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Polymeric Delivery Systems for Poorly Soluble Drugs

Kang Moo Huh
Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

Sang Cheon Lee
Korea Institute of Ceramic Engineering and Technology, Seoul, South Korea

Tooru Ooya
Japan Advanced Institute of Science and Technology, Ishikawa, Japan

Kinam Park
Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

INTRODUCTION

Many existing drugs are poorly water soluble, and this limits their clinical applications. A large number of newly developed drug candidates are frequently found to be poorly water soluble, making it difficult to test their bioefficacy and to produce formulations with sufficiently high bioavailability.[1] Increasing the aqueous solubility of poorly soluble drugs has been one of the most important issues in drug discovery and delivery, because the clinical applications of many drugs are limited by their poor water solubility.

There have been various approaches for increasing the aqueous solubility of poorly soluble drugs, and they are usually based on the use of low molecular weight surfactants or their assemblies. Recent advances in polymer science have produced various polymeric systems specifically designed for delivery of poorly soluble drugs. Of the many polymeric systems, polymer micelles have been extensively studied as a promising drug formulation that can effectively dissolve various types of hydrophobic drugs with high drug-loading capacity for increased bioavailability. Polymer micelles can dissolve hydrophobic drugs via a self-assembling process of amphiphilic block copolymers in aqueous solution. Hydrophobic drugs can be dissolved or physically entrapped in the core of polymer micelles at concentrations that can exceed their intrinsic water solubility by orders of magnitude. Polymer micelles can be kept as freeze-dried powders that are stable for long periods of time. The polymer micelles in the powder state can be reconstructed by adding water before use. Recently, new polymeric systems known as the hydrotropic polymers have been introduced. They can increase the solubility of poorly soluble drugs by several orders of magnitude. The monomers of those hydrotropic polymers were designed based on the molecular structures of low molecular weight hydrotropic agents (or hydrotropes), which are effective in solubilizing poorly soluble drugs. This approach of synthesizing hydrotropic polymers based on the effective low molecular weight hydrotropes is unique. To date, various polymeric solubilizing systems, such as hydrotropic polymers, dendrimers, and polymeric micelles, have been used to increase the solubility of poorly soluble drugs. This article introduces applications of such polymeric systems for delivery of poorly soluble drugs.

BACKGROUND

Limitation of Poorly Soluble Drugs

Poor water solubility of drugs often causes significant problems in producing formulations of a sufficiently high bioavailability, preventing effective use of the drugs. Paclitaxel, which is one of the most successful chemotherapeutic drugs, is a good model drug for describing the problems with poorly water-soluble drugs.[2] Owing to its poor water solubility, the only commercial paclitaxel product (Taxol®) is currently formulated in a concentrated solution containing 6 mg paclitaxel in 1 ml of Cremophor EL (polyoxyl 35 castor oil) and dehydrated alcohol, which must be further diluted 5- to 20-fold with 0.9% sodium chloride or other aqueous solutions before intravenous (IV) administration.[3] Despite excellent efficacy of the formulation, it resulted in serious side effects, such as hypersensitivity reactions, neurotoxicity, and nephrotoxicity, owing to the presence of Cremophor EL.[3] Several alternative approaches to solubilize paclitaxel have been tried, but with limited success.

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In addition to paclitaxel, there exist many poorly soluble drugs that have difficulty in designing clinically useful formulations. Examples are alprostadil, amphotericin B, camptothecin, cosalane, chloramphenicol, cyclosporine, dexamethasone, diazepam, digoxin, epirubicin, griseofulvin, glucocorticosteroids, HIV-1 protease inhibitors, hydrocortisone, indomethacin, palmitoylrhizoxin, *p*-boronophenylalanine, phenytoin, pregnanolone, propofol, and tolbutaide.[4–10] Development of drug formulations for poorly soluble drugs is undoubtedly very important for producing patient-friendly formulations with high bioavailability.

Typical Methods for Drug Solubilization

During the last two decades, significant efforts have been made in the development of solubilization systems for poorly soluble drugs. As listed in Table 1, various methods have been explored to increase water solubilities of poorly soluble drugs.

The prodrug and analogue approaches are highly viable, and a number of systems have been studied.[11–14] Despite improved solubility properties, the main limitation of these approaches is that the prodrugs and analogues are not the same as the original drugs, and thus are regarded as new chemical entities. Because many drugs are weak acids or bases, their solubility may be increased by adjustment of pH and/or incorporation of buffers.[15] Such increase in solubility, however, is usually limited to less than 10 times. Poorly soluble drugs have been often formulated into surface-stabilized micron- ($<10\,\mu m$) or submicron-size particulates.[16] The most common way to produce a drug in small particle size is the comminution of previously formed larger particles using milling processes such as jet milling, pearl-ball milling, or high-pressure homogenization.[17] An alternative way to produce small particles is to use controlled processes, including spray drying, precipitation from supercritical fluid, and controlled crystallization. The limitation of this approach is that the increase in water solubility is usually limited to several folds, and a high amount of stabilizing agents is required to stabilize small particles with the high specific surface area. Cosolvents are defined as water-miscible organic solvents that are used to increase the solubility of poorly soluble substances.[18] Cosolvent systems can increase the drug solubility significantly, but the choices of solvents are limited to ethylene glycol, dimethylsulfoxide, *N,N*-dimethylformamide, Cremophor EL, and ethanol. Emulsion is a dispersion of drops of a liquid in another immiscible liquid. Emulsifiers, which are, in general, surfactants, are added to prevent the droplets from coalescence. Liposomes and micelles also have been studied quite extensively for delivery of poorly soluble drugs.[18,19] The main limitation of this approach is that they tend to have poor stability.[7] The complexation approach has been frequently applied using several host molecules, such as cyclodextrins, capable of complexing with drug molecules.[20] The drug molecules of interest need to be fit into the hydrophobic cavity of cyclodextrins and other complexing agents. Solid dispersion is a dispersion of a poorly soluble drug in an inert polymeric carrier (e.g., polyvinylpyrrolidone) at the solid state prepared by the melting or solvent method. This method requires melting of the drug or the use of organic solvents.[21–24] Hydrotropic agents (hydrotropes) have been often used to increase water solubility of poorly soluble drugs. For instance, *N,N*-diethylnicotinamide (DENA) was reported to be an effective hydrotropic agent for paclitaxel and increase the solubility by several orders of magnitude.[25] However, very high concentrations of hydrotropic agents are required, and this may limit clinical applications. It is possible to combine two solubilizing agents with different mechanisms, e.g., poly(ethylene glycol) (PEG) with a molecular weight of 400 and cyclodextrin, to achieve synergistic effects.[26]

Each method listed in Table 1 has advantages and limitations, and there has been no universal formulation approach that can be applicable to various types of hydrophobic drugs. A solubilization method appropriate for a given drug has to be chosen depending on the physicochemical properties of the drug and the requirements for the final formulation such as the desired concentration, dose, stability, etc.

Table 1 Methods commonly used to increase the water-solubility of hydrophobic drugs

Synthesis of prodrugs and analogues
Use of buffers
Physical modification of the drugs (particle size, crystallinity, and crystal form)
Use of cosolvents
Making emulsions, micelles, and liposomes
Complexation approach
Solid dispersion technology
Use of hydrotropes (hydrotropic agents)

POLYMERIC SYSTEMS FOR POORLY SOLUBLE DRUGS

Polymer Micelles

Polymer micelles for drug delivery

Polymer micelles are supramolecular assemblies of amphiphilic block copolymers that have a characteristic

core-shell structure with a size less than 100 nm. As shown in Fig. 1, amphiphilic block copolymers with a balanced hydrophilic/hydrophobic property can self-assemble in aqueous solutions to form spherical micelles. They are generally more stable than low molecular weight micelles owing to the presence of long hydrophobic polymer blocks.

Polymer micelles have been extensively investigated as drug carriers for more than two decades.[27–30] Polymer micelles are known to possess a number of advantages as a drug carrier for poorly soluble drugs over other drug carrier systems. Linear polymeric carriers tend to precipitate in water owing to a localized hydrophobicity caused by interactions between the drug and the hydrophobic portion of the polymer chain.[29] Polymer micelles with characteristic core-shell structure, however, are more stable in water owing to protection of the hydrophobic core by the hydrophilic shell. In addition, polymer micelles have the appropriate size for long circulation half-life in blood, high water solubility, high structural stability, high carrying capacity of hydrophobic drugs, and separated functionality of outer shell and inner core.[31]

The outer shell of hydrophilic polymer chains ensures water solubility and colloidal stability of micelle. The hydrophilic shell around the micellar core can prevent aggregation or precipitation of the loaded drug, protein adsorption, and cellular adhesion.[30] Biodistribution of polymer micelles is mainly determined by the nature of the hydrophilic shell. The micelle core serves as a loading space that can accommodate various poorly soluble drugs. There are a large number of variables, which influence the loading capacity and other micellar properties. Many structural variables, such as the chemical composition, total molecular weight, and block length ratios, can be easily changed, and this allows control of the size and morphology of the micelles.

Amphiphilic block copolymers

Amphiphilic block copolymers have both hydrophilic and hydrophobic segments. The presence of two segments with vastly different water solubility results in spontaneous organization into the core-shell structure.[32] The hydrophilic polymer segment forms a hydrophilic shell, which serves as a stabilizing interface for the hydrophobic core. PEG has been used most widely as a shell-forming block because of its unique solution properties, such as high water solubility and significant chain mobility for steric repulsion, as well as biocompatibility. In addition to PEG, poly(2-ethyl-2-oxazoline) (PEtOz) has also been used to form hydrophilic shell that could form complexes via strong hydrogen bonding with poly(carboxylic acid)s, such as poly(acrylic acid) or poly(methacrylic acid).[33] Use of poly(acrylic acid) as a hydrophilic polymer could lead to a bioadhesive outer shell.[34] Poly(*N*-isopropylacrylamide) that exhibits a reversible thermoresponsive phase transition at 32°C in aqueous media was used for preparing thermoresponsive polymer micelles.[35] Despite the presence of numerous hydrophilic polymers available to date, only a small number of hydrophilic polymers have been used as shell-forming polymers.

Unlike hydrophilic segment, however, the choice for hydrophobic blocks is relatively diverse. Typical examples include poly(propylene oxide),[36] polystyrene,[37] poly(lactic acid),[38] poly(glycolic acid), poly(ε-caprolactone) (PCL),[39] and poly(β-benzyl-L-aspartate).[40] Block copolymers with biodegradable core-forming blocks, such as polyesters and poly(aminoacid)s, are of interest because they may undergo hydrolytic and/or enzymatic degradation, producing biocompatible monomers. Poly(aminoacid)s are degradable into amino acids, which are natural components of the body. Biodegradable hydrophobic segments are widely used in preparation of polymer micelles for pharmaceutical and biomedical applications.[29]

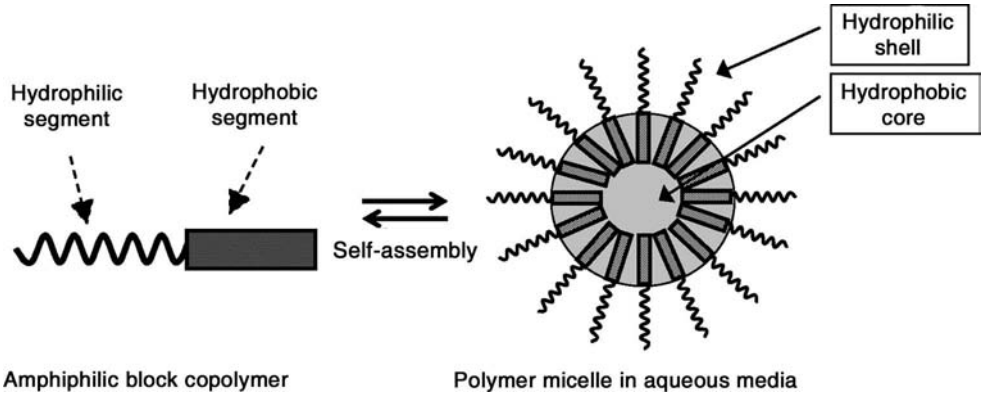

Fig. 1 Self-assembly of amphiphilic block copolymers to a micellar structure in aqueous solution.

Drug solubilization and loading methods

Effective drug loading into the polymer micelle cores is important for clinical applications. In principle, a drug can be loaded into polymer micelles by simply dissolving the polymer and the drug in water. Unfortunately, however, such direct solubilization is applicable only to highly hydrophilic block copolymers and does not proceed often to any significant extent, leading to low drug-loading capacity and efficiency.[41] Furthermore, most amphiphilic block copolymers developed for micelle formation are barely water soluble. For this reason, in many cases, both drug and polymer need to be dissolved in an organic solvent first.

Several methods for effective solubilization of drugs into polymer micelles have been developed (Fig. 2). The dialysis method (Fig. 2A) is most widely used for many polymeric micelle systems. The first step involves the dissolution of both polymer and drug in a water-miscible organic solvent such as acetonitrile, acetone, dimethylformamide, or ethanol. Then, the polymer–drug solution is dialyzed against water. As the organic solvent is removed from the dialysis bag and replaced by water, the hydrophobic segments of polymer chains begin to self-assemble to form the micellar core. At the same time, drug molecules also participate in the core-forming process to be incorporated in the hydrophobic cores. The limitation of the dialysis method is that the process requires a large volume of water and a long processing time (more than two days), with possible drug loss.[42]

The solid dispersion method (Fig. 2B) was used for solubilization of paclitaxel into PEG-poly(D,L-lactide) diblock copolymer micelles.[43] Paclitaxel and the polymer were dissolved in acetonitrile followed by evaporation of the solvent under a stream of nitrogen at 60°C to obtain a gel-like polymer–drug matrix. Dissolution of the solid matrix in water at about 60°C with stirring led to formation of drug-loaded micelles. Because a heating is needed to completely dissolve the polymer–drug matrix, this method may not be not desirable for thermally unstable drugs.

The oil-in-water (o/w) emulsion method (Fig. 2C) was proposed by Kwon et al. to improve the drug-loading

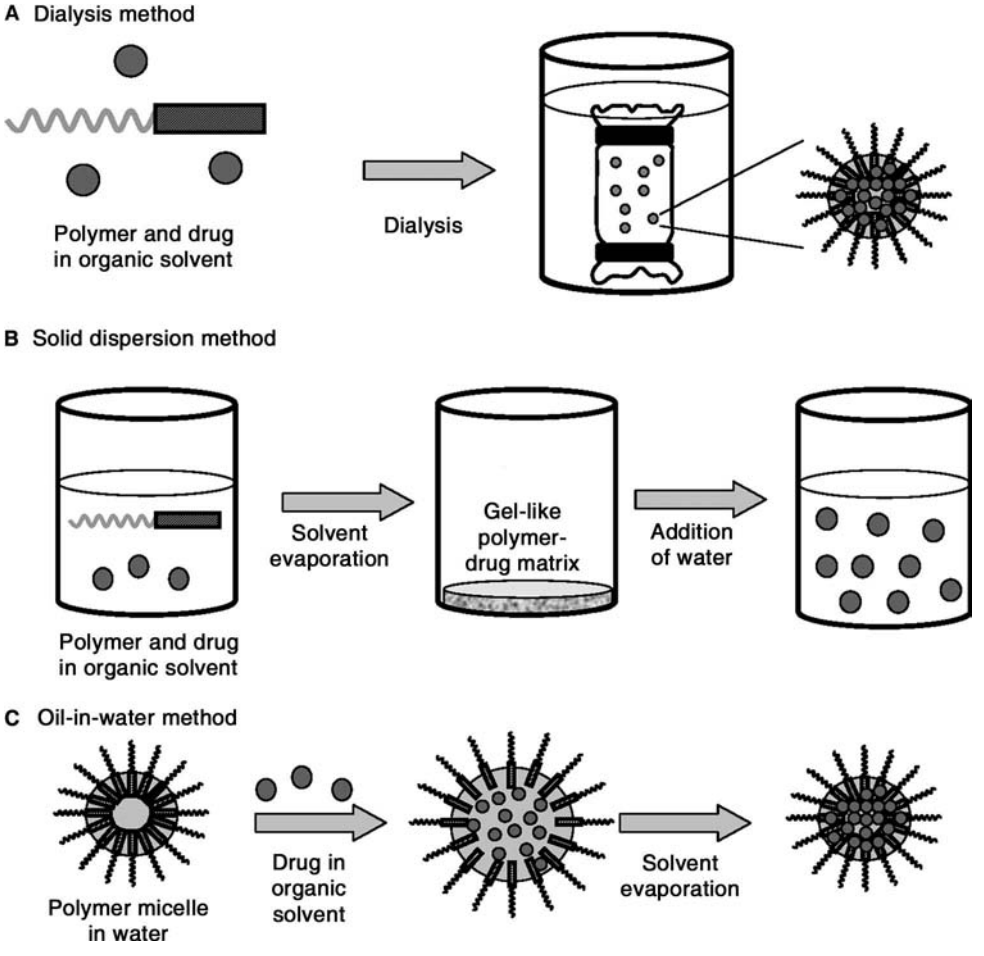

Fig. 2 Typical methods used for drug solubilization in polymeric micelles.

efficiency.[44] In this method, the drug is first solubilized in a water-immiscible volatile solvent such as chloroform and added to aqueous polymer solution, forming the o/w emulsion. The o/w emulsion is kept in an open atmosphere, allowing evaporation of the volatile solvent. Drug-loaded micelles are formed as the volatile solvent evaporates. This method may lead to higher loading efficiency, but the use of toxic volatile solvents would not be desirable.

Recently, a novel one-step drug-loading procedure has been developed.[42] In this procedure, both the polymer and the drug are dissolved in a water/*tert*-butanol mixture and subsequently freeze dried. Drug-loaded polymer micelles could be obtained by rehydrating the freeze-dried cake in an injectable vehicle. This procedure is simple and thus can be very useful, as long as the freeze drying process is available and the hydrophobic drugs are soluble in the water/*tert*-butanol mixture.

In most polymer micelles, poorly soluble drugs can be incorporated into the micelle cores by hydrophobic interaction and other additional interactions such as the metal–ligand coordination bond[45,46] and the electrostatic interaction.[47] It is believed that drugs that are more compatible with the cores of the polymer micelles can be dissolved to the higher extent.[48] Although the interaction between the core-forming polymer and the drug plays an important role in drug solubilization into micellar structure, there are other factors, which influence the solubilizing properties of polymer micelles. Such factors include the drug properties, the hydrophobic block length of the copolymer, the total copolymer molecular weight, the drug concentration, and, to a lesser extent, the nature and block length of the shell-forming polymer.[28] In addition, the drug-loading method applied and the solvent used influence the loading amount (or the content) of the drug. Table 2 shows the change in the loading content of paclitaxel according to the drug-loading methods and the polymer structural variations.[41,43,44,49–52]

Hydrotropic Polymers and Hydrogels

Hydrotropic agents for drug solubilization

Hydrotropic agents (or hydrotropes) are a diverse class of water-soluble compounds that, at high concentrations, enhance the water solubility of poorly soluble solutes.[53] The hydrotrope approach has a great potential for delivery of poorly soluble drugs. Using hydrotropes 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. Hydrotropes have been used to enhance the water solubility of poorly soluble drugs, and, in many instances, the water-solubility of drugs increased by orders of magnitude.[54] The use of hydrotropes offers many benefits over other solubilization methods such as micellar solubilization, miscibility, cosolvency, and salting-in.[55] For this reason, various hydrotropes have been utilized to enhance the aqueous solubility of many hydrophobic drugs. Table 3 lists typical examples of hydrotropic agents used to enhance the aqueous solubility of poorly soluble drugs.[53,56–68]

The term ''hydrotropy'' does not mean a specific mechanism, but represents a collective solubilization phenomenon, which is still incompletely understood. There have been various theoretical and experimental studies aiming at explanation of hydrotropic solubilization.[56,58,69] Most of proposed mechanisms of hydrotropic solubilization can be classified into the following two schemes: complexation between hydrotropes and solutes, and self-association of hydrotropes. The first one involves the complex formation between a hydrotrope and a solute. For example, nicotinamide has been shown to enhance the solubilities of a wide variety of hydrophobic drugs through complexation.[58,59,70] It was shown by molecular orbital calculations that the complex formation of heteroaromatic drug molecules with nicotinamide occurred through π-donor and π-acceptor mechanism.[70] Studies using nicotinamide

Table 2 Typical amphiphilic polymers and their drug-loading capacity

Polymer micelle	Block length (g/mol)	Loading method	Loading content, (% w/w)
poly(D,L-lactic acid) (PDLLA)-PEG	2000–2000	Solid dispersion	25
PDLLA-PEG	1300–2000	Solid dispersion	25
PDLLA-PEG	2100–5000	Solid dispersion	10
PCL-PetOz	1400–6200	Dialysis	2.4
PCL-PetOz	2600–6200	Dialysis	6.2
PCL-PetOz	3300–6200	Dialysis	7.6
PCL-PEG	5500–5000	Dialysis	21
poly(phenyl alanine) (PPhe)-PEG	1100–5000	Solid dispersion	9
PDENA-PEG	4500–5000	Dialysis	37

Table 3 Hydrotropes used for solubilizaton fo poorly water-soluble drugs

Hydrotropes	Drugs
Nicotinamide	Riboflavin, allopurinol, diazepam, Nifedipine, progesterone, oxamniquine, moricizine, testosterone, griseofulvin, 17-β-estradiol, indomethacin
N,N-diethylnicotinamide	Diazepam, griseofulvin, nifedipine
Sodium benzoate	Indomethacin, nifedipine, allopurinol, ketoprofen, oxamniquine, nalidixic acid, Carbamazepine, etoposide
Sodium *p*-aminobenzoate	Phenacetin
Sodium salicylate	Ketoprofen, nifedipine, piroxicam, etoposide, indomethacin
Resorcinol	Riboflavin, nalidixic acid
Piperazine	Nimesulide
Sodium butyl monoglycol sulfate	6-aminopenicillanic acid
Lysine, urea, gentisic acid ethanolamide	Acetazolamide

and its derivatives, such as *N*-methylnicotinamide and DENA, showed that the aromaticity of the pyridine ring, which might promote the stacking of molecules through its planarity, was the most significant contributor in complexation.[57] The ability of aromatic amide ligands to enhance the aqueous solubilities of tested drugs was higher than those of the aliphatic amide ligands.[57] On the other hand, it was also demonstrated that the hydrophobicity of ligands including nicotinamide was the general determinant of water-soluble complex formation, and donor–acceptor interactions did not control complex formation.[71] The other proposed 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.[54,71] Studies on the nicotinamide–riboflavin system showed that the self-association of nicotinamide contributed to the solubility increase of riboflavin rather than complexation between two species.[54]

In general, each hydrotrope is specific in increasing the water solubility of selected hydrophobic drugs, and, thus, there is no universal hydrotrope that can be applicable to all types of hydrophobic drugs. The same hydrotrope, however, should be effective for the hydrophobic drugs with similar chemical structures. To find good hydrotropic agents for a hydrophobic drug of interest, it is important to investigate first the structural requirements for effective solubilization. The structure-activity relationship for the hydrotropic solubilization of paclitaxel was studied using more than 60 candidate hydrotropic agents and their analogues.[25] Several effective hydrotropic structures were identified for their ability to solubilize paclitaxel, and some of them are shown in Fig. 3. Among them, DENA was found to be the most effective hydrotropic agent for paclitaxel. The solubility of paclitaxel was increased to 39 mg/ml and 512 mg/ml at the DENA concentration of 3.5 M and 5.95 M, respectively, which are ~5–6 orders of magnitude greater than the intrinsic solubility of 0.30 ± 0.02 μg/ml. PNA, *N*-allylnicotinamide, and sodium salicylate were also found to have high-solubilizing capacity for paclitaxel. This information can be used to find other hydrotropic compounds and to design new hydrotropic analogues that are effective for paclitaxel and other poorly soluble drugs.

Hydrotropic polymers

Despite their ability to increase the paclitaxel solubility by several orders of magnitude, the hydrotropes have a limitation in developing effective formulations. The main concern is that the use of such high concentrations of low molecular weight hydrotropes may result in coabsorption of a significant amount of the hydrotropes along with the drug. In addition, hydrotropic properties may be lost when the hydrotropic solution is diluted, resulting in precipitation of the dissolved

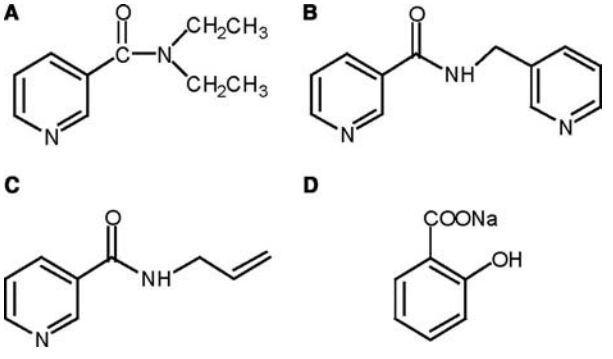

Fig. 3 Hydrotropic agents identified for paclitaxel solubilization: *N,N*-diethylnicotinamide (A); *N*-picolylnicotinamide (PNA) (B); *N*-allylnicotinamide (C); and sodium salicylate (D).

drug. For this reason, the concept of transforming low molecular weight hydrotropes into the polymeric forms was proposed. The first question to answer was whether the polymeric form of hydrotropes maintained their hydrotropic properties.

A number of new polymerizable monomers were synthesized by modification of PNA and DENA.[25,72] Various types of polymeric structures containing PNA moieties were tested for their hydrotropic properties. The pendent hydrotropic PNA moieties were attached to the polymer backbone through either an oligo(ethylene glycol) or a phenyl group as a spacer. The PNA moiety was bound to the polymer backbone either at 2-position or at 6-position of the pyridine ring of nicotinamide to result in poly(2-(4-vinylbenzyloxy)-*N*-PNA) (*P*(2-VBOPNA)) or poly(6-(4-vinylbenzyloxy)-*N*-PNA) (*P*(6-VBOPNA)), respectively. Fig. 4 shows various types of hydrotropic monomers and a typical synthetic procedure for *P*(2-VBOPNA).[73]

It is important to ensure that the modified forms, both monomers and polymers, of hydrotropic agents maintain their hydrotropic properties. Fig. 5A shows the enhancement of aqueous solubility of paclitaxel as a function of the concentration of 2-VBOPNA, 6-VBOPNA, and PNA. Two monomers, 2-VBOPNA and 6-VBOPNA, with a vinylbenzyloxy group linked to 2- and 6-position of pyridine ring, retained the hydrotropic property for paclitaxel. Of the two monomers, 2-VBOPNA was more effective than 6-VBOPNA for the tested concentration range. Fig. 5B shows the enhancement in the paclitaxel solubility by monomeric and polymeric form of 2-VBOPNA. It is noted that the polymer increased the paclitaxel solubility substantially higher as compared with its monomeric counterpart. The effect of the polymeric form was more pronounced at the low concentration range.

While the structure of the hydrotropic moiety of the polymer is the most important factor in hydrotropy, other factors can also contribute to the overall hydrotropic property of the polymers. The spacer between the polymer backbone and the hydrotropic moiety is one key factor affecting the overall hydrotropy. Two different hydrotropic polymers based on *N*-PNA have different hydrotropic properties depending on the nature of the spacer. The paclitaxel solubility in *P*(6-VBOPNA) increased to a larger extent than in poly(6-allyloxy-*N*-PNA) (*P*(6-APNA)), where the aromatic spacer was replaced with a linear chain.

Hydrotropic copolymers can also be synthesized using two different hydrotropic monomers. The concept

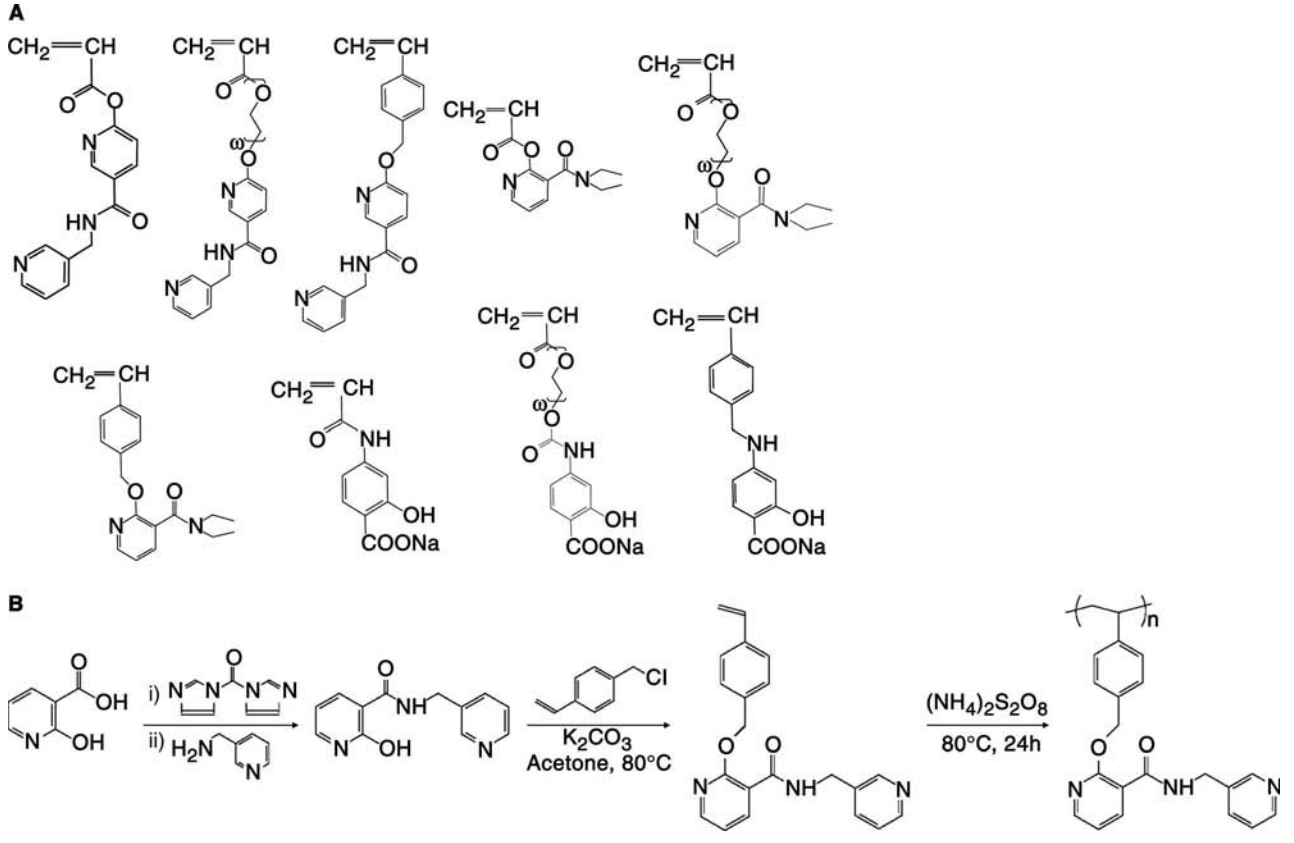

Fig. 4 Various hydrotropic monomers (A), and an exemplary synthetic scheme of a hydrotropic polymer, poly(2-(4-vinylbenzyloxy)-*N*-picolylnicotinamide) [P(2-VBOPNA)] (B).

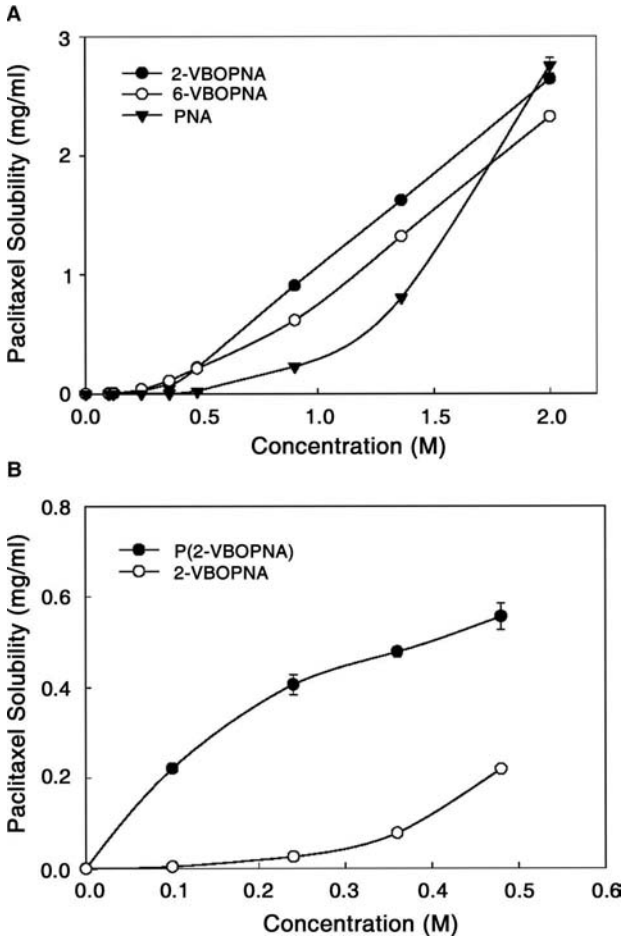

Fig. 5 Aqueous solubility of paclitaxel as a function of the concentration of 2-VBOPNA, 6-VBOPNA and PNA (A), and in the presence of P(2-VBOPNA) and 2-VBOPNA (B). (Modified from Ref.[73].)

of using two different hydrotropes on the same polymer backbone is based on facilitated hydrotropy, where the use of combination of different hydrotropes is known to yield higher hydrotropic property, as compared with individual hydrotropes.[74] The maximum synergistic hydrotropic effect would be obtained by optimizing the factors such as type and length of spacers, orientations of a hydrotrope, and combination of different hydrotropes.

Hydrotropic hydrogels

Because hydrotropic polymers can be diluted when introduced into aqueous solution, cross-linked hydrotropic polymers, i.e., hydrotropic hydrogels, were prepared. Hydrotropic hydrogels are prepared by polymerization of hydrotropic monomers in the presence of cross-linking agents. Despite the cross-linking of linear hydrotropic polymer chains, the hydrogels maintained the hydrotropic property. The hydrotropic hydrogel

Table 4 Hydrotropic properties of 2-VBOPNA used for hydrogel synthesis

Hydrotropes	Drug solubility ± SD (mg/ml)
Paclitaxel	
None (solubility in pure water)	0.0003
2-VBOPNA (0.66 M)	0.519
Griseofulvin	
None (solubility in pure water)	0.007 ± 0.000
2-VBOPNA (0.5 M)	0.343 ± 0.019
Progesterone	
None (solubility in pure water)	0.001 ± 0.000
2-VBOPNA (0.5 M)	0.683 ± 0.022

systems provide several advantages.[73] Owing to their cross-linked nature, hydrotropic hydrogels maintain the local high concentration of hydrotropic moieties, even in excess amounts of water. The hydrogels may swell but do not dissolve, and thus the local concentration of hydrotropic moieties is not diluted as much as in non-cross-linked polymers. Because hydrogels can be dried and processed as a particulate form, they may offer a simple way of formulating poorly soluble drugs. In one approach, paclitaxel was dissolved directly into 2-VBOPNA (1.2 M) to make the final

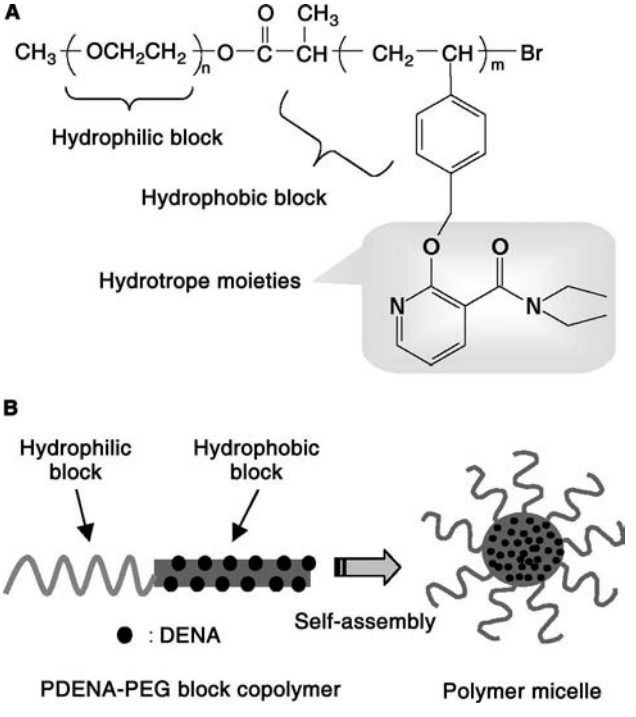

Fig. 6 Chemical structure of hydrotropic amphiphilic block copolymer (A) and self-assembly into micellar structure in aqueous medium (B). (Modified from Ref.[52].)

concentration of 1.2 mg/ml before formation of the 2-VBOPNA hydrogel. The formed hydrogel kept its transparency, indicating that paclitaxel existed in the dissolved state. Table 4 shows examples of hydrotropic hydrogels used for solubilization of poorly water-soluble drugs, paclitaxel, griseofulvin, and progesterone.

Hydrotropic polymer micelles

The studies on hydrotropic polymers and hydrogels led to the development of hydrotropic polymer micelles consisting of a hydrophilic PEG shell and a hydrotrope-rich core.[52,75] A DENA-based hydrotropic polymer was synthesized and used as a building block for constructing amphiphilic block copolymers (Fig. 6). These block copolymers self-assembled in aqueous media to form micellar structures with a size 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. The enhanced stability is owing to attractive interactions between paclitaxel and the hydrotropic moieties. The drug loading into the hydrotropic polymeric micelle core is mainly based on the attractive interactions between the hydrotropic moiety and paclitaxel. This results in more stable polymeric micelles than those that depend on hydrophobic interaction alone.

Other Polymeric Systems

Hydrophobically modified polymers can associate in aqueous media to form micelle-like structures above their critical association concentrations (CACs).[76] The nano-sized self-aggregates were prepared using modified natural polysaccharides such as pullulan,[77] curdlan,[78] and glycol chitosan.[79] The modified polysaccharides provide excellent biocompatibility, biodegradability, low immunogenicity, and biological activities.

PEG-400 has been frequently used as a hydrotrope or a cosolvent to dissolve poorly water-soluble drugs.[80] For example, PEG-400 increased the solubility of β-estradiol by ~4–5 orders of magnitude when its concentration was higher than 80 wt%.[81] At such high concentrations, PEG-400 self-associate through hydrogen bonding mediated by water molecules, which may alter the water structure to increase the solubility of poorly soluble drugs. Based on the PEG effect on solubilization, ethylene glycol-based graft,

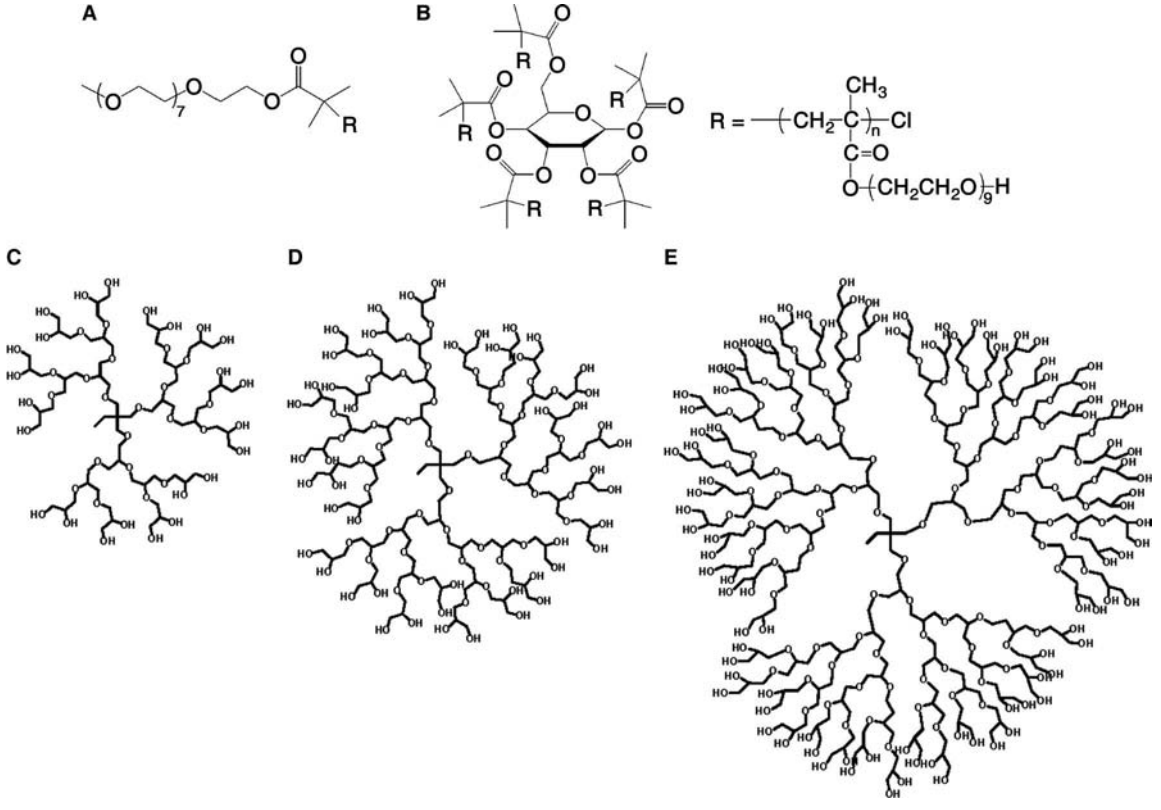

Fig. 7 Chemical structures of poly(oligo(ethylene glycol) [poly(OEGMA)] methacrylate) (A); 5-arm star-shaped poly(OEGMA) (B); and polyglycerol dendrimers with generation 3 (C); 4 (D); and 5 (E). (Modified from Ref.[82].)

star-shaped, and dendritic polymers have been synthesized to create the highly localized structures of ethylene glycol units.[82] Fig. 7 shows the chemical structures and architectures of ethylene glycol-based graft, star-shaped, and dendritic polymers. While the graft and star-shaped polymers were observed to increase the paclitaxel solubility in water by three orders of magnitude, the dendritic PEG structure was most effective. The enhanced paclitaxel solubility does not depend on the molecular weight of the polymer. The paclitaxel solubility did not increase significantly as the molecular weight of PEG was increased up to 2000. The paclitaxel solubility in a dendrimer solution was 10-fold higher than that in a linear PEG solution at the same molecular weight and concentration. These results strongly suggest that the high density of ethylene glycol units in the dendritic structure is the main contributor to substantial increase in the paclitaxel solubility. The dendrimers with the highest density of ethylene glycol units increased the solubility of paclitaxel 10,000 fold at 80 wt%. The dendritic PEG structure, which does not require a hydrophobic segment as in polymeric micelles, provides an alternative method of hydrotropic solubilization of poorly soluble drugs.

Phospholipid polymers having a 2-methacryloyloxyethyl phosphorylcholine (MPC) were investigated as a solubilizer for paclitaxel.[83] The paclitaxel solubility was observed to increase up to 5.0 mg/ml in the presence of a copolymer of MPC and *N*-butyl methacrylate (BMA), poly(MPC-co-BMA), with 70 mol% of the BMA unit. The MPC polymer forms a polymer aggregate with the diameter of 23 nm, called a polymeric lipid nanosphere, in aqueous media by hydrophobic interaction, which may solubilize hydrophobic drugs.

Water-soluble polymers conjugated with lipids can form micelles in aqueous media, and they can be used for the solubilization and enhanced delivery of a variety of sparingly soluble drugs. The basic structures of these polymer–lipid conjugates are similar to amphiphilic block copolymers except for the fact that hydrophobic parts are composed of lipids instead of hydrophobic polymers. For example, a hydrophilic PEG block is conjugated with phosphatidylethanolamine.[84]

CONCLUSIONS

Poor water solubility of drugs and new chemical entities presents major challenges in the development of clinically useful formulations. Of the various approaches used for enhancing the solubility of poorly soluble drugs, polymeric delivery systems have been used effectively. Paclitaxel has been used as a model hydrophobic drug to show the effectiveness of solubility-enhancing properties of various polymeric delivery systems. Recently, hydrotropic polymers were developed based on the molecular structure of low molecular weight hydrotropes. Hydrotropes maintained their hydrotropic properties even in their polymeric states, and this led to the development of hydrotropic polymer micelles. The hydrotropic polymer micelles present unique advantages over conventional polymer micelles in that the interaction between the polymer segment and paclitaxel is based on miscibility between the two, instead of the hydrophobic interaction alone. For this reason, the hydrotropic polymer micelles in aqueous solution are more stable than the conventional polymer micelles. Various polymer systems based on hydrotropic polymers are possible as shown by block copolymers, star-shaped polymer, and dendrimers. The new polymer systems based on hydrotropic polymers provide an alternative approach of developing delivery systems for poorly soluble drugs.

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ARTICLE OF FURTHER INTEREST

Cosolvents and Cosolvency, p. 806.

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