WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SJIF Impact Factor 6.041

Volume 5, Issue 4, 617-635 Review Article ISSN 2278 – 4357

MICELLES DRUG DELIVERY FOR POORLY SOLUBLE DRUG: A REVIEW

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Article Received on
28 Jan 2016,

Revised on 18 Feb 2016,
Accepted on 10 March 2016

DOI: 10.20959/wjpps20164-6408

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ABSTRACT

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability especially for BCS class II and IV. There are various methods to increase the solubility of drug i.e. are chemical changing, utilizing pro-drug approaches. Micelles are colloidal particles with a size usually within a range of 5–100 nm. Micelles consist of amphiphiles or surface-active agents (surfactants), which exist of two distinct regions: mostly a hydrophilic head-group and a hydrophobic tail. There are various factor i.e. solubility and cloud point, CMC, krafft temperature which effect the concentration and temperature on micelles formulation. Surfactant, oil phase and aqueous phase are three main components for micelles formulation. Two mechanisms for drug release from micelle are drug diffusion and micelles dissociation. Micelles formulations are used for various drug delivery including targeted delivery, cancer therapy, ocular delivery, antifungal agent etc.

KEYWORDS: Micelles, Poor solubility drugs, CMC.

INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, and flexibility in the design of dosage form.[1] However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism,

presystemic metabolism. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.[2]

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.[3] Poor solubility leads to a variety of issues. Low solubility limits the drug dissolution rate, which frequently results in low bioavailability of the orally administered drug.[7] In such a case the therapeutic drug concentration in the blood can be achieved by dose escalation. However, dose escalation is often undesirable for the following reasons: 1) possibility of increased toxicity and therefore decreased patient compliance; 2) difficulty in designing formulations for drug product with high drug load; and 3) increase in manufacturing costs associated with higher consumption of active pharmaceutical ingredients (API). These types of drugs have slow drug absorption which leads to inadequate and variable bioavailability.[4]

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.[1, 4, 5] Especially for BCS class II i.e. low solubility and high permeability and class IV i.e. low solubility and low permeability the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.

Various methods to overcome the poor aqueous solubility of drug candidates have been investigated in the research and development of oral formulations. These methods include changing the chemical structure of drug candidate in lead optimization phase and utilizing pro-drug approaches whereby a polar functional group is introduced into the structure of the drug molecule.[6] The most often used approach is to enhance the dissolution of these poorly water-soluble drugs, especially in the case of BCS class II and IV drugs.

A wide variety of solubility-enabling formulation approaches have been developed and are routinely used to tackle the problem of inadequate aqueous solubility, e.g., the use of surface active agents, lipid-based formulations, self-emulsifying drug delivery systems, cyclodextrins, cosolvents, amorhous solid dispersions and other techniques.[8]

Structure and composition

Micelles are colloidal particles with a size usually within a range of 5–100 nm. Micelles consist of amphiphiles or surface-active agents (surfactants), which exist of two distinct

regions: mostly a hydrophilic head-group and a hydrophobic tail. The formation of micelles are shown in figure.1.

At low concentrations in an aqueous medium, the amphiphiles exist as monomers in true solution, but when the concentration increases, aggregation and self-assembly take place within a narrow concentration window, and micelles are formed.[9] The concentration at which micelles are formed is referred to as the critical micelle concentration (CMC). Below the CMC the polymer exist as unimers or single units and above the CMC, unimers still exist, but they also spontaneously self-assemble in micelles.[23]

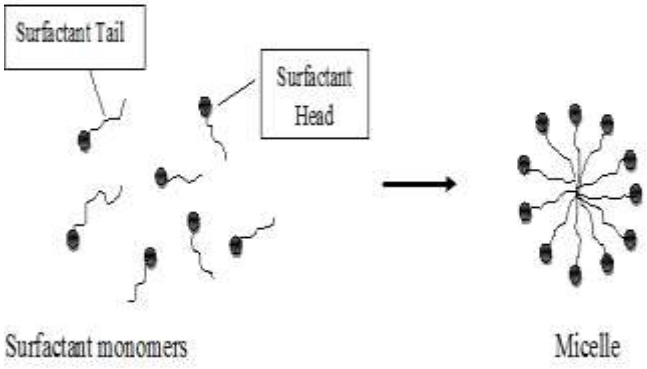

Figure 1. Micelle formulation.

Core of Polymeric Micelles

The hydrophobic core is a key component in determining the micelle's capacity to solubilize a poorly water-soluble compound. The ability of the core to encapsulate drug is largely dependent upon the compatibility between the hydrophobic core and the drug molecule.[10] Generally, a good indication of compatibility is structural similarity between drug molecule and the hydrophobic part or hydrophobic side chain of core-forming amphiphilic polymer. Compatibility can also be estimated by comparing the polarity of the poorly water-soluble drug compound and the hydrophobic segment of polymer.

In terms of the composition of the hydrophobic core, biocompatibility and non-toxicity are key prerequisites in selecting the appropriate hydrophobic segment. Commonly used coreforming hydrophobic polymers for drug delivery can be classified into the following groups: poly(propylene oxide) (PPO) as in Pluronics®[11]; poly(esters) such as poly(lactic acid) (PLA)[12] and poly(ε-caprolactone) (PCL)[13,14]; poly(L-amino acids) such as poly(Llysine)[15]; and phospholipids and lipid-derivatives such as phosphatidyl

ethanoloamine.[16] In addition, core-forming polymers such as polystyrene have been used in both in drug delivery systems[17] as well as fundamental research regarding polymer micelles.[18] These core-forming constituents cover a wide range of structural diversity and polarity for solubilizing a wide range of poorly water-soluble drugs. The encapsulation of drug within hydrophobic cores constructed from these polymers occurs via hydrophobic interactions that are thermodynamically driven. Besides hydrophobic interactions, micelles can also take up bioactive compounds by electrostatic interactions such as in the case of PEGylated gene nanocarriers based on block catiomers with ethylenediamine repeating units,[19] but such polyion complex micelles and interactions are not within the scope of this article. Polymeric micelle core can also take up drug through metal complexation, though this approach is less commonly employed than the previous two approaches.

Shell of Polymeric Micelles

The shell of polymeric micelles is composed of hydrophilic portion of amphiphilic polymer. Poly(ethylene glycol) (PEG) is invariably the shell-forming polymer of choice. There are several reasons for using PEG because it's non-toxic and one of the few synthetic polymers already approved by FDA for use in the drug products. Second, in aqueous environment, PEG is highly hydrated and can move rapidly to sweep out a large exclusion volume. In micelles, PEG forms a dense, brush-like shell that stretches away from the core. These characteristics act to limit micelle interaction with other micelles (leading to aggregation) and proteins (opsonin), which promote uptake and removal by the mononuclear phagocytic system. Third, PEG can be easily functionalized to tether ligands for targeted drug delivery. This particular property has generated a lot of excitement in delivery of highly potent compounds such as anti-cancer agents, which would benefit immensely both in terms of efficacy and safety profiles. The above mentioned reasons all contribute to the large number of studies on polymer micelles involving PEG.[22] Besides PEG, several other hydrophilic shell-forming polymers have been used in polymer micelle formation. Poly(N-vinyl-2-pyrrolidone) (PVP) is a frequently used PEG alternative.[20] Another alternative is the hydrophilic, non-immunogenic and biocompatible polymer poly[N-(2-hydroxypropyl) methacrylamide] (pHPMA).[21] pHPMA has been investigated for use as the building block for hydrophilic shell. An advantage of pHPMA over PEG is greater multi-functionality, which allows multiple drugs or targeting ligands to be conjugated to the same polymer chain.

Effect of concentration and temperature on micelles formulation

- **Solubility and cloud point**

Specific temperature at a specific pressure at which large groups of micelles begin to precipitate out into a quasi-separate phase. As temperature is raised above the cloud point this causes the distinct surfactant phase to form densely packed micelle groups known as aggregates. The phase separation is a reversible separation controlled by enthalpy (promotes aggregation/separation) above the cloud point, and entropy (promotes miscibility of micelles in water) below the cloud point. The cloud point is the equilibrium between the two free energies.[26]

- **Critical micelle concentration**

The critical micelle concentration (CMC) is the exact concentration of surfactants at which aggregates become thermodynamically soluble in an aqueous solution. Below the CMC there is not a high enough density of surfactant to spontaneously precipitate into a distinct phase. Above the CMC, the solubility of the surfactant within the aqueous solution has been exceeded. The energy required to keep the surfactant in solution no longer is the lowest energy state. To decrease free energy of the system the surfactant is precipitated out. CMC is determined by establishing inflection points for pre-determined surface tension of surfactants in solution. Plotting the inflection point against the surfactant concentration will provide insight into the critical micelle concentration by showing stabilization of phases.[27]

- **Krafft temperature**

The Krafft temperature is the temperature at which the CMC can be achieved. This temperature determines the relative solubility of surfactant in an aqueous solution. This is the minimum temperature the solution must be at to allow the surfactant to precipitate into aggregates. Below this temperature no level of solubility will be sufficient to precipitate aggregates due to minimal movement of particles in solution. The Krafft Temperature (T_k) is based on the concentration of counter-ions (C_{aq}). Counter-ions are typically in the form of salt. Because the T_k is fundamentally based on the C_{aq}, which is controlled by surfactant and salt concentration, different combinations of the respective parameters can be altered. Although, the C_{aq} will maintain the same value despite changes in concentration of surfactant and salt, therefore, thermodynamically speaking the Krafft temperature will remain constant.[28]

Components of micelles

Three main components of micelles formulation are surfactant, oil phase and aqueous phase.

- **Surfactants**

Surfactants are amphiphilic molecules composed of a hydrophilic or polar moiety known as *head* and a hydrophobic or nonpolar moiety known as *tail*. The surfactant head can be charged (anionic or cationic), dipolar (zwitterionic), or non-charged (nonionic).

Anoinic surfactant

Anionic surfactants are surfactants that carry a negative charge on at least one part of the molecule. Typical anionic surfactants are derivative of the nonionic alkoxylates, but are not restricted to molecules comprising an alkylene oxide unit. Typical anionic functional units are sulfate, sulfonate, phosphate and carboxylate groups.

Example

Sodium dodecyl sulfate (SDS), Carboxylates, Sulphonates, Petroleum Sulphonates, Alkylbenzenesulphonates, Olefin Sulphonates, Alkyl Sulphates, Sulphates, Sulphated Natural Oils & Fats, Sulphated Esters, Sulphated Alkanolamides, Alkylphenols, Ethoxylated & Sulphated.

Cationic surfactant

Cationic surfactants are surfactants that carry a positively charge on one part of the molecules.

Example

Benzethonium chloride (BZT), Quaternary Ammonium Salts, Amines With Amide Linkages, Polyoxyethylene Alkyl & Alicyclic Amines, 2- Alkyl 1- Hydroxethyl 2-Imidazolines.

Nonionic surfactant

Nonionic surfactants are a distinct type of surfactant with an uncharged polar head. In horticultural contexts, nonionic surfactants may be known as wetting agents because they help hydrophobic, or water repelling, soils to quickly and evenly absorb water by breaking the water's surface tension, allowing water molecules to spread for greater and faster water penetration.

Example

n-dodecyl tetra (ethylene oxide), Ethoxylated Aliphatic Alcohol, Polyoxyethylene Surfactants, Carboxylic Esters, Polyethylene Glycol Esters, Anhydrosorbitol Ester & It's Ethoxylated Derivatives, Glycol Esters of Fatty Acids, Carboxylic Amides, Monoalkanolamine Condensates, Polyoxyethylene Fatty Acid Amides.

Zwitterionic surfactants

Zwitterionic surfactants have both cationic and anionic centers attached to the same molecule. The cationic part is based on primary, secondary, or tertiary aminesor quaternary ammonium cations. The anionic part can be more variable and include sulfonates, as in the sultaines CHAPS (3-[(3-Cholamidopropyl) dimethylammonio]-1-propanesulfonate) and cocamidopropyl hydroxysultaine. The most common biological zwitterionic surfactants have a phosphate anion with an amine or ammonium, such as the phospholipids phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, andsphingomyelins.

The surfactant tail is usually a long chain hydrocarbon residue and less often a halogenated or oxygenated hydrocarbon or siloxane chain.[30,31] A surfactant, when present at low concentrations in a system, adsorbs onto surfaces or interfaces significantly changing the surface or interfacial free energy. Surfactants usually act to reduce the interfacial free energy, although there are occasions when they are used to increase it.[31] When surfactant molecules are dissolved in water at concentrations above the *critical micelle concentration (cmc)*, they form aggregates known as micelles. In a micelle, the hydrophobic tails flock to the interior in order to minimize their contact with water, and the hydrophilic heads remain on the outer surface in order to maximize their contact with water.[32, 33] The micellization process in water results from a delicate balance of intermolecular forces, including hydrophobic, steric, electrostatic, hydrogen bonding, and vander Waals interactions. The main attractive force results from the hydrophobic effect associated with the nonpolar surfactant tails, and the main opposing repulsive force results from steric interactions and electrostatic interactions between the surfactant polar heads. Whether micellization occurs and, if so, at what concentration of monomeric surfactant, depends on the balance of the forces promoting micellization and those opposing it.[33,34]

- **Oil phase**

All type of triglyceride is use as the oil phase for micelles formulation. Mainly medium chain triglyceride are highly use, because they form a fine microemulsion with low HLP value surfactant. Examples of medium chain triglyceride are labrafec, coconet oil, hydrogenated palm oil, olive oil.

- **Aqueous phase**

Water is used as aqueous phase for micelles formulations.

Drug release from micelles formation

Two major pathway exist by which the encapsulated drug released from the micellar core. These pathways involve the micelles dissociation followed by the drug cleavage from the unimer and the drug cleavage within the micelle followed by diffusion out of the drug delivery system [fig. 2].[24] There are various ways to control the cleavage. For micellar dissociation, three machanisms exist by which the degradation occurs.[25] For drug cleavage followed by diffusion, the release depends on the chemical conjugation of the drug to the hydrophobic polymer.[24]

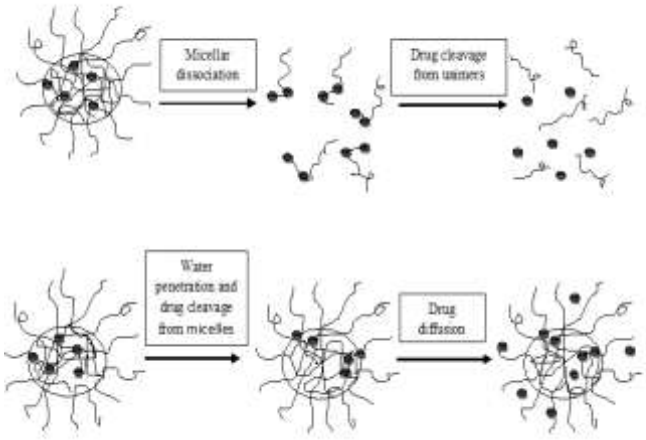

Figure 2: Two mechanisms for drug release from micelle-forming.[24]

Evaluation of micelles

- **Morphological Characterization**

Transmission electron microscopy (TEM) is one of the most common methods used to characterize the morphology of nanoscopic and mixed micelles. The morphology of the prepare micelles in water is observe using TEM. One drop of the diluted micelles is place on

a copper grid with nitrocellulose covering. Prior to observation, the sample is negatively stained with 2% (w/v) phosphotungstic acid for 5 minutes and dry at room temperature.[29]

- **Determination of the particle size and zeta potential of the micelles**

The particle size and zeta potential of the prepare micelles are determine by dynamic light scattering using a Zetasizer. The measurements are performed at a scattering angle of 90°, after 5 minutes of equilibration of the micelles solution. The temperature is maintained at 25°C during the measurements.[29]

- **Differential scanning calorimetry (DSC)**

The physicochemical properties of the PPD in micelles are evaluated with differential scanning calorimetry. The solid sample is dried at 40°C to remove residual water. The analysis of the PPD, phospholipid, Labrasol, the physical mixture, and mixed micelles is performe using a nitrogen atmosphere DSC and each sample is heated from 10°C to 500°C at an increasing temperature speed of 10°C per minute.[29]

- **Drug loading (DL) and drug entrapment effiiency (EE)**

DL and EE are measure using a high-performance liquid chromatography (HPLC) method. The HPLC system is use with a UV detector set at 203 nm. The separation is performe on a RP-C18 column. The mobile phase of the drug and deionized water (90/10, v/v) is use at a flow rate of 1.0 mL/ min, and the column temperature is maintaine at 30°C. The EE and DL are measure as follows: Briefl, the prepared micelles is dissolve in ethanol and then centrifuged at 13,000 rpm for 15 minutes to obtain the supernatant. The resulting solution is then analyzed by HPLC. Each sample are measure three times. The DL and EE were calculated using the following equations:[29]

EE (%) = Amount of drug in micelles/Amount of drug added; (1)

DL (%) = Amount of drug in micelles/Amount of phospholipid complex (2)

- **Solubility measurements**

The water solubility is determine by shaking excess solute in water. Excess amounts of the micelles are then disperse in 2 ml of water and are shaken at a speed of 40 r/min for 24 hours, in a heated water bath at 37°C, until the solution reach a balance. The solution is then centrifuged at 13,000 rpm for 15 minutes and filtered using a 0.45 μm membrane.[29]

- **In vitro release studies**

The in vitro release of PPD from the mixed micelles under sink conditions is investigate using dialysis in a simulated intestinal medium, with the addition of 0.5% Tween®-80 as the release medium. 5 ml of prepared micelles solution is added into a dialysis bag and the dialysis bag is placed into the release medium, with a paddle revolution speed of 100 rpm, at 37°C. At specific time intervals, 2 ml of the medium is withdrawn for sample analysis and replaced with an equal volume of prewarmed fresh media. The cumulative release profile of the drug at each time point was verified. Each experiment is performed in triplicate.[29]

Applications

- **Delivery of anticancer agents to treat tumors**

Chemotherapy is an essential component in the multidisciplinary management of most cancers. Cancer is a leading cause of death world-wide and is responsible for approximately 13% of all deaths, according to the World Health Organization. A very promising approach to overcome systemic toxicity is the application of drug-loaded micelles. Currently, many drug-loaded micelles for anticancer therapy are under investigation in preclinical Studies to improve drug efficacy.

- **Drug delivery to the brain to treat neurodegenerative diseases**

By restricting drug transport to the brain, the blood brain barrier (BBB) represents a formidable impediment for the treatment of brain tumors and neurodegenerative diseases such as HIV-associated dementia, stroke, Parkinson's and Alzheimer's diseases. Two strategies using micelles have been evaluated to enhance delivery of biologically active agents to the brain. The first strategy is based on the modification of micelles with antibodies or ligand molecules capable of transcytosis across brain microvessel endothelial cells, comprising the BBB. The second strategy uses Pluronic block copolymers to inhibit drug efflux systems, particularly, and selectively increase the permeability of BBB. An earlier study used micelles of Pluronic block copolymers for the delivery of the CNS drugs to the brain.[35,36]

- **Delivery of antifungal agent**

The need for safe and effective modalities for the delivery of chemotherapeutic agents to treat systemic fungal infections in immune compromised AIDS, surgery, transplant and cancer patients is very high. The challenges to the delivery of antifungal agents include low

solubility and sometimes high toxicity of these agents. These agents, such as amphotericin B, have low compatibility with hydrophobic cores of polymer micelles formed by many conventional block copolymers. Thus, to increase solubilization of amphotericin B, the core-forming blocks of methoxy-PEOb- poly (Laspartate) were derivatized with stearate side chains.[37-38] The resulting block copolymers formed micelles. Amphotericin B interacted strongly with the stearate side chains in the core of the micelles, resulting in an efficient entrapment of the drug in the micelles, as well as subsequent sustained release in the external environment. As a result of solubilization of amphotericin B in the micelles, the onset of hemolytic activity of this drug toward bovine erythrocytes was delayed, relative to that of the free drug.[38] Using a neutropenic murine model of disseminated Candidas, it was shown that micelle incorporated amphotericin B retained potent in vivo activity. Pluronic block copolymers were used by the same group for encapsulation of another poorly soluble antifungal agent, nystatin.[39] This is a commercially available drug that has shown potential for systemic administration, but has never been approved for that purpose, due to toxicity issues. The possibility to use Pluronic block copolymers to overcome resistance to certain antifungal agents has also been demonstrated.[37,39] Overall, one should expect further scientific developments using polymer micelle delivery systems for the treatment of fungal infection.

- **Ocular drug delivery**

Various efforts in ocular drug delivery have been made to improve the bioavailability and to prolong the residence time of drugs applied topically onto the eye. While it has been known since long that conventional topical formulations are amenable to application to the anterior portion, most of the applied dose is lost due to the defensive mechanism of the eye. Consequently, much concerted effort has been directed towards increased retention of the applied dose on the eye surface, with the premise that such increased retention will result in better therapeutic effect and lowered local and/or systemic effects. Since most drugs poorly penetrate the cornea, fulminating diseases of the posterior segment viz. vitreous, retina and choroid are required to be treated with either systemic administration or through intravitreal injections and vitreal implants. While therapy with systemic administration requires large doses due to strong blood-ocular tissue barrier, the other two routes are very invasive requiring skilled administration, and are associated with a high degree of risk, such as development of retinal detachment and endophthalmitis. Clearly there is a strong case in favor of formulating ocular delivery systems by focusing on improved ocular bioavailability

and extended drug effect in targeted tissues. Prolonging pre-corneal residence time through viscosity enhancers and gels has only a limited value, because such liquid formulations are eliminated by the usual routes in the ocular domain. The highly sensitive corneal/conjuctival tissues towards penetration enhancers to maximize drug transport require great caution in the selection of the enhancer. An alternative approach is to develop a drug delivery system that would circumvent the problems associated with the conventional systems, and provide the advantages of targeted delivery of drugs for extended periods of time and be patient-friendly. The latter requisite becomes more crucial in cases where the patient has to use the drug preparation throughout his life, e.g. in glaucoma. These advantages have been reported in the literature through the use of micelles.[41] Micro and nanoparticles for topical ophthalmic application are presently being researched based grossly on nanotechnology in which drugs can be administered as an eye drop. Also poorly water soluble or insoluble drugs can be successfully fabricated as effective systems to provide easy administration to ocular tissues and convenience to the patient as well as ophthalmologist to adjustment of dose and dosing frequency according to disease therapy. It has been found that biodegradable polymers can be combined with drugs in such a way that the drug is released into the eye in a very precise and controlled manner. The formulation of biodegradable polymers as micelles holds significant promise for ophthalmic drug delivery, since it is suitable for poorly water-soluble drugs and would allow drop- By interaction with the glycoproteins of the cornea and conjunctiva they can form a precorneal depot resulting in a prolonged release of the bound drug. Nanoparticle formulations provide protection for agents susceptible to degradation or denaturation in region of harsh pH, and also prolong the duration of exposure of a new drug by increasing retention of the formulation through bioadhesion. In this context, more clinical studies are necessary to provide further information and insight into this new ophthalmic drug delivery system.[40]

Table1. PATANT RELEATED TO MICELLES.

S No.	Patent No.	Title	Year	Patentee/ Assignee	References
1.	US 9,260,461	Water-soluble derivatives and prodrugs of acacetin and methods of making and using there of	February 16, 2016	Li; Gui-Rong (Hong Kong, CN), Lin; Feng (Shanghai, CN), Versitech Limited (Hong Kong, HK).	Li et al.[42]
2.	US 9,260,501	Peptide extended insulins	February 16, 2016	Hoeg-Jensen; Thomas (Klampenborg, D), Kjeldsen; Thomas Borglum (Virum, DK), Markussen; Jan (Herlev, DK), Novo Nordisk A/S	Hoeg-Jensen et al.[43]

				(Barsvaerd, DK)	
3.	US 9,260,502	Protease-stabilized insulin analogues	February 16, 2016	Nielsen; Peter Kresten (Holte, DK), Hubalek; Frantisek (Herlev, DK), Lautrup-Larsen; Inger (Virum, DK), Balschmidt; Per (Horsholm, DK), Ludvigsen; Svend (Lynge, DK), Kjeldsen; Thomas Borglum (Virum, DK, Novo Nordisk A/S (Bagsvaerd, DK)	Nielsen et al.[44]
4.	US 9,260,647	Metallic particle mediated viscosity reduction of viscoelastic surfactants	February 16, 2016	Crews; James B. (Willis, TX), Baker Hughes Incorporated (Houston, TX)	Crews et al.[45]
5.	US 9,260,752	Compositions and methods of nucleic acid-targeting nucleic acids	February 16, 2016	Andrew Paul (San Francisco, CA), Haurwitz; Rachel E. (Kensington, CA), Doudna; Jennifer A. (Berkeley, CA), Berger; James M. (Baltimore, MD), Carter; Matthew Merrill (North Granby, CT), Donohoue; Paul (Berkeley, CA), Caribou Biosciences, Inc. (Berkeley, CA)	Paul et al.[46]
6.	US 9,265,742	Compositions and methods for treating inflammatory pain	February 23, 2016	Robin M. (Essex, GB), Brew; John (Hertfordshire, GB), Infirst Healthcare Limited (GB)	Robin et al.[47]
7.	US 9,265,833	Lipid dipeptide and gel	February 23, 2016	Miyamoto; Misao (Chiyoda-ku, JP), Miyachi; Nobuhide (Chiyoda-ku, JP), Iwama; Takehisa (Funabashi, JP), NISSAN CHEMICAL INDUSTRIES, LTD. (Tokyo, JP)	Miyamoto et al.[48]
8.	US 9,267,095	Low pH detergent composition comprising nonionic surfactants	February 23, 2016	Sarah Ann (Hebron, KY), Sadlowski; Eugene Steven (Cincinnati, OH), Thomas; Cheyne (Independence, KY), Teyssier; Peggy Marion (Milford, OH), The Procter & Gamble Company (Cincinnati, OH)	Ann et al.[49]
9.	US 9,267,134	Methods of modulating Micro RNAs in the treatment of pulmonary arterial hypertension	February 23, 2016	Baker; Andrew (Glasgow, GB), MacLean; Margaret (Glasgow, GB), Morrell; Nicholas (Cambridge, GB), The University Court of the University of Glasgow (Glasgow, GB) Cambridge Enterprise Limited (Cambridge, GB)	Baker et al.[50]

10.	US 9,267,212	Method and system for production of oxalic acid and oxalic acid reduction products	February 23, 2016	Twardowski; Zbigniew (Burnaby, CA), Cole; Emily Barton (Houston, TX), Kaczur; Jerry J. (North Miami Beach, FL), Teamey; Kyle (Washington, DC), Keets; Kate A. (Lawrenceville, NJ), Parajuli; Rishi (Kendell Park, NJ), Bauer; Alexander (Monmouth Junction, NJ), Sivasankar; Narayanappa (Plainsboro, NJ), Leonard; George (Princeton, NJ), Kramer; Theodore J. (New York, NY), Majsztrik; Paul (Cranbury, NJ), Zhu; Yizu (North Andover, MA), Liquid Light, Inc. (Monmouth Junction, NJ)	Twardowski et al.[51]
11.	US 9,267,948	Compositions and methods for cancer management using antibodies binding to nucleotide salvage pathway enzymes and complexes thereof	February 23, 2016	O'Neill; Kim Leslie (Provo, UT), Whitehurst; Robert Alan (Buena Vista, VA), Evans; Jaden Duss (Centerville, UT), Sharp; Daniel Williar (Buckeye, AZ), Alegre; Melissa Marie (Saginaw, TX), Brigham Young University (Provo, UT)	O'Neill et al.[52]
12.	US 9,267,951	Micellar compositions for use in biological applications	February 23, 2016	Mark (London, GB), Howes; Philip (Huntingdon, GB), King's College London (London, GB)	Mark et al.[53]

CONCLUSION

Micelles have the distinct advantages of having a small size, less toxicity, solubilizing the drug and targetability. As drug carrier systems micelle systems have shown potential to improve hydrophobic drug and protein delivery through enhanced solubility, increased stability, and controllable drug release properties. Micelles have been investigated for both oral and IV administration of poorly soluble compounds. Although oral delivery of drugs using micelles is an attractive approach, few studies have been carried out in vivo. Several micelle-based formulations for anticancer drugs, ocular drug delivery and antifungal drugs are commercially available. Still, in order to fully realize the potential of micelles as a solubilisation strategy for poorly water-soluble drugs, more fundamental research promoting deeper understanding of amphiphilic copolymer degradation mechanisms and micelle stability characterization in vivo is needed.

REFERENCES

1. S. R. K. Yellela. (Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs). *Journal of Bioequivalence & Bioavailability*, 2010; 2(2): 28–36.
2. K. H. Edward and D. Li. (Solubility in Drug like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization)., 2008; 56.
3. V. R. Vemula, V. Lagishetty, and S. Lingala. (Solubility enhancement techniques). *International Journal of Pharmaceutical Sciences Review and Research*, 2010; 5(1): 41–51.
4. D. Sharma, M. Soni, S. Kumar, and G. D. Gupta. (Solubility enhancement—eminent role in poorly soluble drugs). *Research Journal of Pharmacy and Technology*, 2009; 2(2): 220–24.
5. Kumar, S. K. Sahoo, K. Padhee, P. S. Kochar, A. Sathapathy, and N. Pathak. (Review on solubility enhancement techniques for hydrophobic drugs). *Pharmacie Globale*, 2011; 3(3): 001–7.
6. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. (Formulation design for poorly watersoluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications). *International Journal of Pharmaceutics*, 2011; 420(1): 1–10. [PubMed: 21884771].
7. Horter D, Dressman JB. (Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Advanced Drug Delivery Reviews)., 2001; 46(1-3): 75–87. [PubMed: 11259834].
8. Arik Dahan1, 3 and Jonathan M. Miller. (The Solubility–Permeability Interplay and Its Implications in Formulation Design and Development for Poorly Soluble Drugs) *AAPS Journal*, 2012; 14(2).
9. Torchilin VP. (Micellar nanocarriers: pharmaceutical perspectives). *Pharm Res.*, 2007; 24: 1–16.
10. Nagarajan R, Barry M. (Unusual selectivity in solubilization by block copolymer micelles). *Abstracts of Papers of the American Chemical Society*, 1986; 191: 287.
11. Rapoport N. (Combined cancer therapy by micellar-encapsulated drug and ultrasound). *International Journal of Pharmaceutics*., 2004; 277(1-2): 155–162. [PubMed: 15158978].
12. Ruan G, Feng SS. (Preparation and characterization of poly(lactic acid)-poly(ethylene glycol)- poly(lactic acid) (PLA-PEG-PLA) microspheres for controlled release of paclitaxel. Biomaterials)., 2003; 24(27): 5037–5044. [PubMed: 14559017].

13. Vangeyte P, Gautier S, Jerome R. (About the methods of preparation of poly(ethylene oxide)-bpoly(epsilon-caprolactone) nanoparticles in water analysis by dynamic light scattering). *Colloids and Surfaces Physicochemical and Engineering Aspects*., 2004; 242(1-3): 203–11.
14. Meier MAR, Aerts SNH, Staal BBP, Rasa M, Schubert US. PEO-b-PCL block copolymers: Synthesis, detailed characterization, and selected micellar drug encapsulation behaviour). *Macromolecular Rapid Communications*., 2005; 26(24): 1918–24.
15. Stapert HR, Nishiyama N, Jiang DL, Aida T, Kataoka K. Polyion.(complex micelles encapsulating light-harvesting ionic dendrimer zinc porphyrins)., 2000; 16(21): 8182–88.
16. Woodle MC, Engbers CM, Zalipsky S. (New amphipatic polymer lipid conjugates forming longcirculating reticuloendothelial system-evading liposomes). *Bioconjugate Chemistry.*, 1994; 5(6): 493–96. [PubMed: 7873652].
17. Jiang GH, Wang Y, Zhang R, Wang RJ, Wang XH, Zhang M, Sun XK, Bao SY, Wang T, Wang S. (Preparation of Redox-Sensitive Shell Cross-Linked Nanoparticles for Controlled Release of Bioactive Agents). *ACS Macro Letters*., 2012; 1(4): 489–93.
18. Tian M, Qin A, Ramireddy C, Tuzar Z, Munk P. (Hybridization of block-copolymer micelles). *Abstracts of Papers of the American Chemical Society*., 1993; 206: 89. PMSE.
19. Arnida, Nishiyama N, Kanayama N, Jang WD, Yamasaki Y, Kataoka K. (PEGylated gene nanocarriers based on block catiomers bearing ethylenediamine repeating units directed to remarkable enhancement of photochemical transfection). *Journal of Controlled Release.*, 2006; 115(2): 208–215. [PubMed: 16959359].
20. Lukyanov AN, Torchilin VP. (Micelles from lipid derivatives of water-soluble polymers as delivery systems for poorly soluble drugs). *Advanced Drug Delivery Reviews*., 2004; 56(9): 1273–1289. [PubMed: 15109769].
21. Talelli M, Rijcken CJF, van Nostrum CF, Storm G, Hennink WE. (Micelles based on HPMA copolymers). *Advanced Drug Delivery Reviews.*, 2010; 62(2): 231–239. [PubMed: 20004693].
22. Ying Lu1 and Kinam Park. (Polymeric Micelles and Alternative Nanonized Delivery Vehicles for Poorly Soluble Drugs) *Int J Pharm*., 2013; 453(1): 198–214.
23. Mondon Karine, Gurny Robot, Moller Michael. (Colloidal drug delivery system-recent advances with polymeric micelles). *Chimia*, 2008; 62: 832-840.
24. Aliabadi HM, Lavasaniafar A. (Polymeric micelles for the drug delivery. Expert opinion on Drug Delivery)., 2006; 3(1): 139-62.

25. Bilgicer B. (Biomedical Engineering. Class Notes Biomolecular Topics in Engneering)., 2009.
26. Paleologos, Evangelos K.; Giokas, Dimosthenis L.; Karayannis, Miltiades I. (Micelle-mediated separation and cloud-point extraction). *Trends in Analytical Chemistry*., 2005; 24(5): 426–36.
27. Daniel E. Klle, Cary, Chlou. (Water Solubility Enhancements of DDT and Trichlorobenzene by Some Surfactants Below and Above the Critical Micelle Concentration). *Environ. Sci Technol*., 1989; 23: 832-38.
28. Carolina Vautier-Giongo, Barney L. Bales. (Estimate of the Ionization Degree of Ionic Micelles Based on Krafft Temperature Measurements), *J. Phys. Chem. B*, 2003; 107: 5398-403.
29. Hai-jian Xia, Zhen-hai Zhang, Xin Jin, Qin Hu, Xiao-yun Chen, Xiao-bin Jia. (A novel drug–phospholipid complex enriched with micelles: preparation and evaluation in vitro and in vivo) *International Journal of Nanomedicine*, 2013; 8: 545–554.
30. Jones, M.N., Chapman, D. (Micelles, monolayers and biomembranes)., 1995.
31. Rosen, M.J. (Surfactants and interfacial phenomena)., 1989.
32. Chevalier, Y., Zemb, T. (The structure of micelles and microemulsions). *Rep Prog Phys*, 1990; 53: 279-371.
33. Tanford, C. (The hydrophobic effect: Formation of micelles and biological membranes)., 1980.
34. Israelachvili, J.N. (Intermolecular and surface forces)., 1991.
35. Kabanov AV, Batrakova EV, MelikNubarov NS, Fedoseev NA, Dorodnich TY, Alakhov VY, Chekhonin VP, Nazarova IR and Kabanov VA (A new class of drug carriers: Micelles of poly(oxyethylene)-poly(oxypropylene) block copolymers as microcontainers)., 1992.
36. Kabanov AV, Chekhonin VP, Alakhov VY, Batrakova EV, Lebedev AS, Melik Nubarov NS, Arzhakov SA, Levashov AV, Morozov GV, Severin ES and Kabanov VA. (The neuroleptic activity of haloperidol increases after its solubilization in surfactant)., 1989.
37. Kwon GS. (Polymeric micelles for delivery of poorly water-soluble compounds). *Crit Rev The Drug Carrier System*, 2003; 20: 357-403.
38. Jagannath C, Emanuele MR and Hunter RL (Activity of poloxamer CRL- 1072 against drug-sensitive and resistant strains of Mycobacterium tuberculosis in macrophages and in mice). *Int J Antimicrob Agents*, 2000; 15: 55-63.

39. Kabanov AV, Chekhonin VP, Alakhov VY, Batrakova EV, Lebedev AS, Melik Nubarov NS, Arzhakov SA, Levashov AV, Morozov GV, Severin ES and Kabanov VA. (The neuroleptic activity of haloperidol increases after its solubilization in surfactant)., 1989.
40. Ramesh C. Nagarwal, Shri Kant, P.N. Singh, P. Maiti, J.K. Pandit. (Review Polymeric nanoparticulate system: A potential approach for ocular drug delivery Journal of Controlled Release)., 2009; 136: 2–13.
41. M. Hamidi, A. Azadi, P. Rafiei. (Hydrogel nanoparticles in drug delivery). Adv. Drug Deliv. Rev., 2008; 60: 1638–49.
42. Li; Gui-Rong, Lin; Feng. Water-soluble derivatives and prodrugs of acacetin and methods of making and using thereof. US, 2016; 9: 260,461.
43. Hoeg-Jensen; Thomas, Kjeldsen; Thomas Borglum, Markussen. Peptide extended insulins. US 9,260,501.2016.
44. Nielsen; Peter Kresten, Hubalek; Frantisek, Lautrup-Larsen; Inger, Balschmidt; Per, Ludvigsen; Svend, Kjeldsen; Thomas Borglum. Protease-stabilized insulin analogues. US, 2016; 9: 260,502.
45. Crews; James B. Metallic particle mediated viscosity reduction of viscoelastic surfactants. US, 2016; 9: 260,647.
46. Andrew Paul, Haurwitz; Rachel E, Doudna; Jennifer A, Berger; James M, Carter; Matthew Merrill, Donohoue; Paul. Compositions and methods of nucleic acid-targeting nucleic acids. US, 2016; 9: 260,752.
47. Robin M, John. Compositions and methods for treating inflammatory pain. US, 2016; 9: 265,742.
48. Miyamoto; Misao, Miyachi; Nobuhide, Iwama; Takehisa. Lipid dipeptide and gel. US, 2016; 9: 265,833.
49. Sarah Ann, Sadlowski; Eugene Steven, Thomas; Cheyne, Teyssier; Peggy Marion. Low pH detergent composition comprising nonionic surfactants. US, 2016; 9: 267,095.
50. Baker; Andrew, MacLean; Margaret, Morrell; Nicholas. Methods of modulating Micro RNAs in the treatment of pulmonary arterial hypertension. US, 2016; 9: 267,134.
51. Twardowski; Zbigniew, Cole; Emily Barton, Kaczur; Jerry J, Teamey; Kyle, Keets; Kate A, Parajuli; Rishi, Bauer. Method and system for production of oxalic acid and oxalic acid reduction products. US, 2016; 9: 267,212.
52. O'Neill; Kim Leslie, Whitehurst; Robert Alan, Evans; Jaden Duss, Sharp; Daniel Williar , Alegre; Melissa Marie. Compositions and methods for cancer management using

antibodies binding to nucleotide salvage pathway enzymes and complexes thereof. US, 2016; 9: 267,948.

53. Mark, Howes; Philip. Micellar compositions for use in biological applications. US, 2016; 9: 267,951.