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Hydrotropic polymer micelle system for delivery of paclitaxel

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Abstract

Hydrotropic polymer micelle system has been developed for delivery of poorly water-soluble drugs such as paclitaxel. Hydrotropic polymers based on *N*,*N*-diethylnicotinamide were synthesized and used as a hydrophobic block for constructing amphiphilic block copolymers. The hydrotropic block copolymers self-assembled to form micelles in aqueous media. The size of the prepared polymer micelles was in the range of 30–50 nm, and increased to 100–120 nm after paclitaxel loading. The critical micelle concentrations (CMCs) of the block copolymers were higher by an order of magnitude than those of other typical polymer micelles, due to less hydrophobicity of the hydrotropic blocks. The drug loading capacity and physical stability of the polymer micelles were characterized and compared with those of other polymer micelles. The hydrotropic polymer micelles containing hydrotrope-rich cores showed not only higher loading capacity but also enhanced physical stability in aqueous media. They could be redissolved in aqueous media by simple vortexing and/or a mild heating. The hydrotropic polymer micelles provide an alternative approach for formulation of poorly soluble drugs.

Keywords: Hydrotropic polymer; Polymer micelle; Paclitaxel; Solubilization; Poorly soluble drugs; Stability

1. Introduction

Delivery of poorly water-soluble drugs with clinically useful bioavailability is one of the most important problems in formulation [1,2]. For example, paclitaxel is an anticancer agent effective against a wide range of tumors, but its clinical applications have been hindered by its extremely low solubility (<1 μg/ml) [3]. The current formulation contains Cremophor EL, which can cause severe side effects. Several methods have been developed to increase the water-solubility of poorly soluble drugs, but with limited successes.

Recently, polymer micelles have attracted increased attention as a promising vehicle for poorly soluble

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drugs [4,5]. Polymer micelles are self-assemblies of amphiphilic block copolymers in aqueous media, Many advantages of using polymer micelles have been demonstrated with their unique core-shell architecture. The hydrophobic cores are segregated by hydrophilic shells from the aqueous exterior. Hydrophobic drugs can be solubilized into the hydrophobic core structures of polymer micelles at concentrations much higher than their intrinsic water-solubility. Polymer micelles are known to have high drug loading capacity, high water-solubility, and appropriate size for long circulation in blood [6,7]. The hydrophilic shell surrounding the micellar core can protect undesirable phenomena, such as inter-micellar aggregation or precipitation, protein adsorption, and cell adhesion. The chemical composition of polymer micelles can be tailor-made to have desirable physico-chemical properties for drug solubilization. In most polymer micelles, hydrophobic drugs are incorporated into the hydrophobic core of micelles by hydrophobic interaction as well as other additional interactions such as metal-ligand coordination bonding [8,9] and electrostatic interaction [10]. The extent of drug solubility depends on the compatibility between the drug and the micelle core [11]. One of the limitations of drug-loaded polymer micelles is low stability in aqueous solution, and the stability becomes even lower as the drug loading content increases [12].

In this study, we have explored new polymer micelle systems to overcome some of the limitations of currently available polymer micelles, namely maintaining long-term stability of polymer micelles with high drug loading. In our previous studies, a large number of hydrotropic agents were screened and identified for their abilities to increase water-solubility of paclitaxel [13]. Nicotinamide derivatives were found to increase the water-solubility of paclitaxel by several orders of magnitude. It was also found that low molecular weight hydrotropic agents maintained their hydrotropic property in their polymeric structures (hydrotropic polymers) [14]. In our new polymer micelle systems a new hydrotropic polymer, poly(2-(4-vinylbenzyloxy)-*N*,*N*-diethylnicotinamide) (PDENA), was used as a building-block for constructing amphiphilic block copolymers that can form micelles in aqueous media. Poly(ethylene glycol) (PEG) was chosen as a hydrophilic block for its well-known biocompatibility and unique aqueous properties. Other polymer micelle systems, such as poly(D,L-lactide)-PEG (PLA-PEG) and poly(phenylalanine)-PEG (PPA-PEG) micelles, were also synthesized and used as controls. PLA-PEG micelles have been frequently used in the literature [15,16]. Hydrophobic aromatic side-groups of PPA were expected to interact strongly with the aromatic entities of paclitaxel.

This study involves synthesis of a series of new amphiphilic block copolymers, characterization of their micelles, comparative evaluation of drug loading capacity and physical stability, and in vitro release studies from the polymer micelles.

2. Materials and methods

2.1. Materials

Paclitaxel was supplied by Samyang Genex (Taejeon, South Korea). Monomethoxy PEGs (Mn=5000 and 2000 g/mol) were purchased from Sigma (St. Louis, MO) and used after drying in vacuo for 24 h. 2-Bromopropionyl bromide (BPB) was purchased from Aldrich (Milwaukee, WI) and freshly distilled under vacuum before use. α-Methoxy-ω-aminopoly(ethylene glycol) (Mn=5000 g/mol, 98%) was purchased from Nektar Therapeutics (San Carlos, CA). D,L-Lactide (Polysciences) was purified by recrystallization in ethyl acetate. Copper(I) bromide (99.99%), *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA), 4-vinylbenxyl chloride, triethylamine (TEA), pyrene, bis (trichloromethyl) carbonate (triphosgene), L-phenylalanine, and sodium salicylate were purchased from Aldrich and used without further purification. All solvents used for synthesis were dried or distilled before use. The other chemicals were used without further purification.

2.2. Synthesis of PDENA-PEG diblock copolymers

Monomethoxy PEG (10 g, 2 mmol) and TEA (1.42 g, 14 mmol) were placed into a two-neck round flask and dissolved in 50 ml of dry methylene chloride. After cooling to 0 °C, BPB (3.02 g, 14 mmol) in 10 ml of methylene chloride was added dropwise with gentle stirring. The reaction mixture was kept at room temperature

under N_2 for 24 h and then precipitated in cold diethyl ether. The resultant PEG macroinitiator, PEG-Br, was purified by repeated recrystallization and dried in vacuo.

DENA monomer, 2-(4-(vinylbenzyloxyl)-*N*,*N*-diethylnicotinamide), was synthesized by reacting 2-hydroxy-*N*,*N*-diethylnicotinamide (HDENA) with 4-vinylbenzyl chloride in dry acetone at 70 °C. The final product was filtered and isolated by column chromatography with THF/*n*-hexane on a silica gel, followed by recrystallization from THF/*n*-hexane. PDENA-PEG block copolymers were obtained by atom transfer radical polymerization of DENA monomers using PEG-Br. DENA monomer (0.366 g, 1.2 mmol), Cu(I)Br (0.046 g, 0.32 mmol), and PEG-Br (0.4 g, 0.08 mmol) were added to a round-bottom flask. The reaction mixture was evacuated and refilled with dry nitrogen. Toluene (1.5 ml) and PMDETA (0.054 g, 0.32 mmol) were added to the flask. After repeating evacuation and N_2 purging three times, the flask was evacuated and kept at 85 °C with vigorous stirring for 3 h. The final product was diluted with methylene chloride and passed through a silica gel column to remove the copper catalyst. The resultant solution was precipitated in cold diethyl ether.

2.3. Synthesis of PPA-PEG diblock copolymers

N-Carboxyanhydride of L-phenylalanine (Phe-NCA) was synthesized according to the Fuchs-Farthing method using triphosgene [17]. α-Methoxy-ω-aminopoly(ethylene glycol) (1.0 g) was dissolved in 10 ml of DMF. Then a solution of Phe-NCA (0.35 g) in 4 ml of DMF was added to the solution with N_2 purging. The reaction mixture was kept at 40 °C under a dry nitrogen atmosphere for 24 h and then precipitated with an excess of diethyl ether. The resultant PPA-PEG diblock copolymer was recrystallized from chloroform/diethyl ether.

2.4. Synthesis of PLA-PEG diblock copolymers

PLA-PEG diblock copolymers were synthesized by ring opening polymerization of D,L-lactide in the presence of monomethoxy PEG (Mn=5000 or 2000 g/mol) as a macroinitiator and stannous octoate as a catalyst [12].

2.5. Characterization

^1H and ^{13}C NMR spectra were obtained on a Bruker ARX300 spectrometer (Billerica, MA) at 300 and 75 MHz, respectively. Molecular weights and molecular weight distributions were determined using a GPC equipped with an Agilent 1100 series RI detector, quaternary pump, and three PLgel 5 um MIXED-D columns in set, and calculated with polystyrene standards. The eluent was DMF containing Bu_4NBr (0.1% w/v) with a flow rate of 0.8 ml/min.

Fluorescence measurements were performed to determine CMCs of polymer micelles. Fluorescence spectra were recorded on a Spex FluoroMax-2 spectrofluorometer at room temperature using pyrene as a fluorescence probe. Dynamic light scattering was used to measure the hydrodynamic diameters of micelles using a PhotoCor Complex photon correlation spectrometer.

2.6. Paclitaxel loading into polymer micelles

Paclitaxel-loaded polymer micelles were prepared by a dialysis method. Each block copolymer was dissolved in 2 ml of acetonitrile and a predetermined amount of paclitaxel was added to the polymer solution. The polymer-drug mixture solution was stirred for 6 h and then dialyzed against distilled water (MWCO=2000), followed by lyophilization. For PPA-PEG and PLA-PEG micelles, a solid dispersion technique was used to load paclitaxel. Paclitaxel (30 mg) and each block copolymer (270 mg) were dissolved in 4 ml of acetonitrile. After 30 min of stirring, acetonitrile was evaporated under reduced pressure at 60 °C to obtain a transparent gel-like matrix. Preheated water (100 ml) was added with gentle stirring. The resultant polymer micelle solution was filtered through a 1.0-μm filter and freeze-dried.

The amount of paclitaxel loaded inside micelles was determined by HPLC analysis. Isocratic reverse-phase HPLC was performed on an Agilent 1100 series HPLC system (Agilent Technologies, Wilmington, DE) using a Symmetry column (Waters, Milford, MA) at 25 °C. The mobile phase consisted of acetonitrile-water (45:55 v/v) with a flow rate of 1.0 ml/min. A diode array detector was set at 227 nm and linked to Chem-Station software for data analysis.

2.7. Paclitaxel releases from polymer micelles

To study the release of paclitaxel from polymer micelles using only a small quantity of a release medium, a sodium salicylate solution was used as a sink medium for the released paclitaxel. The stability of polymer micelles in the hydrotropic medium was investigated. Freeze-dried micelles were suspended in distilled water (0.5 mg/ml) under gentle shaking, followed by sonication for 10 min to give optically clear solution. The sodium salicylate solutions of different concentration were obtained by dilution of 3.0 M stock solution with distilled water. The concentration of polymer micelles was fixed to 0.1 mg/ml. The change in micelle size was observed by dynamic light scattering measurements.

Release of paclitaxel from polymer micelles was examined using a 0.8 M sodium salicylate solution. The total amount of loaded paclitaxel in polymer micelle solution was 0.1 mg/ml. The polymer micelle was introduced into a dialysis membrane bag (MWCO=6000–8000), and the whole bag was placed in 40 ml of 0.8 M sodium salicylate solution (37 °C) for release experiments. Sampling was done from the media outside the dialysis bag at predetermined time intervals. The paclitaxel concentrations of the samples were determined by HPLC analysis.

3. Results and discussion

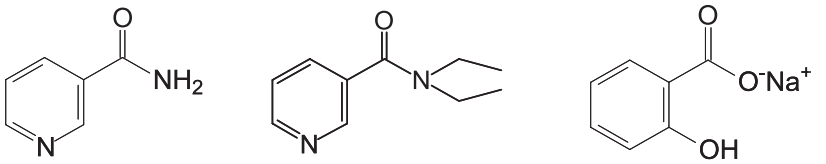
3.1. Hydrotropic agents for solubilization of paclitaxel

Hydrotropic agents (hydrotropes) have been often used to increase water-solubility of poorly soluble drugs in the pharmaceutical and biomedical fields [18]. Hydrotropic agents are attractive due to their ability to enhance water-solubility of poorly soluble drugs by orders of magnitude. Moreover, the use of hydrotropic agents has several advantages over other solubilization methods, such as high structural selectivity to drugs, no need for emulsification, and no use of organic solvents. A systematic study on the relationship between hydrotropic activity and structure was performed by screening more than 60 candidate hydrotropic agents for their ability to increase the aqueous solubility of paclitaxel [13]. Several hydrotropic agents were found to be effective for paclitaxel solubilization. Fig. 1 shows the chemical structures of the identified hydrotropic agents. Nicotinamide analogues and sodium salicylate exhibited excellent solubilizing capacity for paclitaxel.

DENA is one of the best hydrotropic agents for paclitaxel. The solubility increase as a function of DENA concentration is shown in Fig. 2. The aqueous paclitaxel solubility was observed to be 39 and 512 mg/ml at the DENA concentration of 3.5 and 5.95 M, respectively. These values are five to six orders of magnitude increase in the aqueous solubility over the intrinsic solubility of paclitaxel (0.3 μg/ml). There have been several methods to improve the water-solubility of poorly soluble drugs, but the increase does not exceed 5–10 folds at best. No currently known methods can be compared with hydrotropic agents in its effectiveness. Using hydrotropic agents for solubilization is a promising approach for increasing drug solubility and thus bioavailability.

3.2. Synthesis of hydrotropic amphiphilic block polymers

Hydrotropic agents were highly effective for increasing water-solubility of poorly soluble drugs, but their applications have been limited due to their low molecular weight nature. The problems of



(a) Nicotinamide (Vitamin B_3) (b) *N,N*-Diethylnicotinamide (c) Sodium salicylate

Fig. 1. Chemical structures of hydrotropic agents for paclitaxel.

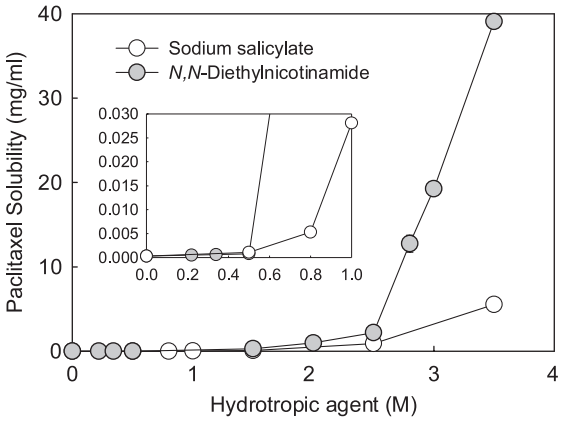


Fig. 2. Solubility increase of paclitaxel in the presence of *N*,*N*-diethylnicotinamide and sodium salicylate.

undesirable coabsorption of a large amount of hydrotropic agents into the body along with the drug and the subsequent side effects cannot be ignored. For this reason, hydrotropic agents were modified to form polymeric structures (hydrotropic polymers) [14]. It was demonstrated that hydrotropic agents could maintain their hydrotropic property even in the polymeric structures. An interesting observation was that hydrotropic polymers showed higher solubilizing capacity than their corresponding low molecular weight entities at low concentrations. This may be due to the high local concentration of hydrotropic moieties in polymeric structures.

In this study, a hydrotropic polymer was investigated as a hydrophobic building block of a polymer micelle system. Various types of PEG-based amphiphilic block copolymers having different hydrophobic block species were synthesized and tested for their ability to solubilize paclitaxel. Fig. 3 shows the chemical structures of the block copolymers used for micelle formation. Synthetic results and micellar properties of block copolymers are summarized in Table 1.

PDENA-PEG block copolymers were obtained by atom transfer radical polymerization (ATRP) of DENA monomers using a macroinitiator PEG-Br. The length of hydrotropic polymer block was controlled by varying the initial feed ratio of DENA monomer and PEG-Br. The calculated molecular weights of synthesized block copolymers corresponded well with theoretical values, and low polydispersities were obtained, indicating no side reaction. The polymers were highly water-soluble and observed to form micelles. The other block copolymers were successfully synthesized to have comparable properties. In the case of PPA-PEG block copolymer, the relatively shorter hydrophobic block was used because longer PPA blocks led to water-insoluble polymers due to highly hydrophobic nature of PPA.

3.3. Micellar characterization

Hydrotropic amphiphilic block copolymers self-assembled to form micellar structures in aqueous media (Fig. 4). The micelle size measured by dynamic light scattering was in the range of 30–50 nm and showed narrow size distribution (polydispersity factor <0.15). The size increased as the hydrophobic block

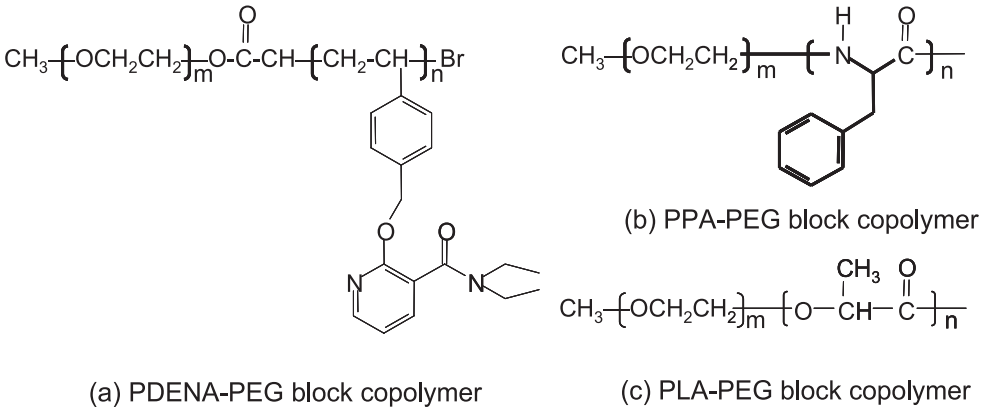


Fig. 3. Chemical structures of amphiphilic block copolymers.

Table 1
Properties of hydrotropic polymer micelles

Block copolymer	Block length[a] (g/mol)	MwMn[b]	Micelle size[c] (nm)	CMC[d] (mg/ml)	Max. paclitaxel loading[e] (wt.%)
PDENA-PEG	2790/5000	1.11	35.2	0.0700	–
PDENA-PEG	4350/5000	1.12	39.9	0.0360	37.4
PPA-PEG	1130/5000	–	55.1	0.0025	14.7
PLA-PEG	2030/2000	1.11	93.0	0.0038	27.6

[a] Calculated from the peak integration of ^{1}H NMR spectra.
[b] Molecular weight distribution obtained by GPC measurements.
[c] Measured by dynamic light scattering.
[d] Critical micelle concentration determined by fluorescence measurements.
[e] Maximum paclitaxel loading content determined by HPLC measurements.

length became longer. Also, the size increased to 100–120 nm with no significant change in size distribution when paclitaxel was loaded. The CMC values of PDENA-PEG micelles measured by a fluorescence technique using pyrene as a probe were 0.036 and 0.070 mg/ml for the micelles with hydrophobic block lengths (number average molecular weight) of 4350 and 2790 g/mol, respectively. The CMC values of hydrotropic polymer micelles were higher by one order of magnitude than those of other polymer micelles (for examples, 0.0038 mg/ml for PLA-PEG micelle and 0.0025 mg/ml for PPA-PEG micelle). This is presumably attributed to less hydrophobic nature of PDENA than PPA or PLA. Although PPA-PEG had the shortest hydrophobic block length of those tested in this study, it showed the lowest CMC value due to the most hydrophobic nature of PPA block.

3.4. Drug loading capacity of polymer micelles

The drug loading capacity of the polymer micelles was examined using paclitaxel. Paclitaxel was loaded into hydrotropic polymer micelles by a dialysis method. For PPA-PEG and PLA-PEG micelles, the effective paclitaxel loading could be achieved using a solid dispersion technique, because application of the dialysis method to those micelles led to a significant precipitation of the drug and polymers, giving micelles with low yield and low loading level. The loading experiments were performed by varying the feed weight ratio of drug to polymer to determine the maximum loading capacity for each polymer. The maximum loading content of paclitaxel in each polymer micelle system was listed in Table 1. For hydrotropic micelles, the polymer with longer PDENA block showed higher loading capacity (data not shown), and thus it was used for further experiments. The maximum loading content of PDENA-PEG micelles was 37.4 wt.%, and such a high loading has never been achieved by other polymer micelles. PLA-PEG block copolymer was found to have a maximum loading content of 27.6 wt.% that is slightly higher than the value reported in the literature (25 wt.%) [12,19]. The maximum loading content of PPA-PEG micelle remained at the level of 14.7 wt.% although aromatic side groups of the polymer were expected to contribute to enhance the solubility of paclitaxel. All polymer micelles showed high drug loading efficiency (>90%) if the drug content is below 30 wt.%. Usually, the lower drug loading efficiency was observed with the higher drug composition in feeds.

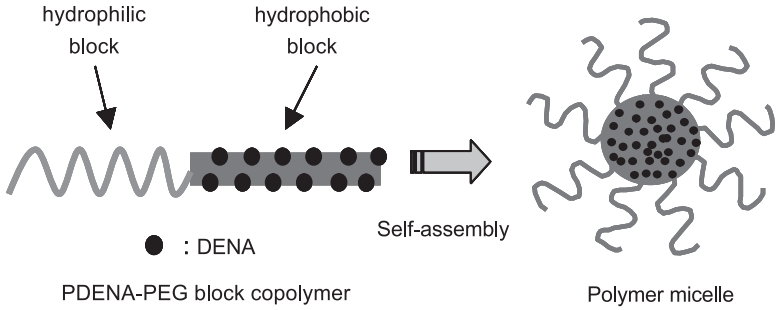


Fig. 4. Self-assembly of hydrotropic block copolymer into micelle structure.

3.5. Stability of drug-loaded micelles

The current polymer micelles have poor physical stability after drug loading. In general, the stability of polymer micelle systems decreases as the drug loading content increases. It is because that a hydrophilic and hydrophobic balance that is critical for micellar stability may be lost with the introduction of hydrophobic drugs. The loading content of paclitaxel in polymer micelles was observed as a function of time to examine the stability of the drug-loaded micelles. PLA-PEG micelles that have been extensively used in the literature to solubilize paclitaxel were used as a control in this study. As shown in Fig. 5, PLA-PEG micelles did not have a long-term stability. The initial transparent micelle solution became translucent or turbid after 24 h, and the paclitaxel dissolved in the solution became almost zero after 3 days. Drug-loaded PLA-PEG polymer micelles broke up to result in drug precipitation. The similar results have been reported in the literature [12,19], where PLA-PEG micelles maintained their stability after paclitaxel loading only for a day or so. The results in Fig. 5 show that the paclitaxel content in PDENA-PEG micelles was maintained for more than 30 days. The stability study is on-going for more than a few months and PDENA-PEG micelle solutions maintain their stability without drug precipitation at the same or even higher loading contents of paclitaxel than in the PLA-PEG micelles. The good stability of drug-loaded PDENA-PEG micelles was also confirmed by dynamic light scattering measurements. There have been no changes in micelle size and scattering intensity of the PDENA-PEG micelles.

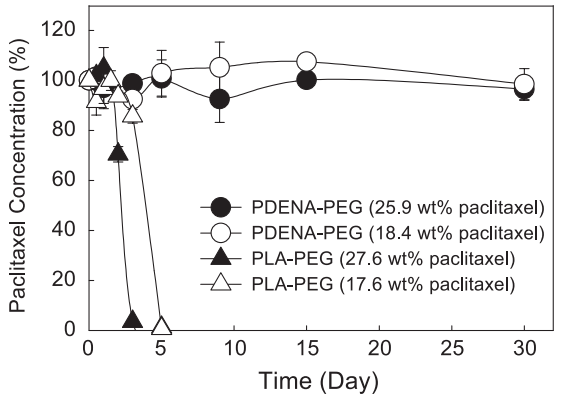


Fig. 5. Changes in paclitaxel concentration of polymer micelles in distilled water.

Consequently, the poor physical stability of paclitaxel-loaded micelles was overcome by introducing hydrotropic property into the core structure of the polymer micelle. PLA-PEG micelles demonstrated a high loading capacity, but with low stability, showing drug precipitation after 24 h. PPA-PEG block copolymers were able to form stable micelles with the drug but its loading capacity was not high as other polymer micelles. The hydrotropic polymer micelles showed an excellent loading capacity with enhanced long-term stability. Such combined properties of high loading capacity and high stability in water have not been reported in the literature so far. These unique properties may be ascribed to hydrotropic effect of DENA, which comprises a significant portion (57 wt.%) of the hydrophobic core. In polymer micelles the hydrotrope-rich hydrophobic core may allow a higher loading capacity and a higher colloidal stability for longer period of time. Such a long-term stability in aqueous media may allow preparation of liquid formulations that are ready to be used without freeze-drying and subsequent reconstitution.

It is often the case that freeze-dried polymer micelles do not redissolve in aqueous media to recover their micellar structure. For this reason, lyoprotectants such as trehalose are frequently added before freeze-drying [20]. It was observed that freeze-dried PDENA-PEG micelles could be easily redissolved in aqueous media by applying a simple vortexing process with or without a mild heating at 60 °C for 1 min. In the redissolution of freeze dried, paclitaxel-loaded PDENA-PEG micelles, no difficulty was observed if the paclitaxel loading content was less than 30%. When the paclitaxel loading content was higher than 30%, the freeze-dried micelles could not be completely redissolved to produce translucent solutions.

3.6. In vitro release system for paclitaxel-loaded polymer micelles

It is difficult to conduct release experiments from polymer micelles for poorly soluble drugs due to

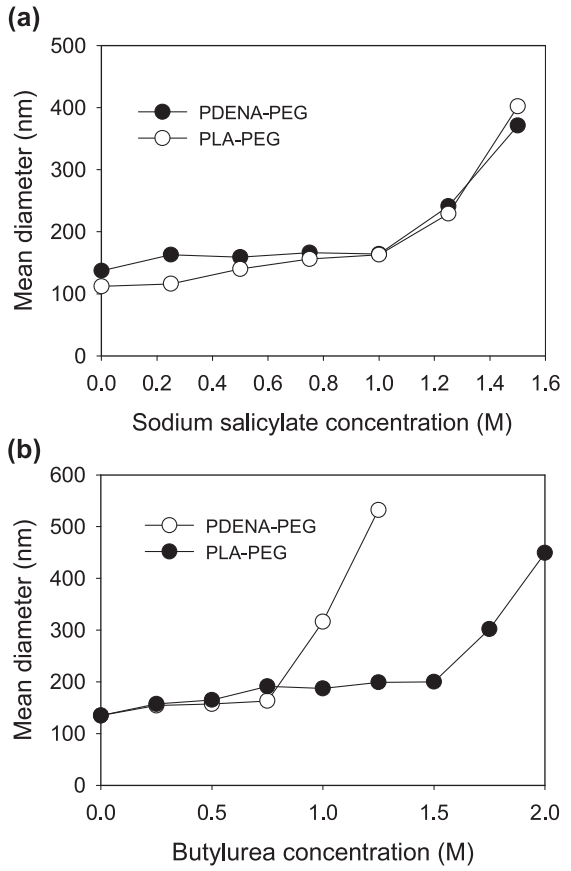


Fig. 6. Changes in micelle size of PDENA-PEG and PLA-PEG micelles as a function of sodium salicylate (a) and butylurea concentrations (b). The micelle concentration was 0.5 mg/ml.

extremely low water solubility of the drugs. Therefore, maintaining the sink condition in the release experiments has been an important issue for in vitro release studies of poorly soluble drugs such as paclitaxel. Several methods using organic solvents or surfactants were developed for drug release [21,22], but in most cases their potential effects on release kinetics and stability were often neglected or not studied enough. Thus, there is a need to develop a simple system that allows a sink condition using a small volume of aqueous media.

In this study, hydrotropic release media were explored for paclitaxel release from polymer micelles. Hydrotropic agents that can solubilize paclitaxel were used to maintain the sink condition of the aqueous release media. Effect of each hydrotropic agent on the micelle stability was examined by light scattering. As shown in Fig. 6a, sodium salicylate did not significantly affect the physical stability of micelles up to the concentration of 1.0 M. Above the concentration, a dramatic increase in micelle size was observed, indicating disruption of micellar structures. On the other hand, PDENA-PEG micelles were significantly affected by the presence of butylurea (Fig. 6b). PDENA-PEG micelles were more stable in sodium salicylate solution than in butylurea solution. Thus, in vitro release profiles of paclitaxel from polymer micelles were examined in an aqueous medium containing 0.8 M sodium salicylate, where the paclitaxel solubility was 0.0053 mg/ml (Fig. 1) and more than 10 times of its original solubility in water. There was no significant change in micellar properties, such as micelle size and scattering intensity, observed with the use of 0.8 M sodium salicylate solution.

Fig. 7 shows the paclitaxel release profiles of PDENA-PEG and PLA-PEG micelles. The release from paclitaxel bulk power was also carried out to examine the possible effect of the hydrotropic agent on the release rate. In all cases, the total amount of paclitaxel used for release was fixed to 0.1 mg. The release from paclitaxel bulk powder was negligible even after 74 h, thus the presence of sodium salicylate was found to hardly affect the release rate. For PDENA-PEG micelles, the micelle with 25.9 wt.% loading amount released almost all drug within 48 h,

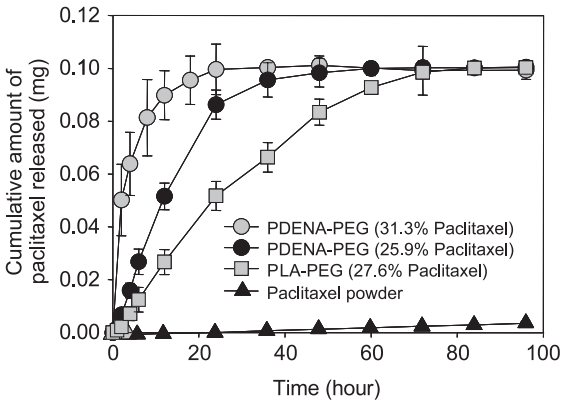


Fig. 7. Release kinetics from polymer micelles and paclitaxel powders in 0.8 M sodium salicylate solution at 37 °C. The total amount of loaded paclitaxel was 0.1 mg.

while the micelle with 31.3 wt.% drug loading showed complete release within 24 h. The release from the micelle with a higher drug loading was faster. The micelle with a higher drug loading leads to a relatively lower polymer concentration. Therefore, there is less polymer-drug interaction in the micelles, resulting in faster release kinetics. The in vitro release data showed that paclitaxel was released faster from the hydrotropic polymer micelles than from PLA-PEG micelles. It took almost 72 h to release all the loaded paclitaxel from the PLA-PEG micelle. As indicated by the higher CMC values of PDENA-PEG micelles than those of other typical polymer micelles, the PDENA block is less hydrophobic, thus form less hydrophobic cores. Such relatively lower hydrophobicity of hydrotropic micelle cores may make the paclitaxel release from the micelles easier, inducing faster release kinetics than from the micelles of more hydrophobic PLA cores.

4. Conclusions

Hydrotropic polymer micelles, consisting of a hydrophilic PEG shell and a hydrophobic core that contains a significant amount of hydrotropic moieties, were developed for solubilization of poorly soluble drugs. Based on synergistic effect of the unique micellar characteristics and hydrotropic activity, the hydrotropic polymer micelles exhibited a high drug loading capacity with enhanced long-term stability. The hydrotropic polymer micelle formulation presents an alternative and promising approach in formulation of poorly soluble drugs.

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