region or even lower, and the loading efficacy towards a hydrophobic drug should be between 5 and 25% wt. Almost every possible drug administration route has benefited from the use of micellar forms of drugs in terms of either increased bioavailability or reduction of adverse effects (33,37). Micellar compositions of various drugs have been suggested for parenteral (38–40), oral (41,42), nasal (43,44), and ocular (44–46) application.

POLYMERIC MICELLES—NOVEL FAMILY OF PHARMACEUTICAL CARRIERS

The use of micelles prepared from amphiphilic copolymers for solubilization of poorly soluble drugs has also attracted much attention recently (23,31,47–49). Polymeric micelles are formed by block-copolymers consisting of hydrophilic and hydrophobic monomer units with the length of a hydrophilic block exceeding to some extent that of a hydrophobic one (31). If the length of a hydrophilic block is too high, copolymers exist in water as unimers (individual molecules), while molecules with very long hydrophobic block forms structure with non-micellar morphology, such as rods and lamellae (50). The major driving force behind self-association of amphiphilic polymers is again the decrease of free energy of the system due to removal of hydrophobic fragments from the aqueous surroundings with the formation of micelle core stabilized with hydrophilic blocks exposed into water (24,51). In different amphiphilic polymers, monomer units with different hydrophobicity can be arranged into two conjugated blocks each consisting of monomers of the same type (A-B-type copolymers), or can form alternating blocks with different hydrophobicity (A-B-A type copolymers) (23). The hydrophilic polymer can also represent a backbone chain to which hydrophobic blocks are attached as side chains (graft copolymers) (31). Similar to micelles formed by conventional detergents, polymeric micelles comprise the core of the hydrophobic blocks stabilized by the corona of hydrophilic chains. Polymeric micelles often

are more stable compared to micelles prepared from conventional detergents (have lower CMC value), with some amphiphilic co-polymers having CMC values as low as 10^{-6} M (52,53), which is about two orders of magnitude lower than that for such surfactants as Tween 80. The core compartment of the pharmaceutical polymeric micelle should demonstrate high loading capacity, controlled release profile for the incorporated drug, and good compatibility between the core-forming block and incorporated drug, while the micelle corona is responsible for providing an effective steric protection for the micelle and determines the micelle hydrophilicity, charge, the length and surface density of hydrophilic blocks, and the presence of reactive groups suitable for further micelle derivatization, such as an attachment of targeting moieties (54–56). These properties control important biological characteristics of a micellar carrier, such as its pharmacokinetics, biodistribution, biocompatibility, longevity, surface adsorption of biomacromolecules, adhesion to biosurfaces and targetability (1,54,55,57). The use of polymeric micelles often allows for achieving extended circulation time, favorable biodistribution and lower toxicity of a drug (23,31,47). Polymeric micelles are currently a subject of many publications addressing various aspects of their formation and properties, see for example refs (29–31,47,52,58–65).

Composition of Polymeric Micelles

Usually, amphiphilic micelle-forming unimers include poly(ethylene glycol) (PEG) blocks with a molecular weight from 1 to 15 kDa as hydrophilic corona-forming blocks (60). This polymer is inexpensive, has a low toxicity, serves as an efficient steric protector of various biologically active macromolecules (66–70) and particulate delivery systems (3,71–73), and has been approved for internal applications by regulatory agencies (32,70,74). Still, some other hydrophilic polymers may be used as hydrophilic blocks (75). Among possible alternatives to PEG, poly(*N*-vinyl-2-pyrrolidone) (PVP) is frequently considered as a primary alternative to PEG (76,77). Similar to PEG, this polymer is highly biocompatible (78) and was used in formulations of such particulate drug carriers as liposomes (79), nanoparticles (80), microspheres (81) and diblock polymer micelles (82). Another hydrophilic candidate is poly(vinyl alcohol), and poly(vinylalcohol-co-vinyloleate) co-polymer was used to prepare micelles enhancing transcutaneous permeation of retinyl palmitate (83). Polyvinyl alcohol substituted with oleic acid was also used for carrying lipophilic drugs (84). Block-copolymers of hydrophilic oligomeric polyethyleneimine and hydrophobic poly(D,L-lactide-co-glycolide) have also been described (85). Still PEG remains the hydrophilic micelle corona-forming block of choice. At the same time, a variety of monomers may be used to build hydrophobic core-forming blocks: propylene oxide (86,87), L-lysine (88,89), aspartic acid (90,91), β-benzoyl-L-aspartate (92,93), γ-benzyl-L-glutamate (94), caprolactone (95,96), D,L-lactic acid (55,97), spermine (98), and some others. Some of these monomers form hydrophobic polymeric blocks, which "directly" build the hydrophobic core of the micelles, while other compounds (lysine, spermine) form hydrophilic polymeric chains, which first, electrostatically complex hydrophobic substances, and only after that can build the micelle core. Block copolymers of poly(ortho esters) and PEG form 40–70 nm micelles with CMC of around 10^{-4} g/l and may be lyophilized (99). Micelle-forming ABC-type triblock copolymers composed of monomethoxy-PEG, poly(2-(dimethylamino)ethyl methacrylate) and poly(2-(diethylamino)ethyl methacrylate) with the last component forming a hydrophobic core have been also suggested that allow for the slow release for incorporated poorly soluble compounds (100). New polylactone-PEG double and triple block copolymers (101) have been suggested as micelle-forming polymers as well as poly(2-ethyl-2-oxazoline-block-poly(epsilon-caprolactone), which forms 20 nm micelles with good load of paclitaxel (102). Chitosan grafted with hydrophobic groups, such as palmitoyl, is currently becoming popular for preparing pharmaceutical micelles due to its high biocompatibility (103,104). Dendrimeric micelles, such as biaryl-based ones, have also been suggested (105,106). New materials for pharmaceutical micelles include both, new copolymers of PEG (107) and completely new macromolecules, such as scorpion-like polymers (108,109) and some other star-like and core-shell constructs (110,111).

Lipid-Core Micelles

In some cases, phospholipid residues—short, however, extremely hydrophobic due to the presence of two long-chain fatty acyl groups—can also be successfully used as hydrophobic core-forming groups (37). The use of lipid moieties as hydrophobic blocks capping hydrophilic polymer (such as PEG) chains can provide additional advantages for particle stability when compared with conventional amphiphilic polymer micelles due to the existence of two fatty acid acyls, which might contribute considerably to an increase in the hydrophobic interactions between the polymeric chains in the micelle's core. Conjugates of lipids with water-soluble polymers are commercially available, or can be easily synthesized (71,76,79). Diacyllipid-PEG conjugates have been introduced into the area of controlled drug delivery as polymeric surface modifiers for liposomes (71). However, diacyllipid-PEG molecule itself represents a characteristic amphiphilic polymer with a bulky hydrophilic (PEG) portion and a very short but very hydrophobic diacyllipid part. Similar to other PEG-containing amphiphilic block-copolymers, diacyllipid-PEG conjugates were found to form micelles in an aqueous environment (112). A series of PEG–phosphatidylethanolamine (PEG–PE) conjugates was synthesized using PE and *N*-hydroxysuccinimide esters of methoxy–PEG succinates (molecular weight of 2, 5 and 12 kDa) (71). Micelle preparation from the lipid-polymer conjugates is a simple process, since similar to conventional detergents, such polymers form micelles spontaneously in an aqueous media. All versions of PEG–PE conjugates form micelles with the size of 7 to 35 nm. No dissociation into individual polymeric chains was found following the chromatography of the serially diluted samples of PEG(5 kDa)–PE up to polymer concentration of ca. 1 μg/ml which corresponds to a micromolar CMC value, which is at least 100-fold lower than those of conventional detergents (21,113). Micelles formed from conjugates with polymer (PEG) blocks of higher molecular weight have a slightly larger size indicating that the micelle size may be tailored for a particular application by varying the length of PEG. With the size of PEG blocks going above 15 kDa, the

stability of PEG–PE micelles begins to decrease. Preparation of lipid-based micelles by a detergent or water-miscible solvent removal method results in formation of particles with very similar diameters. Usually, such micelles have a spherical shape and uniform size distribution (114). From a practical point of view, it is important that micelles prepared from these polymers will remain intact at concentrations much lower than required for drug delivery purposes. Another important issue is that PEG_{2000}–PE and PEG_{5000}–PE micelles retain the size characteristic for micelles even after 48 h incubation in the blood plasma (115), i.e., the integrity of PEG–PE micelles should not be immediately affected by components of biological fluids upon parenteral administration.

Amphiphilic PVP–lipid conjugates with various polymer lengths have also been prepared by the free-radical polymerization of vinylpyrrolidone and further modification by the attachment of long-chain fatty acid acyls, such as palmityl (P) or stearyl (S) residues, to one of the polymer termini (76,79). Amphiphilic PVPs with a MW of the PVP block between 1,500 and 8,000 Da form micelles in an aqueous environment (76). CMC values and the size of micelles formed depend on the length of the PVP block and vary between 10^{-4} and 10^{-6} M and 5 and 20 nm, respectively. Similar to PEG–PE-based micelles, micelle made of amphiphilic PVP could also be used for the solubilization of poorly water-soluble drugs yielding highly stable biocompatible formulations. The application of micelles prepared from a similar lipidated polymer, polyvinyl alcohol substituted with oleic acid, for transcutaneous delivery of retinyl palmitate has been also proposed (83). See some properties of polymer–lipid conjugate micelles in Table I.

The micelles made of such lipid-containing conjugates can be loaded with various poorly soluble drugs (tamoxifen, paclitaxel, camptothecin, porphyrins, etc.) and demonstrate good stability, longevity, and ability to accumulate in the areas with damaged vasculature (EPR effect in leaky areas, such as infarcts and tumors) (37,115,116). Mixed micelles made of PEG–PE and other micelle-forming components are described that provide even better solubilization of certain poorly soluble drugs due to the increase in the capacity of the hydrophobic core (114,117,118). Certain PEG–PE-based mixed micelles, containing charged components capable of destabilization of endosomal membranes, may allow for an increased intracellular delivery of micelle-incorporated drugs (117). A drug incorporated in lipid-core polymeric micelles is associated with micelles firmly enough: when PEG–PE micelles loaded with several drugs were dialyzed against aqueous buffer at sink conditions, all tested preparations retain more than 90% of encapsulated drug within first 7 h of incubation. The micelles retain 95, 75, and 87% of initially incorporated chlorine e6 trimethyl ester, tamoxifen and paclitaxel, respectively, even after 48 h incubation (119).

Table I. CMC Values and Particle Diameters of the Micelles Formed by Various Polymer–Lipid Conjugates

Micelle-forming Conjugate	CMC (M)	Particle Size (nm)
PEG750-DSPE	1×10^{-5}	7–15
PEG2000-DSPE	1×10^{-5}	7–20
PEG5000-DSPE	6×10^{-6}	10–40
PEG2000-DOPE	9×10^{-6}	7–20
PEG5000-DOPE	7×10^{-6}	10–35
PVP1500-P	3×10^{-6}	5–15
PVP8000-P	4×10^{-5}	7–20
PVP15000-P	2×10^{-4}	N/A
PVP1500-S	2×10^{-6}	5–15
PVP8000-S	5×10^{-5}	10–20
PVP15000-S	2×10^{-4}	N/A

The associated number indicates the molecular weight of PEG or PVP.
DSPE Distearoyl-PE, *DOPE* dioleoyl-PE, *P* palmityl, *S* stearyl.

Drug Loading

The process of solubilization of water-insoluble drugs by micelle-forming amphiphilic block-copolymers was investigated in details (120). The mathematical simulation of the solubilization process (121) demonstrated, that the initial solubilization proceeds via the displacement of solvent (water) molecules from the micelle core, and later a solubilized drug begins to accumulate in the very center of the micelle core "pushing" hydrophobic blocks away from this area. Extensive solubilization may result in some increase of micelle size due to the expansion of its core with a solubilized drug. Among other factors influencing the efficacy of drug loading into the micelle one can name the size of both core- and corona-forming blocks (122). In the first case, the larger the hydrophobic block the bigger core size and its ability to entrap hydrophobic drugs. In the second case, the increase in the length of the hydrophilic block results in the increase of the CMC value, i.e., at a given concentration of the amphiphilic polymer in solution the smaller fraction of this polymer will be present in the micellar form and the quantity of the micelle-associated drug drops.

Drugs, such as diazepam and indomethacin (123,124), adriamicin (90,125–127), anthracycline antibiotics (128), polynucleotides (129,130), and doxorubicin (131) were effectively solubilized by various polymeric micelles, including Pluronic® (block co-polymers of PEG and polypropelene glycol) (52). Doxorubicin incorporated into Pluronic® micelles demonstrated superior properties as compared with free drug in the experimental treatment of murine tumors (leukemia P388, myeloma, Lewis lung carcinoma) and human tumors (breast carcinoma MCF-7) in mice (131). Micellar drugs show also a lower toxicity (132) than free drugs. The circulation time and biodistribution of polymeric micelles formed by the copolymer of PEG and poly(aspartic acid) (PEG-b-PAA) with covalently bound adriamycin [PEG-b-PAA(ADR)] depended on relative size of the copolymer blocks. Longer PEG blocks and shorter PAA segments favor longer circulation times and lower uptake of the micelles by the reticuloendothelial system (33,90,133,134). The whole set of micelle-forming co-polymers of PEG with poly(L-amino-acids) was used to prepare drug-loaded micelles by direct entrapment of a drug into the micelle core (53,135–137). PEG-b-poly(caprolactone) co-polymer micelles were successfully used as delivery vehicles for dihydrotestosterone (138). PEG–PE micelles can efficiently incorporate a variety of sparingly soluble and amphiphilic substances including paclitaxel, tamoxifen, camptothecin, porphyrine, vitamin K3, and others (117,119,139). Micelle-forming co-polymers of PEG with poly(L-aminoacids) were used to prepare drug-

loaded micelles by direct entrapment of a drug into the micelle core and without covalent attachment of drug molecules, such as indomethacin, to core-forming blocks (53). PEG-b-poly (caprolactone) co-polymer micelles were successfully used as delivery vehicles for dihydrotestosterone (138). Much attention is paid to preparing micellar forms of such popular anticancer drugs as paclitaxel and camptothecin. In addition to already mentioned research, micellar paclitaxel was described in (140–142) and micellar camptothecin in (143–145). Numerous studies are also dealing with micellar forms of platinum-based anti-cancer drugs (146–148) and cyclosporin A (149,150). Poly(lactide)–poly(ethylene glycol) micelles were used as a carrier for griseofulvin (42), 17-beta-estradiol was solubilized in polycaprolactone-block-PEG micelles (151), amphotericin B—in PEG–phospholipid micelles (152), ellipticin—in polycarbonate-based PEG–copolymer micelles (153), risperidone—in PEG–poly(caprolactone/trimethylene carbonate) micelles (154). Mixed polymeric micelles made of positively charged polyethyleneimine and Pluronic were used as carriers for antisense oligonucleotides (155). Micelle-forming derivatives of poorly soluble drugs have also been prepared, such as paclitaxel derivatives modified with PEG via the hydrolysable ester bond (156). In such micelles, the drug itself forms a micelle core and liberates as the micelle degrades. Prodrug micelles with haloperidol have also been described (157). Some examples of drug loaded into various polymeric micelles as well as current developmental status of these preparations are presented in Table II.

A typical protocol for the preparation of drug-loaded polymeric micelles from amphiphilic co-polymers and without involving the electrostatic complex formation includes the following steps. Solutions of an amphiphilic polymer and a drug of interest in a miscible volatile organic solvents are mixed, and organic solvents are evaporated to form a polymer/drug film. The film obtained is then hydrated in the presence of an aqueous buffer, and the micelles are formed by intensive shaking. If the amount of a drug exceeds the solubilization capacity of micelles, the excess drug precipitates in a crystalline form and is removed by filtration. The loading efficiency for different compounds varies from 1.5 to 50% by weight. This value apparently correlates with the hydrophobicity of a drug. In some cases, to improve drug solubilization, additional mixed micelle-forming compounds may be added to polymeric micelles. Thus, to increase the encapsulation efficiency of paclitaxel, egg phosphatidylcholine (PC) was added to the PEG–PE-based micelle composition, which approx. doubled the paclitaxel encapsulation efficiency (from 15 to 33 mg of the drug per gram of the micelle-forming material (118,119,158). This may be explained by the fact that ePC, unlike PEG–PE, does not have a large hydrophilic PEG domain, and its addition into micelle composition results in particles with higher hydrophobic content (159). Paclitaxel in mixed PEG–PE/ePC micelles demonstrated high cytotoxic activity against MCF-7 human mammary adenocarcinoma cells (158).

TARGETED AND STIMULI-SENSITIVE MICELLES

Targeting micelles to pathological organs or tissues can further increase pharmaceutical efficiency of a micelle-encapsulated drug. There exist several approaches to enhance the accumulation of various drug-loaded pharmaceutical nanocarriers including pharmaceutical micelles in required pathological areas.

Passive Targeting

Preferential accumulation of various pharmaceutical nanocarriers, including pharmaceutical micelles, in target sites could proceed via the already mentioned enhanced permeability and retention (EPR) effect (6) based on the spontaneous penetration of long-circulating macromolecules, particulate drug carriers, and molecular aggregates into the interstitium through the compromised leaky vasculature, which is characteristic for solid tumors, infarcts, infections and inflammations (5,6,32). Clearly, the prolonged circulation of drug-loaded micelles facilitates the EPR-mediated target accumulation. Direct correlations between the longevity of a particulate drug carrier in the circulation and its ability to reach its target site have been observed on multiple occasions (32,160). The prolonged circulation provides a drug with a better chance to reach and/or interact with its target (32). The results of the blood clearance study of various micelles clearly demonstrated their longevity: micellar formulations, such as PEG–PE-based micelles, had circulation half-lives in mice, rats, of around 2 h with certain variations depending on the molecular size of the PEG block (115). The increase in the size of a PEG block increases the micelle circulation time in the blood probably by providing a better steric protection against opsonin penetration to the hydrophobic micelle core. Still, circulation times for long-circulating micelles are somewhat shorter compared to those for long-circulating PEG-coated liposomes (71), which could be explained in part by their more rapid extravasation of the micelles from the vasculature associated with their considerably smaller size compared to liposomes (161). Slow dissociation of micelles under physiological conditions due to continuous clearance of unimers with a micelle-unimer equilibrium being shifted towards the unimer formation (89) can also play its role.

Because of their smaller size, micelles may have additional advantages as a tumor drug-delivery system, which utilizes the EPR effect compared to particulate carriers with larger size of individual particles, since the transport efficacy and accumulation of microparticulates, including micelles, in the tumor interstitium is to a great extent determined by their ability to penetrate the tumor vascular endothelium (35,162). Diffusion and accumulation parameters were shown to be strongly dependent on the cutoff size of tumor blood vessel wall, and the cutoff size varies for different tumors (35,163,164). Adriamycin in polymeric micelles was shown to be much more efficient in experimental treatment of murine solid tumor colon adenocarcionoma than the free drug (165). Since tumor vasculature permeability depends on the particular type of the tumor (163), the use of micelles as drug carriers could be specifically justified for tumors, whose vasculature has the low cutoff size (below 200 nm). Thus, 15–20 nm PEG–PE micelles effectively delivered a model protein drug to a solid tumor with the very low cut off size, Lewis lung carcinoma, in mice (36), while even small 100 nm long-circulating liposomes did not provide an increased accumulation of liposome-encapsulated drug in this tumor (166). The accumulation

Table II. Some Block Copolymers Used to Prepare Micelles Loaded with Various Pharmaceuticals

Block Co-polymers	Micelle-incorporated Pharmaceuticals	Comments	References
Pluronics	Doxorubicin	Mice	(131)
	Cisplatin		
	Carboplatin	*In vitro*	(147)
	Epirubicin		
	Haloperidol	Mice	(86)
			(157)
	ATP	*In vitro*	(218)
	Polynucleotides		
Pluronic/polyethyleneimine	Antisense oligos	*In vitro*	(130,155)
Polycaprolactone-b-PEG	FK506	*In vitro*	(96)
	L-685,818	*In vitro*	(96)
	125-I (diagnostic)		
	Cyclosporine A	*In vitro*	(149)
		Rats	(150)
	17beta-estradiol	*In vitro*	(151)
		In vivo	(151)
Poly(delta-valerolactone)-b-methoxy-PEG	Paclitaxel		
Polycaprolactone-b-methoxy-PEG	Indomethacin		
	Cisplatin	*In vitro*	(146)
	Paclitaxel		(40)
Poly(caprolacton/trimethylene carbonate)-PEG	Risperidone	*In vitro*, rats	(154)
	Ellipticin	*In vitro*	(153)
Poly(aspartic acid)-b-PEG	Doxorubicin	Preclinical, clinical	(219)
	Cisplatin		
	Lysozyme		(91)
	Adriamycin	Mice	(90)
			(126)
	Camptothecin		
Poly(glutamic acid)-b-PEG	Cisplatin	Rats	(220)
Poly(benzyl-L-glutamate)-b-PEG	Clonazepam		(94)
Poly(D,L-lactide)-b-methoxy-PEG	Paclitaxel	Preclinical, Phase I	(221)
			(97)
	Testosterone		
	Griseofulvin	*In vitro*	(222)
Poly(benzyl-L-aspartate)-b-	Indomethacin		(53)
Poly(hydroxy-ethylene oxide)	Doxorubicin		(93)
	Adriamycin		(92)
Poly(benzyl-L-aspartate)-b-PEG	Doxorubicin		
	Indomethacin	*In vitro*	(53)
	Amphotericin B		
	Camptothecin		(145)
Poly(L-lysine)-b-PEG	DNA		(88)
	^{125}I	Rabbits	(89)
		Rats	(217)
Poly(2-ethyl-2-oxazoline)-b-poly(ε-caprolactone)	Paclitaxel	*In vitro*	(223)
Poly(2-ethyl-2-oxazoline)-b-poly(L-lactide)	Doxorubicin	*In vitro*	(175)
Poly(vinylalcohol-co-vinyloleate)	Retinyl palmitate		(83)
Poly(*N*-vinyl-2-pyrrolidone)-b-poly(D,L-lactide)	Indomethacin	*In vitro*	(82)
PEG-lipid	Dequalinium		
	Soya bean trypsin inhibitor	Mice	(36)
	Paclitaxel		(119)
		In vitro	(140)
	Camptothecin		
	Tamoxifen		(119)
	Porphyrine		
	Vitamin K3	*In vitro*	(117)
	Amphotericin B		(152)
	Chlorine e6 trimethyl ester		(119)
	^{111}In (via DTPA-PE, diagnostic)	Rabbit	(212)
	Gd (via DTPA-PE, diagnostic)	Rabbit	(212)
	Phtalocyanine	*In vitro*	(224)
PEG–PE/egg phosphatidylcholine (mixed micelles)	Paclitaxel	*In vitro*	(140,158)

Table II. (Continued)

Block Co-polymers	Micelle-incorporated Pharmaceuticals	Comments	References
	Camptothecin	*In vitro*	(144)
Various polymer-lipid conjugates	Corticosteroids		
	Sulfonylbenzoylpiperazine		
Poly(*N*-isopropylacrylamide)-b-poly(D,L-lactide) (thermosensitive)	Miscellaneous		
	Phtalocyanine		
	Paclitaxel	*In vitro*	(38)
Poly(*N*-isopropylacrylamide)-poly(vinylpyrrolidone)-poly (acrylic acid)	Ketorolac	Rabbits	(225)
Poly(*N*-isopropylacrylamide)-based micelles(pH-sensitive)	Phtalocyanine	Mice	(77)
Poly(*N*-isopropylacrylamide)-b-poly(alkyl(meth)acrylate) (pH-sensitive)	Phtalocyanine	Mice	(226)
	Doxorubicin		
Poly(L-histidine)-b-PEG (folate-targeted)	Doxorubicin	Mice	(198)
Poly(L-lactic acid)-b-PEG (folate-targeted)	Doxorubicin	Mice	(198)
Chitosan grafted with palmitoyl	Ibuprofen		(103)
	Puerarin	*In vitro*	(104)

pattern of PEG–PE micelles prepared from all versions of PEG–PE conjugates is characterized by the peak tumor accumulation times of about 5 h post-injection. In case of PEG–PE-based micelles, the largest total tumor uptake of the injected dose within the observation period (AUC) was found for micelles formed by PEG_{5000}–PE. This was explained by the fact that these micelles had the longest circulation time and little extravasation into the normal tissue compared to micelles prepared from the "shorter" PEG–PE conjugates. Micelles prepared from PEG–PE conjugates with shorter versions of PEG, however, might be more efficient carriers of poorly soluble drugs because they have a greater hydrophobic-to-hydrophilic phase ratio and can be loaded with drug more efficiently on a weight-to-weight basis. Some other recent data also clearly indicate spontaneous targeting of PEG–PE-based micelles into other experimental tumors (114) in mice as well as into the damaged heart areas in rabbits with experimental myocardial infarction (116).

Stimuli-Sensitivity

Another delivery approach is based on the fact that many pathological processes in various tissues and organs are accompanied with local temperature increase (by 2–5°C) and/or pH decrease by 1–2.5 pH units (acidosis) (167,168). So, the efficiency of the micellar carriers in local drug delivery can be improved by making micelles capable of disintegration and local drug released under the increased temperature or decreased pH values in pathological sites, i.e., by combining the EPR effect with stimuli-responsiveness. For this purpose, micelles are made of thermo- or pH-sensitive components, such as poly(*N*-isopropylacrylamide) and its co-polymers with poly(D,L-lactide) and other blocks, and acquire the ability to disintegrate in target areas releasing the micelle-incorporated drug (6,169,170). pH-sensitive block copolymers made of PEG and *t*-butyl methacrylate, ethyl acrylate, or *n*-butyl acrylate were used to prepare micelles loaded with indomethacin and progesterone (171). pH-responsive polymeric micelles loaded with phtalocyanine seem to be promising carriers for the photodynamic cancer therapy (77), while doxorubicin-loaded polymeric micelles containing acid-cleavable linkages provided an enhanced intracellular drug delivery into tumor cells and thus higher efficiency (172). Similarly, pH-sensitive unimolecular polymeric micelles—star-shaped polymers—have been made of hydrophobic ethyl methacrylate and *t*-butyl methacrylate and hydrophilic poly(ethylene glycol)methacrylate (173). Micelles have the size of 10 to 40 nm, their ionization and possibly drug release should depend on pH. Such micelles are also considered for oral delivery. Micelles based on poly(2-ethyl-2-oxazoline)-b-poly(L-lactide) diblock copolymer have been also described loaded with doxorubicin and capable of releasing the drug at pH values typical for late endosomes (pH around 5.5) and secondary lysosomes (pH around or below 5.0) (174,175). Phosphorylcholine-based diblock copolymer micelles also demonstrated distinct pH-sensitivity (176). Some more interesting pH-sensitive micelle-forming block copolymers are described in (177–179). Thermosensitive micelles have been prepared of thermosensitive copolymers of PEG block and *N*-isopropylacrylamide/2-[mono(mono/di)lactoyloxypropylmethacrylamide] (180). Some related thermosensitive micelle compositions based on poly(*N*-isopropylacrylamide) have been also described in (181–183). Thermo-responsive polymeric micelles were shown to demonstrate an increased drug release upon temperature changes (184). Micelles combining thermosensitivity and biodegradability have also been suggested (38). The penetration of drug-loaded polymeric micelles into cells (tumor cells) as well as drug release from the micelles can also be enhanced by externally applied ultrasound (185,186).

Ligand-Mediated Targeting

Drug delivery potential of polymeric micelles may be still further enhanced by attaching targeting ligands to the micelle surface, i.e., to the water-exposed termini of hydro-

philic blocks (187). Among those ligands one can name antibodies (46,114,188,189), sugar moieties (190,191), transferrin (188,192,193), and folate residues (194,195). The last two ligands are especially useful in targeting to cancer cells, since many cancer cells over-express transferrin and folate receptors on their surface. It was shown that galactose- and lactose-modified micelles made of PEG–polylactide co-polymer specifically interact with lectins thus modeling targeting delivery of the micelles to hepatic sites (189,191). Transferrin-modified micelles based on PEG and polyethyleneimine with the size between 70 and 100 are expected to target tumors with over-expressed transferrin receptors (188). Mixed micelle-like complexes of PEGylated DNA and PEI modified with transferrin (192) were designed for the enhanced DNA delivery into cells over-expressing transferrin receptors. Similar approach was successfully tested with becoming more and more popular folate-modified micelles (42,195,196). Poly(L-histidine)/PEG and poly(L-lactic acid)/PEG block co-polymer micelles carrying folate residue on their surface were shown to be efficient for the delivery of adriamycin to tumor cells *in vitro* demonstrating potential for solid tumor treatment and combined targetability and pH-sensitivity (197,198).

Several attempts to covalently attach an antibody to a surfactant or polymeric micelles (i.e., to prepare immunomicelles) have been described (31,86,114,188). Thus, micelles modified with fatty acid-conjugated Fab fragments of antibodies to antigens of brain glia cells (acid gliofibrillar antigen and alpha 2-glycoprotein) loaded with neuroleptic trifluoperazine increasingly accumulated in the rat brain upon intracarotide administration (86,189). PEG–PE-based immunomicelles modified with monoclonal antibodies have been prepared by using PEG–PE conjugates with the free PEG terminus activated with *p*-nitrophenylcarbonyl (pNP) group (199). Diacyllipid fragments of such bifunctional PEG derivative firmly incorporate into the micelle core, while the water-exposed pNP group stable at pH values below 6, interacts with amino-groups of various ligands (antibodies and their fragments or peptides) at pH values above 7.5 yielding a stable urethan (carbamate) bond. To prepare immunotargeted micelles, the corresponding antibody could be simply incubated with drug-loaded pNP–PEG–PE-containing micelles at pH around 8. Using fluorescent labels or by SDS-PAGE (114,158), it was calculated that several antibody molecules could be attached to a single 20 nm micelle. Antibodies attached to the micelle corona preserve their specific binding ability, and immunomicelles specifically recognize their target substrates as was confirmed by ELISA. For tumor targeting, PEG–PE-based micelles were modified with monoclonal 2C5 antibody possessing the nucleosome-restricted specificity (mAb 2C5) and capable of recognition of a broad variety of tumor cells via the tumor cell surface-bound nucleosomes (200). Rhodamine-labeled 2C5-immunomicelles effectively bind to the surface of various unrelated tumor cells lines, and drug loading into the immunomicelles does not affect their specificity and targetability, so that paclitaxel-loaded 2C5-immunomicelles demonstrated same high binding to the surface of various cancer cells as did "empty" immunomicelles (114). Such specific targeting of cancer cells by drug-loaded mAb 2C5-immunomicelles results in dramatically improved *in vitro* cancer cell killing by such micelles: with human breast cancer MCF-7 cells, paclitaxel-loaded 2C5-immunomicelles showed a clearly superior efficiency compared to paclitaxel-loaded plain micelles or free drug (158). *In vivo* experiments with Lewis lung carcinoma-bearing mice have revealed an improved tumor uptake of paclitaxel-loaded radiolabeled 2C5-immunomicelles compared to non-targeted micelles. In addition, unlike plain micelles, 2C5-immunomicelles, should be capable of delivering their load not only to tumors with a mature vasculature, but also to tumors at earlier stages of their development and to metastases. It was shown that mAb 2C5-immunomicelles were capable in bringing into tumors substantially higher quantities of paclitaxel than in the case of paclitaxel-loaded non-targeted micelles or free drug formulation, which resulted in a higher therapeutic efficiency of paclitaxel-loaded mAb 2C5-micelles (significantly smaller tumor size) (114).

Intracellular Delivery of Micelles and Intracellular Trafficking

One may try to further improve the efficiency of drug-loaded micelles by enhancing their intracellular delivery compensating thus for an excessive drug degradation in lysosomes as a result of the endocytosis-mediated capture of therapeutic micelles by cells. One approach to achieve this is by controlling the micelle charge. It is known that the net positive charge enhances the uptake of various nanoparticles by cells. Cationic lipid formulations such as Lipofectin® (an equimolar mixture of *N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride—DOTMA, and dioleoyl phosphatidylethanolamine—DOPE), noticeably improve the endocytosis-mediated intracellular delivery of various drugs and DNA entrapped into liposomes and other lipid constructs made of these compositions (201–204). After endocytosis, the Lipofectin®-based particles are believed to escape from the endosomes and enter a cell's cytoplasm through disruptive interaction of the cationic lipid with endosomal membranes (205). Some PEG-based micelles, such as PEG–PE micelles, have been found to carry a net negative charge (116), which might hinder their internalization by cells. The compensation of this negative charge by the addition of positively charged lipids to PEG–PE-based micelles could improve their uptake by cancer cells. It is also possible that after the enhanced endocytosis, drug-loaded mixed micelles made of PEG–PE and positively charged lipids could escape from the endosomes and enter the cytoplasm of cancer cells. With this in mind, the attempt was made to increase an intracellular delivery and, thus, the anticancer activity of the micellar paclitaxel by preparing paclitaxel-containing micelles from the mixture of PEG–PE and positively charged Lipofectin® lipids (LL). The cell interaction (BT-20 breast adenocarcinoma cells were used in this case) and intracellular fate of paclitaxel-containing PEG–PE/LL micelles and similar micelles prepared without the addition of the LL were investigated by fluorescence microscopy. It was clearly demonstrated that fluorescently-labeled PEG–PE and PEG–PE/LL micelles were both endocytosed by cancer cells, however, in the case of PEG–PE/LL micelles, endosomes were shown to degrade and release drug-loaded micelles into the cell cytoplasm as a result of the de-stabilizing effect of the LL component on the endosomal membranes (140). The *in vitro* anticancer effects of drug-loaded micelles (evaluated

using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] method (206) were significantly improved for intracellularly delivered paclitaxel-containing PEG–PE/LL compared to that of free paclitaxel or paclitaxel delivered using LL-free PEG–PE micelles: in A2780 cancer cells (human ovarian carcinoma), the IC50 values of free paclitaxel, paclitaxel in PEG–PE micelles, and paclitaxel in PEG–PE/LL micelles were 22.5, 5.8 and 1.2 μM, respectively.

MICELLES AS CARRIERS FOR DIAGNOSTIC AGENTS

The micellar transport of contrast agents represents a relatively new field (37,207). However, there are already some approaches suggesting the use of micellar contrast agents for both pure diagnostic/imaging purposes and for the visual control over the drug delivery by micellar pharmaceutical carriers. Chelated paramagnetic metals, such as Gadolinium (Gd), Manganese (Mn) or Dysprosium (Dy), are the major interest for the design of magnetic resonance (MR) positive (T1) contrast agents. Mixed micelles obtained from monoolein and taurocholate with Mn-mesoproporphyrin, were shown to be a potential oral hepatobiliary imaging agent for T1-weighted MR imaging (MRI) (208). Since chelated metal ions possess a hydrophilic character, to be incorporated into micelles, such structures should acquire amphiphilic nature. Several amphiphilic chelating probes, where a hydrophilic chelating residue is covalently linked to a hydrophobic (lipid) chain, have been developed earlier for the liposome membrane incorporation studies, such as diethylene triamine pentaacetic acid (DTPA) conjugate with phosphatidyl ethanolamine (DTPA–PE) (209), DTPA–stearylamine, DTPA–SA (210), and amphiphilic acylated paramagnetic complexes of Mn and Gd (211). The lipid part of such amphiphilic chelate molecule can be anchored into the micelle's hydrophobic core while a more hydrophilic chelating group is localized inside the hydrophilic shell of the micelle. The amphiphilic chelating probes (paramagnetic Gd–DTPA–PE and radioactive ^{111}In–DTPA–SA) were incorporated into PEG(5 kDa)–PE micelles and used *in vivo* for MR and gamma-scintigraphy imaging. The main feature that makes PEG–lipid micelles attractive for diagnostic imaging applications is their small size allowing for better penetration to the target to be visualized. In experiments on lymphatic imaging, amphiphilic chelating probes Gd(^{111}In)–DTPA–PE and ^{111}In–DTPA–SA were incorporated into 20 nm PEG(5 kDa)–PE micelles and successfully used for the experimental percutaneous lymphography in rabbits by gamma-scintigraphy and MR imaging (212). Due to their size and surface properties imparted by the PEG corona, the micellar particulates can move with ease from the injection site along the lymphatics to the systemic circulation with the lymph flow. Their action is based on the visualization of lymph flowing through different elements of the lymphatics, while the action of other lymphotropic contrast media is based primarily on their active uptake by the nodal macrophages.

The efficacy of micelles as contrast medium might be further increased by increasing the quantity of carrier-associated reporter metal (such as Gd or ^{111}In), and thus enhancing the signal intensity. To solve this task, the use of amphiphilic chelating polymers was suggested (213), representing a family of soluble single-terminus lipid-modified polymers containing multiple chelating groups attached to the polylysine chain and suitable for incorporation into the hydrophobic surrounding (such as a hydrophobic core of corresponding micelles). A pathway was developed for the synthesis of the amphiphilic polychelator *N*,ε-(DTPA–polylysyl)glutaryl–PE, which sharply increases the number of chelated metal atoms attached to a single lipid anchor (213). Micelles formed by self-assembled amphiphilic polymers (such as PEG–PE) can easily incorporate such amphiphilic polylysine-based chelates carrying multiple diagnostically important metal ions such as ^{111}In and Gd (212). In addition, in case of MRI contrast agents, it is especially important that chelated metal atoms are directly exposed into the aqueous environment, which enhances the relaxivity of the paramagnetic ions and leads to the enhancement of the micelle contrast properties.

Computed tomography (CT) represents an imaging modality with high spatial and temporal resolution, which uses X-ray absorbing heavy elements, such as iodine, as contrast agents. Diagnostic CT imaging requires the iodine concentration of millimoles per milliliter of tissue (214), so that large doses of low-molecular-weight CT contrast agent (iodine-containing organic molecules) are normally administered to patients. The selective enhancement of blood upon such administration is brief due to rapid extravazation and clearance. Currently suggested particulate contrast agents possess relatively large particle size (between 0.25 and 3.5 μm) and are actively cleared by phagocytosis (215,216). The synthesis and *in vivo* properties of a block-copolymer of methoxy-poly(ethylene glycol) (MPEG) and triiodobenzoic acid-substituted poly-L-lysine have been described (89,217), which easily micellizes in the solution forming stable and heavily iodine-loaded particles (up to 35% of iodine by weight) with a size of 50 to 70 nm. The micellar iodine-containing CT contrast agent was injected intravenously into rats and rabbits, and a 3–4-fold enhancement of the X-ray signal in the blood pool was visually observed in both animal species for at least a period of 2 h following the injection (89,217).

CONCLUSION

Summarizing, micelles and, first of all, polymeric micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. This was repeatedly demonstrated for a broad variety of drugs, mostly poorly soluble anti-cancer drugs, with micelles of different composition. In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised ("leaky") vasculature. Micelle specific targeting to required areas can be also achieved by attaching specific targeting ligand molecules (such as target-specific antibodies, transferrin or folate) to the micelle surface. Varying micelle composition and the sizes of hydrophilic and hydrophobic blocks of the micelle-forming material can easily control properties of micelles, such as size, loading capacity, longevity in the blood. Biodegradable micelles, where the controlled degradation of hydrophilic blocks can facilitate drug liberation from the hydrophobic core, can also become a subject of

interest. Another interesting option may be provided by stimuli-responsive micelles, whose degradation and subsequent drug release should proceed at abnormal pH values and temperatures characteristic for many pathological zones. Micelles are easy to prepare and load with the drug or diagnostic moiety. Such combination of properties should lead to the successful practical application of micellar drugs in the foreseeable future.

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