19 Hydrotropic Polymer Micelles for Cancer Therapeutics

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19.1 INTRODUCTION

Recently, polymer micelles derived from amphiphilic block copolymers in an aqueous phase have attracted attention as a promising formulation for poorly water-soluble drugs.[1–4] Block copolymer micelles are nanosized particles with a typical core-shell structure.[5] The core solubilizes the hydrophobic drugs, while the corona allows the suspension of micelles in an aqueous medium. The use of block copolymer micelles as drug-carrying vehicles was proposed by Ringsdorf's group in the 1980s.[6] The rationale for incorporating low-molecular-weight drugs into micelles is to overcome the problems of drug formulations such as toxic side effects, poor pharmacokinetics,

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and limited solubility in water. Hydrophobic drugs can be solubilized into hydrophobic core structures of polymeric micelles, and solubilized at higher concentrations than their intrinsic water-solubility.[7–10] The chemical composition of polymeric micelles is attractive because it can be tailored to have desirable physicochemical properties for drug solubilization. Therefore, various amphiphilic block copolymers have been synthesized and investigated for micelle formulations of poorly soluble drugs.[11–14] In most polymeric micelles, hydrophobic drugs can be incorporated into the hydrophobic core of micelles by hydrophobic interaction and other additional interactions, such as the metal–ligand coordination bond, receptor–ligand interaction, and the electrostatic interaction.[15–17] It is believed that the more compatible drugs are with the cores of the micelles, the greater their ability to be dissolved.

As drug carriers, polymeric micelles have been widely investigated for a diverse class of anti-cancer agents including paclitaxel, adriamycin, and methotrexate.[3,12,18,19] However, several limitations, for example, limited drug-solubilizing ability, poor stability in water after drug loading, and the lower stability with the higher loading content, are known to limit successful clinical applications.[20,21]

Hydrotropy has many advantages in enhancing the water solubility of poorly soluble drugs. Hydrotropes (or hydrotropic agents) self-associate to form noncovalent assemblies of nonpolar microdomains to solubilize poorly water-soluble solutes.[22] The high concentration of hydrotropes (greater than 1 M) is a key factor in enhancing water-solubility of poorly soluble solutes.[23,24] Hydrotropes often exhibit a higher selectivity in solubilizing guest hydrophobic molecules than in surfactant micelles. Thus, identifying hydrotrope structures that effectively solubilize a specific drug molecule is important. Recently, Park et al. have examined a number of hydrotropes for solubilization of paclitaxel, a model poorly soluble anti-cancer agent.[25] Through screening the effective structures of the hydrotropes for paclitaxel solubilization, *N,N*-diethylnicotinamide (DENA) and *N*-picolylnicotinamide (PNA) were found to be the best hydrotropes. They increased the water-solubility of paclitaxel by 3–5 orders of magnitude over its normal solubility in pure water (about 0.3 μg/mL). They also examined polymers and hydrogels, based on DENA and PNA hydrotropes, to develop new polymeric solubilizing systems maintaining the benefits of hydrotropy.[26] The hydrotropic property of the hydrotropes was maintained in their polymeric forms, and the highly localized concentration of the hydrotrope in polymers and hydrogels was found to be a main contributor to effective solubilization of paclitaxel. However, upon dilution in aqueous media, drugs solubilized in hydrotropic polymers precipitate due to the low physical stability of the formulations. Thus, a need exists for the hydrotropic formulations with a high stability.

To overcome the limitations of current polymeric micelles, hydrotropic polymer micelle systems that have had core components designed with a high solubilizing capacity for poorly soluble anti-cancer agents, like paclitaxel, show enhanced long-term stability even at high drug loading.[27] The key in the polymer system designs is to introduce the identified structure of hydrotropes for a specific drug to the drug-solubilizing micellar cores. The benefit of using self-assembled structures is the congestion of hydrotropic moieties with high local concentration at the micellar inner core. To date, many polymeric micelles have shown limited solubilizing capacity for paclitaxel, and, in most cases, the maximum content of paclitaxel loaded in micelles was around 20 wt%.[20,21] In addition to the limited loading capacity, the stability of the drug-loaded polymeric micelles is poor. Stability decreases as the drug loading increases. The poor colloidal stability of existing polymeric micelles is normally caused by the enhanced hydrophobicity of micelles after solubilization of paclitaxel, leading to aggregation of micelles. Because the hydrotropic moiety is relatively hydrophilic, it retains the hydrophilicity of the colloidal micelles even after loading of large amounts of paclitaxel.

This chapter gives a general review on recent developments of polymer micelles for cancer chemotherapeutics, the basic concept of hydrotropic solubilization, and a systemic rationale of hydrotropic polymer micelle systems. In particular, it focuses on the design strategy and unique properties of hydrotropic micelle formulations for the delivery of poorly soluble anti-cancer drugs.

19.2 GENERAL REVIEW OF POLYMER MICELLE DRUG CARRIERS

Micelles are defined as colloidal dispersions, including a category of a dispersed system that consists of the particulate matter or the dispersed phase in a continuous phase or dispersion medium.[28,29] Micellization phenomena have been studied widely in the field of drug delivery. Amphiphilic small molecules have been utilized for preparing micelles, but amphiphilic macromolecules are better than the small molecules because of their lower critical micelle concentration (CMC) and higher stability. Polymeric micelles represent a separate class of micelles. Polymeric micelles consist of amphiphilic block copolymers which include multi-block copolymers, AB-type di-block copolymers, and ABA-type tri-block copolymers with a hydrophobic core (A or B segment) and a hydrophilic shell (A or B segment). Representative block copolymers are summarized in Table 19.1.[5,9,12] The amphiphilic block copolymer forms spherical micelles in aqueous environments with a hydrophilic shell and hydrophobic core parts (Figure 19.1). In general, the core part represents a molten-liquid globule and a swollen, hydrophilic corona. These micelles have a high solubilization capacity of poorly soluble drugs, and good potential to minimize drug degradation, loss, and harmful side effects. In this chapter, polymeric micelles for drug delivery applications are briefly summarized in terms of methods/mechanism of micelle formation, influencing factors of stabilization, and solubilization of poorly soluble drugs.

19.2.1 Preparative Methods of Polymer Micelles Based on Block Copolymers

There are two ways to prepare polymeric micelles: the direct dissolution method and the dialysis method (Figure 19.2).[1] One can select a method depending on the block copolymer's solubility in an aqueous medium. As for direct dissolution, the block copolymer is simply dissolved in water or buffers at a concentration above its CMC. If needed, the temperature is elevated during the micelle formation. A good example of this method is poly(ethylene oxide)-*block*-poly(propylene oxide)-*block*-poly(ethylene oxide) (PEO–PPO–PEO; Pluronics®).[30,31] If block copolymers are not easily water soluble, the dialysis method is useful to prepare polymeric micelles. In this case, block copolymer is dissolved in a water-miscible organic solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO), and acetonitrile. The mixed solution is then dialyzed against distilled water. During the dialysis, the organic solvent is removed by exchanging the outer medium (distilled water). The pore size of the semi-permeable membrane (usually SpectraPor®) should be carefully selected, based on the expected size of polymeric micelles. The choice of organic solvent is important because the solvent effects the size and size-population distribution of polymeric micelles. La et al. reported that the use of DMSO as the organic solvent gave rise to PEO-*b*-poly(β-benzyl L-aspartate) (PEO–PBLA) micelles, of which size was only 17 nm.[32] However, only

TABLE 19.1
Representative Block Copolymers for Poorly Soluble Drugs

Block Copolymers
Pluronics® (PEO–PPO–PEO)
Methoxy-PEG-*b*-poly(D,L-lactide) (PEG–PLA)
PEG-*b*-poly(lactic acid-*co*-glycolic acid)-*b*-PEG
Methoxy-PEG-*b*-polycaprolactone (PEG–PCL)
Poly(β-maleic acid)-*b*-poly(β-alkylmaleic acid alkyl ester)
Poly(*N*-isopropyl acrylamide)-*b*-PEG
Poly(aspartic acid)-*b*-PEG
PEG-*b*-phosphatidyl ethanolamine

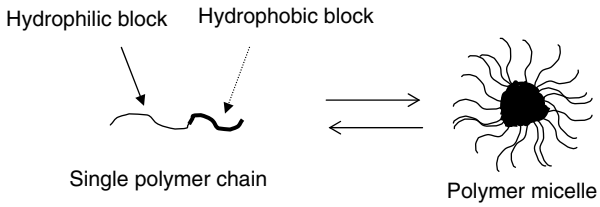


FIGURE 19.1 General scheme of micelle formation using amphiphilic block copolymers.

6% of the PEO–PBLA formed the micelle. When dimethylacetamide (DMAc) was used as the organic solvent, the size was 19 nm with a high yield. Therefore, one should examine the effect of organic solvents on the size and size distribution, as well as the composition, of block copolymers.

19.2.2 Characterization and Properties of the Polymeric Micelles

The micellization of di- or tri-block copolymers is usually characterized by the following methods:

1. Dye-solubilization methods using 1,6-diphenyl-1,3,5-hexatriene (DPH) and pyrene (Figure 19.3)[11,33–37]
2. Static and dynamic light-scattering measurements.[32,38,39]

The dye-solubilization method is useful to determine CMC, local viscosities, and polarity of the micellar core.[40] For example, DPH is preferentially partitioned into the hydrophobic core of micelles with the formation of micelles, which causes an increase in the absorbance of the dyes. When the concentration of the block copolymers changes, CMC can be determined as the cross-point of the extrapolation of the change in absorbance over a wide concentration range. Pyrene has

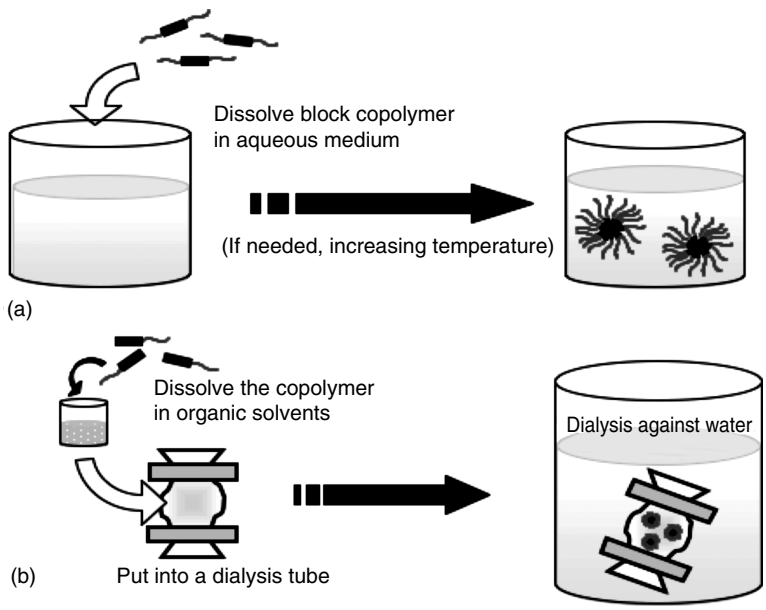


FIGURE 19.2 Preparation of micelles by direct dissolution (a) and dialysis methods (b).

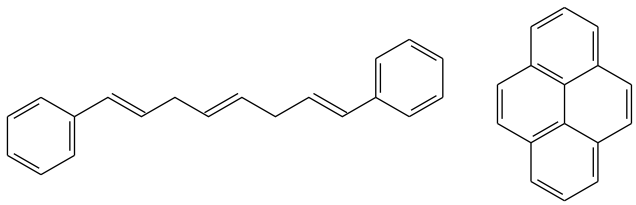


FIGURE 19.3 Chemical structures of DPH and pyrene.

been well-studied as a fluorescent probe to determine CMC, as well as DPH.[4,41] Below CMC, a small amount of pyrene is solubilized in water (the saturated concentration is as low as 6×10^{-7} M). In the presence of polymeric micelles, pyrene is preferentially solubilized in the nonpolar micelle core. By increasing the concentration of the block copolymer in the presence of pyrene, an increase in emission intensity can be seen, at which point pyrene becomes associated with the micelle core. When the concentration of the block copolymers changes, CMC can be determined as the point from which to extrapolate the change in absorbance in a wide range of the concentration.

Weight-average molecular weight (M_W) of micelles is calculated by the results of static light-scattering (SLS) measurements using a Debye plot[39]:

$$K(C-\mathrm{CMC})/(R-R_{\mathrm{CMC}}) = 1/M_W + 2A_2(C-\mathrm{CMC})$$

where K indicates $4\pi^2(\mathrm{d}n/\mathrm{d}c)^2/N_A\lambda^4$, R and R_{CMC} the excess Rayleigh ratios at concentration C and CMC, n is the refractive index of solution at CMC, dn/dc is the refractive index increment, N_A is Avogadro's number, λ is the wavelength of the laser light, and A_2 is the second virial coefficient. Hydrodynamic radii (R_H) of micelles can be determined by dynamic light-scattering (DLS) measurements using the Stokes–Einstein equation[39,41]:

$$R_H = k_BT/(3\pi\eta D)$$
$$D = \Gamma/K^2$$

where k_B is the Boltzmann constant, T is the absolute temperature, η is the solvent viscosity, D is the diffusion coefficient obtained from the average characteristic line width (Γ), and K^2 is the magnitude of the scattering vector. Because polymeric micelles are a kind of spherical assembly, the diffusion coefficients should be independent of the detection angle, due to the undetectable rotational motions.

19.2.3 Key Parameters for Morphology and Stabilization of the Polymeric Micelles

As for AB-type di-block copolymers, one can imagine that the di-block copolymer can form spherical micelles in an aqueous solution. If the hydrophilic block is too long, the di-block copolymers exist in water as a unimer or a macromolecular micelle. On the other hand, if the hydrophobic block is too long, it can show nonmicellar morphology, such as rods and lamellar structures. Eisenberg and his group reported that different morphologies are formed at equilibrium, near-equilibrium, and nonequilibrium conditions.[42] When the length of the hydrophobic segment is significantly shorter than that of the hydrophilic part, the block copolymer usually forms nonspherical micelles. The formation of "crew-cut" aggregates has been suggested by a force-balance effect between the hydrophobic part's degree of stretching, the interfacial energy of the micelle core with water, and the interaction between hydrophilic chains as a shell.[42–44] Copolymer compositions,

concentrations, and organic solvents used for the micelle preparation significantly affect the morphology.

From the pharmaceutical point of view, stability of polymeric micelles in the blood stream is important because administration of micelles into the body always accompanies dilution, which causes dissociation of the micelles.[1] The stability of polymeric micelles both in vitro and in vivo depends on their CMC values. However, the CMC values have been used as a thermodynamic stability: Equilibrium between unimers and micelles can be shifted below or above the CMC. On the other hand, kinetic stability, which represents the actual rate of micelle dissociation below the CMC, depends on the size of the hydrophobic part, the physical state of the micelle core, and the hydrophilic/hydrophobic ratio. The hydrophobic block plays an especially critical role. For example, an increase in the length of the hydrophobic block at a given length of the hydrophilic block causes a significant decrease in the CMC value, and an increase in the stability of the micelle. On the other hand, an increase in the length of hydrophilic block leads to only a small rise of CMC value. Additionally, CMC values of di-block copolymers are generally lower than those of tri-block copolymer of the same molecular weight and hydrophilic/hydrophobic ratio. Thus, the molecular design of block copolymers for polymeric micelles should be optimized for pharmaceutical applications. To increase stability, unimolecular micelles that mimic polymeric micelles regarding their morphological properties have been proposed since 1991.[45,46] These micelles are intrinsically stable upon dilution, because their formation is independent of polymer concentration. Both dendrimers and star polymers have been designed as unimolecular micelles.[45,47–49]

19.2.4 Drug Loading, Solubilization, and Drug Release

Drug loading methods mostly depend on the methods of micelle formation.[50,51] In the case of micelles prepared by the direct dissolution in water, a stock solution of drugs in some organic solvents is prepared in an empty vial. Then the organic solvent is allowed to evaporate, followed by adding an aliquot of water containing the block copolymer. The oil-in-water emulsion method is another method: the drug, in a nonpolar solvent such as chloroform, is added dropwise to the water containing the block copolymer. In the case of the dialysis method, the drug is mixed with the block copolymer in common organic solvents, and the organic solvents in dialysis bags are exchanged with a large amount of water to induce assembly of micelles. Upon micellization, the poorly soluble drugs are trapped in the hydrophobic inner cores of micelles.

It is known that the solubilization of poorly soluble drugs in the micelle core strongly depends on the types and efficacy of the interactions between the solubilized drug and the hydrophobic micelle core.[1] Drug-loading capacity depends on the compatibility between the loaded drug and the hydrophobic core. Drug characteristics such as polarity, hydrophobicity, and charge often affect compatibility; consequently, the structure and the length of hydrophobic block should be carefully examined to determine maximum compatibility with any poorly soluble drugs. A good parameter that has been used to assess compatibility is the Flory–Huggins interaction parameter, χ_{sp}. This parameter is described by the following equation[1]:

$$\chi_{sp} = (\delta_s - \delta_p)^2 V_s / RT,$$

where χ_{sp} is the interaction parameter between the solubilized drug (s) and the hydrophobic block part (p), δ is the Scatchard–Hildebrand solubility parameter of the hydrophobic block part, and V_s is the molar volume of the solubilized drug. If the χ_{sp} shows low value, the compatibility between drug and hydrophobic block part is great. By using this parameter, Gadelle et al. suggested the following mechanism for solubilization of aromatic solutes in PEO-*b*-PPO-*b*-PEO[28]:

1. The addition of apolar solutes (drugs) promotes aggregation of the block copolymer molecules.

2. The micelle core contains some water molecules.
3. Solubilization is initially a replacement process in which water molecules are displaced from the micelle core by the drug.

Drug-release kinetics generally depend upon the rate of the drug's diffusion from the micelles. There are several factors that affect the release rate: Polymer–drug interactions, localization of the drug within the micelle, the physical state of the micelle core, the length of the hydrophobic part of the block copolymer, the molecular volume of the drug, and the physical state of the drug in the micelle.[1] For instance, if the drug is located in the micelle core as a crystal, it may act as a reinforcing filter. If the magnitude of interaction between the copolymer and the surface of crystallite is strong, the drug crystal may cause the glass-transition temperature to increase. Thus, solubilization of the drug, which depends on the characteristics of both the drug and the block copolymer, is important in designing polymeric micelles for poorly soluble drugs, such as anti-cancer drugs.

19.3 POLYMER MICELLES FOR CANCER CHEMOTHERAPY

19.3.1 Polymer Micelles as Carriers of Anti-Cancer Drugs

Significant progress in cancer therapy has been made with the development of new anti-cancer agents and related technologies. However, the major challenge remains in delivery technologies that can effectively, selectively deliver anti-cancer agents to tumor sites, and avoiding systemic toxicity and adverse effects to normal tissues or cells. Recently, polymer micelles have attracted attention as a novel drug carrier system, in particular for anti-cancer agents, due to its various, promising properties. These nanoscaled delivery systems have been developed to demonstrate a series of required properties as drug carriers, such as biocompatibility, stability both in vitro and in vivo, targeting, and drug loading capacity. Recent research into the development of polymer micelle delivery system has focused on two issues, drug solubilization and targeted delivery system, to enhance the efficacy of the delivered drug.[52–55]

19.3.2 Polymer Micelles for Solubilization of Poorly Soluble Anti-Cancer Drugs

Because many anti-cancer drugs and drug candidates are water-insoluble or poorly water-soluble, applicability of solubilizing systems to these drugs is indispensable. For instance, paclitaxel is one of the most effective anti-cancer agents, and currently formulated with use of surfactants, including Cremophor EL, due to its extremely poor water solubility.[56] Despite good efficacy of the formulation, its clinical use is limited by serious side effects resulting from use of Cremophor EL.[57–59] Diverse approaches—such as chemical and physical modification, use of a cosolvent, and emulsification—have been explored for increasing the aqueous solubility of poorly soluble drugs.[60–66] Although several systems have shown high solubilizing effects, they have been limited by their stability and toxicity. Thus, development of nontoxic and stable effective solubilizing systems for poorly soluble drugs is important for enhancing drug efficacy with high bioavailability.

Over the past decade polymer micelles have been extensively investigated as a potent drug carrier that can effectively solubilize poorly soluble anti-cancer drugs. Because polymer micelles have been made with biocompatible polymers such as poly(ethylene oxide), poly(D,L-lactide), etc., they are much less toxic than other solubilizing agents such as cosolvents or surfactants.[20,58] Additionally, recent advances in polymer synthesis make it possible to sophisticate the design of polymer composition and structure so that the resulting micelle shows high solubilizing capacity with prolonged stability.

Presently a number of polymer micelle systems with different compositions and structures have been tried to solubilize and deliver various anti-canter drugs. Several examples of the polymer

micelles used for solubilization of poorly water-soluble anti-cancer drugs are summarized in Table 19.2.[2–14,19,20,42,52,54] Drug-loading tests have shown that, in most polymer micelle systems, not only molecular design of block copolymers, but also the drug incorporation method are crucial factors to increase the solubilizing capacity.[1,14]

19.3.3 Targeting Systems Using Polymer Micelles

Unique core-shell structure of polymer micelle systems with a nanoscaled size may ensure prolonged circulation times that are favorable for passive drug targeting.[10] Furthermore, polymer micelles can be selectively accumulated to tumor sites by the enhanced permeability and retention (EPR) effect, which makes them useful as a tumor-targeting system. An alternative, passive-targeting strategy is to make smart micelles using stimuli-responsive amphiphilic block copolymers that can sense and respond to the unique tumor environment.[54,67] Kataoka et al. have developed a novel intracellular pH-sensitive polymeric micelle drug carrier that controls the systemic, local, and subcellular distributions of pharmacologically-active drugs using amphiphilic block copolymers, poly(ethylene glycol)–poly(aspartate hydrazone adriamycin).[68] Because the anti-cancer drug, adriamycin, is conjugated to the hydrophobic segments through acid-sensitive hydrazone links, this polymer micelle can stably preserve drugs under physiological conditions (pH 7.4), but selectively release the drug by sensing the intracellular pH decrease in endosomes and lysosomes (pH 5–6).

The active targeting is usually achieved by attaching specific-targeting ligand molecules, such as monoclonal antibodies, to the micelle surface, which provides a preferential accumulation in the tumor sites or cells. Such ligand and other targeting moieties are introduced in other literatures.[69] When linked with tumor-targeting ligands, polymer micelles can be used to target tumor sites with

TABLE 19.2
Use of Polymer Micelle Systems for Solubilization of Poorly Soluble Anti-Cancer Agents

Polymer Composition[a]	Loaded Drug	Loading Content (wt%)[b]
PEG–PDLLA	Paclitaxel	5–25
	Methotrexate	3.7–2.8
PEG–PDLLACL	Paclitaxel	15–25
PEG–PGACL	Paclitaxel	8–11
PEtOz–PCL	Paclitaxel	0.5–7.6
PEG–PCL	Paclitaxel	4.1–20.8
PEG–pHPMAmDL	Paclitaxel	22
PVP-*b*-PDLLA	Paclitaxel	5
	Docetaxel	4
	Teniposide	10
	Etoposide	20
PEG-poly(aspartate)	Camptothecin	13
PEG–P(Asp(ADR)	Doxorubicin Ellipticine	8.4–7.8
PEG–PBTMC	Doxorubicin	10
Poly(NIPAAm-*co*-DMAAm)-PLGA		2–8

[a] Calculated by: (weight of loaded drug)×100/(weight of drug-loaded micelle).

[b] PDLLA, Poly(D,L-lactide); PDLLACL, Poly(D,L-lactide-*co*-caprolactone); PGACL, Poly(glycolide-*co*-caprolactone); PEtOz, poly(2-ethyl-2-oxazoline); pHPMAmDL, poly(*N*-(2-hydroxypropyl) methacrylamide lactate); PVP, poly(*N*-vinyl-pyrrolidone); P(Asp(ADR), adriamycin-conjugated poly(aspartic acid) block copolymer; PBTMC, poly(5-benzyloxytrimethylene carbonate); NIPAAm, *N*-isopropylacrylamide; DMAAm, *N*,*N*-dimethylacrylamide; PLGA, poly(D,L-lactide-*co*-glycolide).

high affinity and specificity. Recently a multifunctional polymer micelle system has been proposed to endow enhanced tumor selectivity and endosome-disruption property on the carrier.[68] The polymer micelle is designed to expose the cell interacting ligand (biotin) only under slightly acidic environmental conditions of various solid tumors, and show pH-dependent dissociation, causing the enhanced release of the loaded drug from the carrier in early endosomal pH.

19.3.4 Other Applications of Polymer Micelles for Cancer Therapy

Polymer micelles have supramolecular functionalities that are not available from either individual polymer chains or bulk polymer solids. Based on supramolecular architecture, polymer micelles have much more surface area and a separate core that can be available for chemically or physically introducing other active agents, including optical, radioisotopic, magnetic diagnostic, and photosensitive agents.[70,71] Although the delivery of chemotherapeutic agents by polymer micelle systems is relatively well established, the application for delivering imaging and photosensitive agents remains in the early stages of research.[47,70,71] The polymer design and targeting strategies can be also utilized in delivery of other active agents for cancer treatments. Recently, photodynamic therapy (PDT) has been considered as a promising method of treating cancer and other diseases.[72] PDT involves the systemic administration of photosensitizers followed by a local application of light, introducing photochemical reactions that generate cytotoxical substances that produce necrosis of a cancer cells.[70] Polymer micelles can be a good candidate for delivery of photosensitizers in PDT because of their high solubilizing capacity for hydrophobic drugs and potential targeting property. The delivery of photosensitizers by polymer micelles may allow selective accumulation to solid tumor tissue and resultant higher photocytotoxicity with reduced side effects.[47,72] Also, hydrophobic photosensitizers that are poorly soluble or tend to aggregate in aqueous environments can be effectively solubilized in polymer micelle system, showing high photodynamic efficacy by overcoming problems from intrinsic poor solubility.[70]

19.4 HYDROTROPIC POLYMER MICELLES

19.4.1 Hydrotropy and Hydrotropic Agents

Hydrotropy is a collective molecular phenomenon describing a solubilization process whereby the presence of large amounts of a second solute, called hydrotropes, results in an increased aqueous solubility of a poorly soluble compound.[22,73] Hydrotropic agents are a diverse class of substances with wide industrial usage, including solubilizing agents in drug formulations, agents in the separation of isomeric mixtures, catalysts in heterogeneous phase chemical reactions, and fillers in cleaning formulations and cosmetics. Some examples of hydrotropic agents are nicotinamide and its derivatives, anionic benzoate, benzosulfonate, neutral phenol such as catechol and resorcinol, aliphatic glycolsulfate, and amino acid L-proline.[22,74] Figure 19.4 shows a variety of compounds that are classified as hydrotropic agents. Hydrotropic agents are characterized by a short, bulky, and compact moiety such as an aromatic ring, whereas surfactants have long hydrocarbon chains. In general hydrotropic agents have a shorter hydrophobic segment, leading to a higher water solubility, than that of surfactants. Other examples of hydrotropic materials are sodium gentisate, sodium glycinate, sodium toluate, sodium naphtoate, sodium ibuprofen, pheniramine, lysine, tryptophan, isoniazid, and urea.[22,23] At concentrations higher than the minimal hydrotrope concentration, hydrotropic agents self-associate and form noncovalent assemblies of lowered polarity (i.e., nonpolar microdomains) to solubilize hydrophobic solutes. The self-aggregation of hydrotropic agents is different from surfactant self-assemblies (i.e., micelles), in that hydrotropes form planar or open-layer structures instead of forming compact spheroid assemblies.

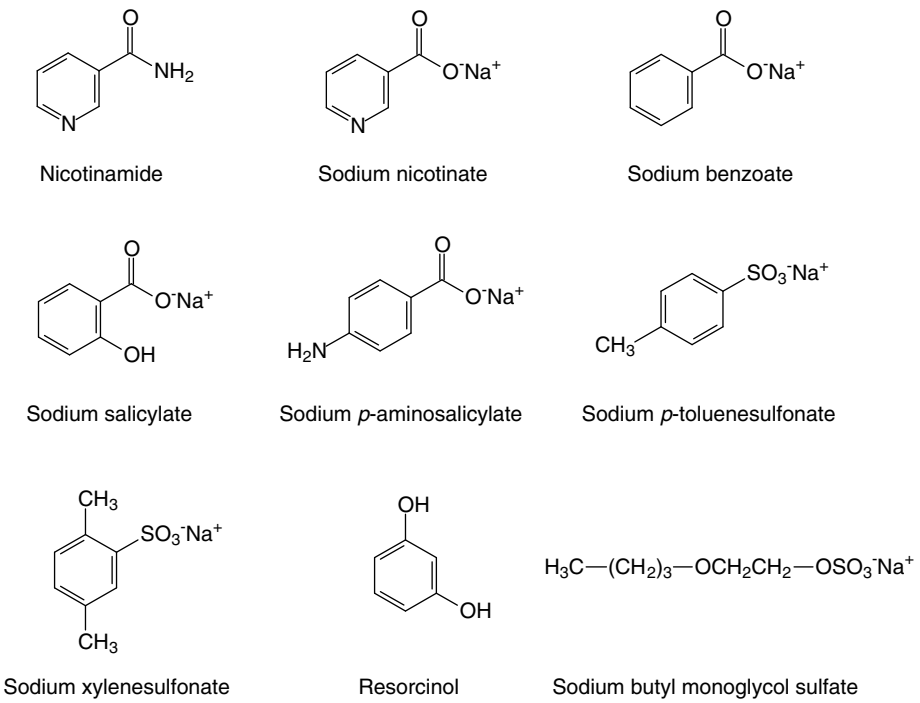


FIGURE 19.4 Chemical structures of hydrotropes used in the literature.

19.4.2 Hydrotropic Agents in Pharmaceutics

Delivery of poorly water-soluble drugs by oral route has been limited by poor absorption from the gastrointestinal tract (GI).[75] One of the governing factors in the transport of drugs across the intestinal barrier is the carrier-mediated efflux mechanism, which is referred to as multidrug resistance (MDR). This phenomenon is mediated by the increased expression of energy-dependent drug efflux proteins such as P-glycoproteins, multidrug-resistance-associated proteins, and lung-resistance proteins. Since the excretion of the absorbed drugs by this mechanism is the saturable process, the solubility enhancement of poorly water-soluble drugs might overcome the barrier. At high concentration of drugs, the efflux protein will be saturated, thereby resulting in the increase of the absorbed amount of drugs and bioavailability. The hydrotrope approach is a promising new method with great potential for poorly soluble drugs. Using hydrotropic agents is one of the easiest ways of increasing water-solubility of poorly soluble drugs because it only requires mixing the drugs with hydrotropes in water.[24,25] Hydrotropic agents are commonly used to enhance the water-solubility of poorly soluble drugs, and in many instances the water-solubility of these drugs is increased by orders of magnitude. The use of hydrotropic agents offers numerous benefits over other solubilization methods such as micellar solubilization, cosolvency, and salting-in.[74] To date, various hydrotropic agents have been utilized to enhance the aqueous solubility of many hydrophobic drugs including paclitaxel, ketoprofen, diazepam, allopurinol, indomethacin, and griseofulvin. In most cases, the high concentration of hydrotropes is key to increasing water solubility of poorly soluble drugs. Thus, the approach to increase the local concentration of hydrotropes may provide an opportunity to develop new hydrotrope-based solubilizing systems. Despite the advantages of hydrotropes, application of low molecular weight hydrotropes in drug delivery has not been practical because it may result in absorption of a significant amount of hydrotropes themselves into the body, along with the drug. Recently polymeric forms of hydrotropes, such as

hydrotropic polymers and hydrogels, were developed to overcome the drug formulations based on low molecular weight hydrotropes.[26] The polymeric hydrotropes were found to maintain the hydrotropic activity of its low molecular weight hydrotropes. Their solubilizing ability for paclitaxel was well examined, and the solubilization mechanism correlated with the assembly of polymeric hydrotropes. However, the low physical stability of drug formulations is also reported to limit the practical applications of these formulations.

19.4.3 Mechanistic Studies and Structure–Property Relationship of Hydrotropic Solubilization

The term hydrotropy does not mean a specific mechanism, but implies a collective solubilization phenomenon that is incompletely understood. There have been various theoretical and experimental studies aimed at explaining hydrotropic solubilization. Most of proposed mechanisms can be classified into following two schemes. The first one involves the complex formation between the hydrotrope and the solute. As a representative example, nicotinamide—a nontoxic vitamin B_3—has been shown to enhance the solubilities of a wide variety of hydrophobic drugs through complexation. Using nicotinamide and its derivatives, such as *N*-methylnicotinamide and *N,N*-diethylnicotinamide (DENA), Rasool et al. described the aromaticity of pyridine ring, which might promote the stacking of molecules through its planarity, as a most significant contributor in complexation, because the abilities of aromatic amide ligands to enhance the aqueous solubilities of tested drugs was higher than those of the aliphatic amide ligands.[76] The other mechanism for hydrotropic solubilization is self-association of the hydrotrope in an aqueous phase. This view is supported by experimental data, proving that some hydrotropes, including nicotinamide and aromatic sulfonates, associate in aqueous solutions. Using nicotinamide-riboflavin system, Kildsig et al. showed that the self-association of nicotinamide contributed to the solubility increase of riboflavin, rather than complexation between two species.[77]

Each hydrotropic agent is effective in increasing the water solubility of selected hydrophobic drugs, and no hydrotropic agents were found that are universally effective. Therefore, the structure–activity relationship between selected pairs of the hydrotropic agent and the drug is another important concern to discuss. Park et al. reported on the intensive studies of the elucidation of structure–activity relationship for the hydrotropic solubilization of paclitaxel using not only nicotinamide and its analogues as aromatic amides, but also various ureas as aliphatic amides.[25] They showed that nicotinamide enhanced the aqueous solubility of paclitaxel to a greater extent than the aliphatic analogues of nicotinamide such as nipecotamide and *N,N*-dimethylacetamide. In addition, the aqueous solubility of paclitaxel was found to be strongly dependent on the alkyl substituent on the amide nitrogen of nicotinamide. DENA of 3.5 M enhanced the aqueous solubility of paclitaxel up to 39.07 mg/mL, whereas *N,N*-dimethylnicotinamide showed paclitaxel solubility of 1.77 mg/mL at the same concentration. They synthesized new hydrotropic agents based on the structure of nicotinamide by varying the substituent to the amide nitrogen with a pyridine ring or an ally group. The aqueous solution of *N*-picolylnicotinamide (PNA) (3.5 M), having another pyridine ring as a substituent on the amide nitrogen, was highly effective in the enhancement of paclitaxel solubility (29.44 mg/mL), compared with the hydrotropic effect of nicotinamide on the paclitaxel (0.69 mg/mL). Besides, *N*-allylnicotinamide highly contributed to the enhancement of paclitaxel solubility (14.18 mg/mL) compared to that of *N,N*-dimethylnicotianmide (1.77 mg/mL). The most interesting find is that the threshold concentration where the association occurred is consistent with the threshold concentration where paclitaxel solubility began to increase.

19.4.4 Design Strategy of Hydrotropic Polymer Micelle Systems

Hydrotropic polymer micelles were firstly developed based on the self-assemblies of amphiphilic block copolymers containing the hydrophilic block, and the hydrophobic block containing pendent

hydrotropic moieties. The main strategy for hydrotropic systems is to maximize the local concentration of hydrotropic structure because the drug solubilizing capacity increases when increasing the local concentration of hydrotropes.[26] The hydrophobic block possesses hydrotropes assembled in the limited volume in micellar core region. Considering several hundreds of aggregation numbers of micelles, the local concentration of hydrotropes would be maximized as compared to other polymeric hydrotropes. In addition to the enhanced solubilizing ability for poorly soluble drugs, the intrinsic hydrophilicity of hydrotropic structure can retain the colloidal stability by compensation of enhanced hydrophobicity of drug-loaded polymer micelles. Using atom-transfer radical polymerization (ATRP) of modified hydrotropes, Park et al. started the synthesis of amphiphilic block copolymers consisting of PEG and poly(2-(4-(vinylbenzyloxyl)-*N*,*N*-diethylnicotinamide) (PDENA) or poly(2-(4-(vinylbenzyloxyl)-*N*-picolylnicotinamide) (P(2-VBOPNA)) as shown in Figure 19.5.[27]

PEG-*b*-PDENA copolymers associated to form polymeric micelles with the hydrotrope-rich core and the PEG outer shell in aqueous media. The mean hydrodynamic diameters were in the range of 30–100 nm. In these polymer systems, the solubilization of paclitaxel is based on a synergistic effect of the unique micelle characteristics and hydrotropic activity. Hydrotropic micelles demonstrated not only higher loading capacity (up to 37 wt% of paclitaxel) but also enhanced physical stability in aqueous media.[27] The enhanced stability is due to the intrinsic hydrophilicity of hydrotropic moieties in the micellar core. The drug loading into the hydrotropic polymeric micelle core is mainly based on the attractive interactions between the hydrotropic moiety and paclitaxel.

The structure of hydrotropic polymer micelles can be varied by introducing a diverse class of hydrotropic structures into the block copolymers through ATRP.[28,29,78–80] Table 19.3 lists some of the block and graft copolymers consisting of poly(ethylene glycol) (PEG) and the hydrotropic polymers that have been synthesized based on the molecular structures of identified hydrotropic agents for paclitaxel, such as DENA and PNA.

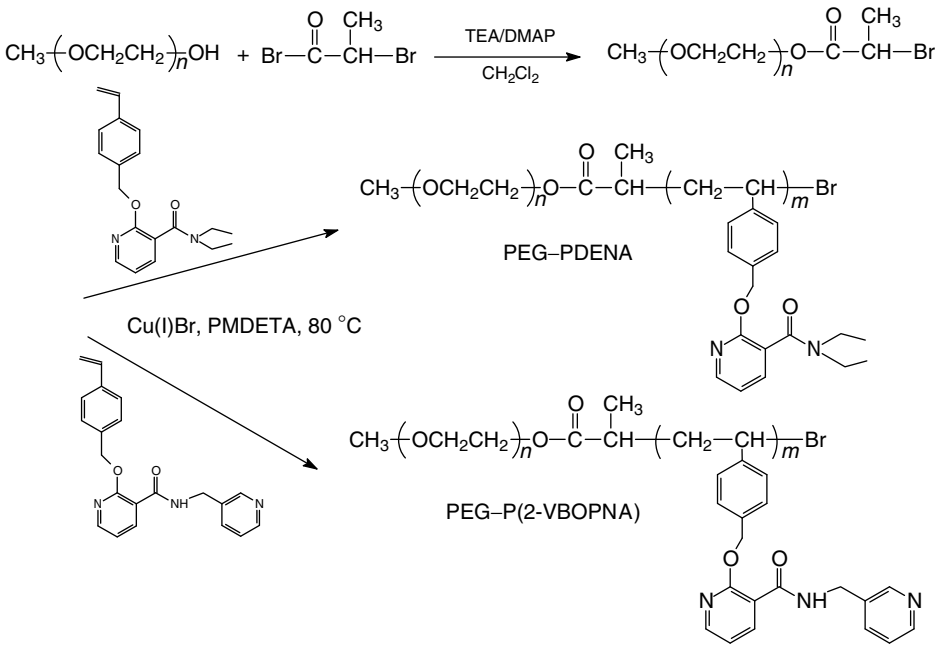


FIGURE 19.5 Synthetic routes for PEG–PDENA and PEG–P(2-VBOPNA) block copolymers.

The main components necessary for the synthesis of the block copolymers are PEG modified with bromine or chlorine, and the modified hydrotropic agent with polymerizable vinyl, acryl, and styryl groups. Table 19.4 lists the useful hydrotropic agents modified with double bond functionality. The relevant combination of monomers listed in Table 19.4 can lead to a diverse class of the copolymers capable of making the hydrotropic micelles.

In addition to the structural variation, a new property such as stimuli-responsibility can be endowed with the hydrotropic polymer micelles. One example is stimuli-responsive hydrotropic polymer micelles which were derived from PEG–P(2-VBOPNA) copolymers. In this system, PEG is freely water-soluble, independent of pH, whereas P(2-VBOPNA) is known to be soluble in water only when the hydrotropic PNA groups are protonated. P(2-VBOPNA) is soluble in low pH but loses its water-solubility above a critical pH (pH 2.5). Thus, the PEG–P(2-VBOPNA) copolymers, as expected, dissolved molecularly as unimers at low pH but become amphiphilic above pH 2.5. The combination of PEG and P(2-VBOPNA) in a block copolymer provides an opportunity to undergo pH-responsive micellization by controlling solution pH. Figure 19.6 shows pH-dependency of scattering intensity of PEG–P(2-VBOPNA) by dynamic light scattering.

As solution pH increases, scattering intensity increases abruptly above pH 2.0, accompanied by the formation of micelles around pH 3.0 of which sizes were about 35 nm. As pH of the aqueous solution of the block copolymers is increased from 2 to 3, the degree of protonation of PNA groups decreased, and thus the P(2-VBOPNA) block becomes progressively more hydrophobic, as expected. ^{1}H NMR analysis is also a good tool to confirm the pH-responsive micellization of PEG–P(2-VBOPNA) (Figure 19.7).

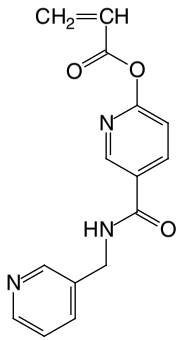
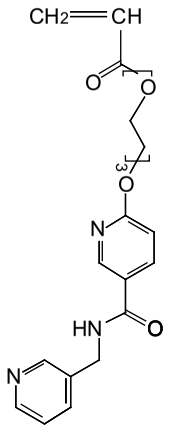
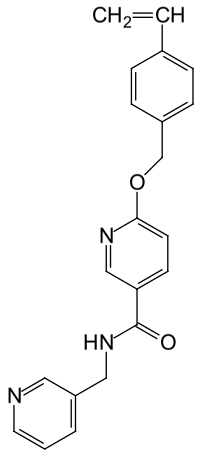
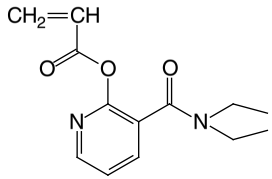
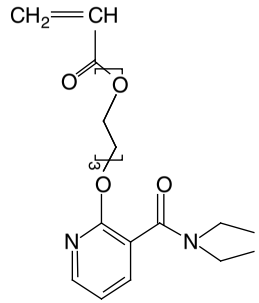
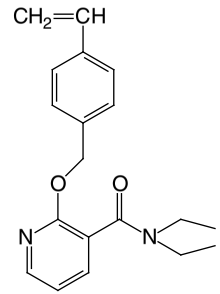
At pH 1, the block copolymers are fully solvated, and thus the signals assigned for the each block are clearly visible. On the other hand, at pH 7.4, the resonance peaks of P(2-VBOPNA) disappear while the signals from PEG are still evident, which indicates the poor solvation and/or limited molecular motion of P(2-VBOPNA) blocks. This result strongly supports the formation of micelles consisting of P(2-VBOPNA) as a hydrophobic inner core and PEG as a hydrated outer shell. Using this unique pH-sensitive micelle system, it may be suggested that PEG-*b*-P(2-VBOPNA) allows a unique drug-loading method into polymeric micelles, where drug molecules are initially solubilized exclusively by the interaction with hydrotropic P(2-VBOPNA) block at low pH, and then drugs are possibly encapsulated into inner core of micelles upon pH-responsive micellization. The use of hydrotropic block copolymers showing pH-responsive micellization does not need organic solvents during the drug loading process.

The ideal oral delivery systems for anti-cancer drugs need the two following physicochemical properties to maximize oral bioavailability of drugs: the fast drug release during the transit of GI, and the prolonged retention time in the GI tract. The former was known to be the characteristic of hydrotropic polymer micelles. Thus, if the design of hydrotropic polymer micelles showing mucoadhesion property is possible, the idealized delivery systems can be developed based on hydrotropic polymer micelles. The study on the degradation kinetics of paclitaxel in aqueous

TABLE 19.3
Exemplary Copolymers of PEG and Hydrotropic Polymers Synthesized from Modified Hydrotropic Agents

Poly(ethylene glycol)-*block*-poly(2-(4-vinylbenzyloxy)-*N,N*-diethylnicotinamide)
Poly(ethylene glycol)-*block*-poly(2-(4-vinylbenzyloxy)-*N*-picolylnicotinamide)
Poly(ethylene glycol)-*block*-poly(2-(4-vinylbenzyloxy)-nicotinamide)
Poly(oligoethylene glycol methacrylate-*co*-poly(2-(4-vinylbenzyloxy)-*N,N*-diethylnicotinamide)
Poly(oligoethylene glycol methacrylate-*co*-poly(2-(4-vinylbenzyloxy)-*N*-picolylnicotinamide)
Poly(oligoethylene glycol methacrylate-*co*-poly(2-(4-vinylbenzyloxy)-nicotinamide)

TABLE 19.4
Modified Hydrotropic Monomers That Can Be Used in the Synthesis of Hydrotropic Polymer Micelles

					
6-acryloyl-*N*-picolylnicotinamide	6-(2-(acryloyl) ethoxyethoxy-ethoxy)-*N*-picolylnicotinamide	6-(4-vinylbenzyl oxy)-*N*-picolyl nicotinamide	2-(2-(acryloyl) ethoxyethoxyethoxy)-*N*, *N*-diethylnicotinamide	2-(4-vinylbenzyloxy)-*N*, *N*-diethyl nicotinamide	2-acryloyl-*N*, *N*-diethylnicotinamide

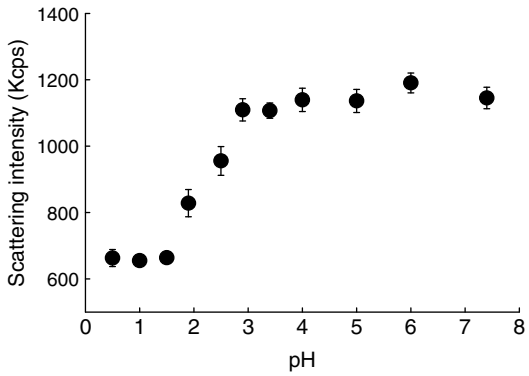


FIGURE 19.6 Variation of scattering intensity (●) as a function of pH for PEG_{5000}-P(2-VBOPNA)$_{2070}$ at 5 mg/mL ($n = 3$).

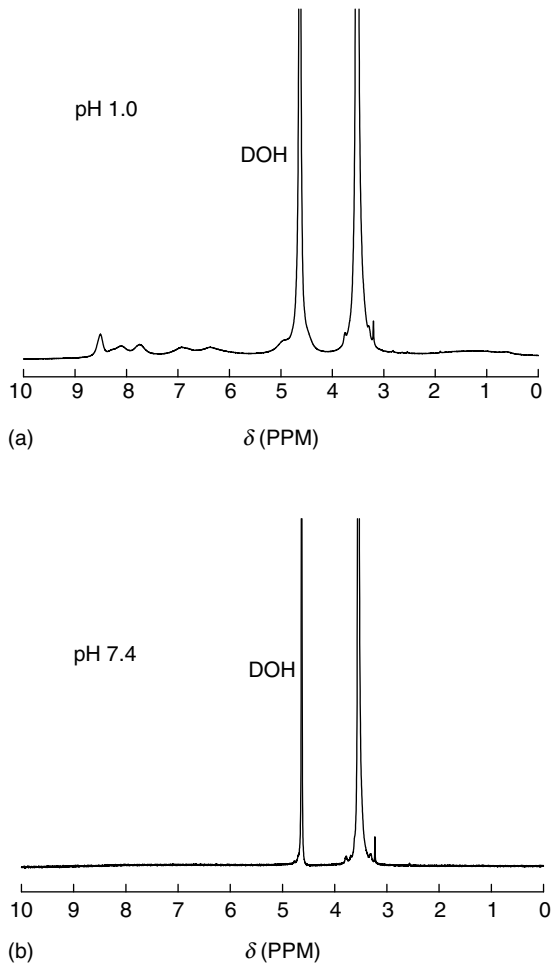


FIGURE 19.7 ^{1}H NMR spectra of PEG_{5000}-P(2-VBOPNA)$_{2070}$ at 20 mg/mL in D_2O: (a) pH 1.0; (b) pH 7.4.

solutions at different pH values shows that a maximum stability of paclitaxel occurred in the pH 3–5 region.[61] This provides a perfect opportunity to prepare mucoadhesive hydrotropic polymer micelle formulation for oral paclitaxel delivery. One of the best mucoadhesive polymers is poly(acrylic acid) (PAA), which is highly adhesion to biological mucosa at a pH lower than 5. PAA at neutral pH is highly charged and highly water-soluble, and can provide a hydrophilic segment of the block copolymers. Upon contact with the stomach's low pH, the polymer becomes highly mucoadhesive. Alternatively, PAA can be treated at pH 5 to provide the mucoadhesive property. Because of the highly hydrophilic properties of PAA, it can replace the PEO segment of the block copolymers. Thus, the design of the block copolymer consisting of PAA and the hydrotropic block may provide the useful oral formulations of poorly soluble anti-cancer agents.

19.4.5 Hydrotropic Polymer Micelles as Carriers for Anti-Cancer Drugs

Hydrotropic micelles were first examined for their ability to solubilize paclitaxel, a good example of an anti-cancer drug with extremely low water solubility.[27] Due to the high potential of paclitaxel, many formulations have been developed to increase water solubility. Although the polymeric micelles based on the amphiphilic block copolymers have shown high potential as drug solubilizing systems, most polymeric micelles have shown limited solubilizing capacity for paclitaxel, and, in most cases, maximum contents of paclitaxel loaded into micelles was around 20 wt%.[9,20,25] Besides, a simple polymer design may not predict whether the resulting polymer micelles show high solubilizing capacity. A more serious limitation is the poor stability of paclitaxel-solubilized polymeric micelles in water, which becomes lower as the content of paclitaxel increases.[20] Of the properties of solubilizing systems, a high solubilizing capacity and a good physical stability are the two most important factors in determining whether the drug delivery systems are clinically useful. The goal of using hydrotropic polymer micelles is to develop a hydrotropic polymeric micelle that has a high solubilizing capacity for poorly water-soluble drugs, as well as a good long-term stability. Because an identified hydrotrope for a specific drug is introduced as a core component in a highly localized way, paclitaxel solubilization may be presented by the synergistic effect of both hydrotropic and micellar solubilization. The poor colloidal stability of existing micelles is normally caused by the enhanced hydrophobicity of micelles after solubilization of paclitaxel. Hydrotropic moieties, characterized by a strong hydrophilic nature, are expected to allow good stability for paclitaxel-loaded micelles in water. Huh et al. described the superiority of the hydrotropic polymer micelles relative to current polymeric micelles, and how the hydrotropic polymer micelles are different from existing systems.[27] These questions can be answered by comparing their drug loading and physical stability. The loading capacity of the normal polymer micelles for poorly soluble drugs is decided by various factors, such as the length of the core-forming polymer, and compatibility between drugs and the core-forming polymers.[1] Of these factors, the compatibility is the most significant in determining the solubilizing capacity. One parameter that has been used to assess the compatibility between solubilizates and the polymer is Flory–Huggins interaction parameter as described in Section 19.2.4.[1] This value is dependent on both the selected drug and the polymer. Due to the uniqueness of each drug, no single core-forming block can maximize the solubilization level for all drugs. Therefore, the first priority is to find or synthesize the right structure for effective solubilization of selected drugs. However, the number of biocompatible polymers is limited, and an added difficulty of the synthesis step is the screening of a large number of the polymer structures for effective solubilization of the selected drug. On the other hand, the hydrotropic approach is simpler and less labor-intensive, even though a screening process is also required. Many hydrotropes can be identified for a selected drug by a simple mixing procedure, and the broad range of the chemical structure can be readily screened.[25] The key concept of the hydrotropic polymer micelles is based on the hydrotrope containing core-forming polymers. Thus, the systematic design affords more efficient systems for solubilizing poorly soluble

anti-cancer drugs. Another advantage of this approach is the enhanced physical stability of the formulations. This property is one measure that distinguishes hydrotropic polymer micelles from normal polymer micelles. Conventional polymer micelles have a polymer with a strong hydrophobic nature, specifically the drug solubilization has been expected only from the hydrophobic interaction between drugs and the inner core. Often, polymer micelles with drugs cannot overcome the enhanced hydrophobicity and the secondary aggregation between micelles, resulting in precipitation. From this point of view, the hydrotropic polymer micelles provide the formulations with good stability, even at a high loading of poorly soluble anti-cancer drugs, due to the hydrophilic nature of the hydrotropes residing in the micellar core domains. Of course, the same approach can be used for solubilization of other poorly soluble drugs. Huh et al. reported results on the solubilizing (loading) effect of the hydrotropic polymer micelle for paclitaxel by a dialysis method. The results are illustrated in Figure 19.8.

The hydrotropic polymeric micelles solubilized paclitaxel at a level of 18.4–37.4 wt%, depending on the organic solvents used in the dialysis and the initial feed weight ratio of paclitaxel to the block copolymer. The loading content normally increases to certain feed-weight ratios of paclitaxel to the block copolymer. However, as the amount of paclitaxel was further increased, precipitates of unloaded paclitaxel formed during dialysis, resulting in the decreased loading contents. The maximum loading was observed with initial feed weight ratio of 1:0.5. When acetonitrile and the feed weight ratio of 1:0.5 were used the loading content was as high as 37.4 wt%, which was not possible with existing polymeric micelle systems. The maximum loading content of paclitaxel in a control micelle of PEG_{2000}–$PDLLA_{2000}$ was estimated to be 27.6 wt%, which is close to the literature value. Loading capacity of PEG–PDENA micelles for paclitaxel was enhanced by increasing the block length of PDENA.

Poor physical stability of drug-loaded micelles, which causes serious problems in drug formulation, has been often addressed. There is often a compromise between loading content and stability in polymeric micelle systems. Drug-loaded micelles may break up more easily in aqueous media, resulting in drug precipitation. The physical stability of polymer micelles was investigated by several methods and compared. PEG–PLA micelles that have been extensively used to solubilize paclitaxel demonstrated a high loading capacity, but showed drug precipitation after 24 h. The initial transparent micelle solution became translucent, or turbid, after 24 h. Similar results have been reported in the literature.[20,21,25] On the other hand, PEG–PDENA micelle solutions were observed to be stable for several weeks without drug precipitation at the same or higher loading contents of paclitaxel.

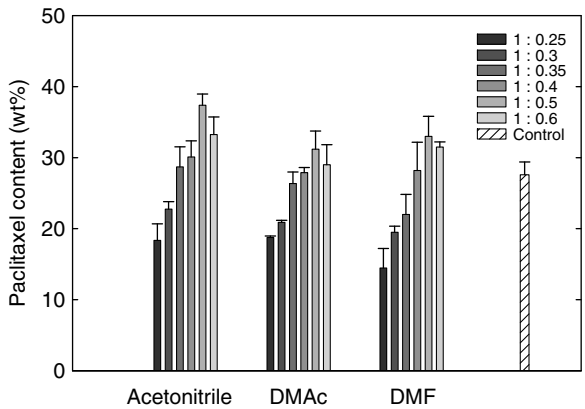


FIGURE 19.8 Paclitaxel lading contents in hydrotropic polymer micelles and comparison with PEG_{2000}–$PDLLA_{2000}$ micelles.

The loading content of paclitaxel in polymer micelles was reported as a function of time. As shown in Figure 19.9, the paclitaxel content in PEG–PDENA micelles was maintained for more than 30 days.[27]

In contrast, the PEG–PLA micelle showed a dramatic decrease in paclitaxel content after three days, which resulted from drug precipitation. The stability of drug-loaded PEG–PDENA micelles was further confirmed by observing no change in micelle size and scattering intensity using dynamic light-scattering measurements.

The paclitaxel release profiles of PEG–PDENA and PEG–PLA micelles were compared as shown in Figure 19.10.[27]

For PEG–PDENA micelles, the micelles of 25.9 wt% loading released the most drug within 48 h, whereas the micelles of 31.3 wt% drug loading showed a much faster drug release that was complete within 24 h. It was found that the faster release was from the micelles with higher drug loading. The micelles with higher drug loading lead to a relatively lower polymer concentration. Thus, there is less polymer–drug interaction in the micelles, thereby resulting in faster release kinetics. The in vitro release data showed that paclitaxel was released faster from the hydrotropic polymer micelles than from PEG to PLA micelles. The PEG–PLA micelles required almost 72 h to release all the loaded paclitaxel. As indicated by the higher CMC values of PEG–PDENA micelles, the hydrotropic polymeric micelles have less hydrophobic cores that may release the loaded paclitaxel faster than more hydrophobic PLA cores. On the other hand, the release from paclitaxel bulk powder was negligible, even after 74 h. (Figure 19.10).

The cytotoxicity of anti-cancer agents loaded in polymer micelle formulations is one measure for determining whether the formulation is effective in delivering the drugs into the tumor cells. The anti-tumor cytotoxicities of hydrotropic polymeric micelles and other control micelle systems on various cell lines, as measured by ED_{50}, are shown in Table 19.5. The resulting cytotoxicity of hydrotropic polymer micelles and control micelles clearly show the superior cytotoxic properties of hydrotropic micelles. The ED_{50} values of hydrotropic micelles are much lower than PEG–PLA and PEG–PPA micelles. The most widely used polymeric micelles is PEG–PLA micelles, with the maximum paclitaxel loading capacity of 24 wt%. Although the hydrotropic polymer micelles have higher paclitaxel, loading up to 37 wt%, hydrotropic polymer micelles with only 20 and 25 wt% paclitaxel loading were used to compare their efficacy with that of PEG–PLA micelles. At equivalent paclitaxel loading, i.e., 25 wt% loading, hydrotropic polymer micelles were

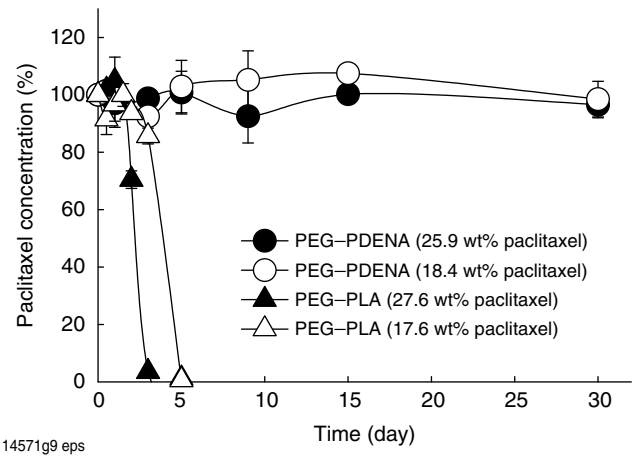


FIGURE 19.9 Changes in paclitaxel concentration of polymer micelles in distilled water. (From Huh, K.M., Lee, S.C., Cho, Y.W., Lee, J., Jeong, J.H., and Park, K., *Journal of Controlled Release*, 101, 59–68, 2005. With permission.)

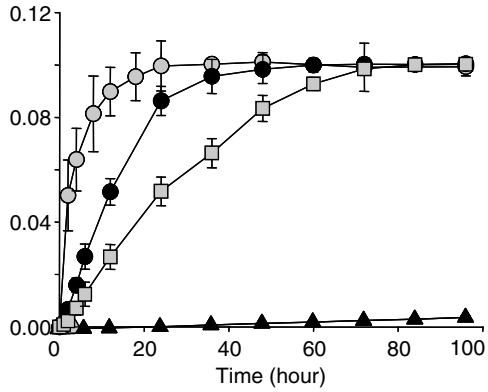


FIGURE 19.10 Release kinetics from polymer micelles and paclitaxel powders in 0.8 M sodium salicylate at 37°C. The total amount of loaded paclitaxel was 0.1 mg. (From Huh, K. M., Lee, S. C., Cho, Y. W., Lee, J., Jeong and Park, K., *Journal of Controlled Release*, 101, 59–68, 2005. With permission.)

substantially more effective. In the case of the MDA231 cell line, hydrotropic polymer micelles were more than two orders of magnitude more effective. The data clearly indicate that hydrotropic polymer micelles are not only more stable in aqueous solution, but also more effective for paclitaxel delivery to the cells.

As mentioned in Section 19.4.2, the enhanced drug solubility can improve oral bioavailability of drugs by suppressing the MDR effect. The excellent solubilizing ability of hydrotropic polymer micelles for poorly soluble drugs can overcome this barrier, thereby enhancing drug absorption in the GI tract. As a preliminary study, PEG–PDENA micelles were examined for the bioavailability of loaded paclitaxel using an in vivo, chronically-catheterized rat model. Our initial study showed that oral delivery of paclitaxel using PEG–PDENA micelles could result in the blood paclitaxel

TABLE 19.5
ED_{50} (μg/mL) of Paclitaxel and Paclitaxel (PTX)-Loaded Polymeric Micelles on Various Tumor Cell Lines

	Cancer Cell Lines			
Samples[a]	**HT-29**	**MDA231**	**MCF-7**	**SKOV-3**
Doxorubicin (positive control)	0.044	0.050	0.773	0.611
Paclitaxel	0.003	0.033	0.043	0.006
PTX-loaded HTM (25 wt% loading)	0.005	0.002	0.002	0.001
PTX-loaded HTM (20 wt% loading)	0.006	0.004	< 0.001	0.008
PTX-loaded PLA-PEG (24 wt% loading)	0.014	0.305	< 0.001	0.015
PTX-loaded PEG–PPA	0.012	1.077	0.002	1.543
HTM alone	4.221	5.650	5.767	0.048
PEG–PLA alone	4.672	8.435	5.533	—
PEG–PPA alone	0.277	4.881	6.194	—

[a] PTX, paclitaxel; HTM, hydrotropic micelle; PLA, poly(lactic acid); PEG, poly(ethylene glycol); PPA, poly(phenylalanine).

concentrations that are clinically significant. To increase oral bioavailability, hydrotropic polymer micelles with other interesting functions can be developed. The systematic design of hydrotropic polymer micelles for its faster drug releasing properties, as well as the prolonged retention during through the GI tract, can provide an opportunity to develop ideal oral delivery systems for poorly soluble anti-cancer drugs.

19.5 CONCLUSIONS AND FUTURE PERSPECTIVES

Hydrotropic polymer micelle formulation presents an alternative and promising approach in formulation of poorly soluble drugs. Based on synergistic effect of the micellar characteristics and hydrotropic activity, the hydrotropic polymer micelles exhibit a high drug loading capacity with enhanced long-term stability in aqueous media. These unique properties make it highly attractive for applications of controlled delivery of poorly soluble anti-cancer drugs. The hydrotropic polymer micelles can be applied to many poorly soluble drugs and drug candidates by introducing the identified hydrotropic structures for specific drug molecules. The hydrotropic polymer micelle is in the early stages of the development, but due to its unique properties, the systematic design may generate effective oral formulations applicable to many poorly soluble anti-cancer agents. The high versatility of the hydrotropic polymer micelle in creating a broad range of drug formulations gives it the potential for a broad range of formulations in pharmaceutical and biomedical applications.

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