Review Article

Nano Micelles an Emerging Platform for Drug Delivery

Nita Deore*[1], Kamlesh Dandgavhal[2], Vipulata Yeole[1], Punam Bagad[1], Pratiksha Aher[1] Sunil Amrutkar[3]
[1]Assistant Professor, Department of Pharmaceutics,
[2] Assistant Professor, Department of Pharmaceutical Chemistry,
[3] Professor and Principal, Department of Pharmaceutical Chemistry,
[1, 2, 3] Gokhale Education Society's,
Sir Dr. M.S. Gosavi College of Pharmaceutical Education and Research, Nashik, Maharashtra, India.
***Corresponding author's E-mail:** nita.deore2009@gmail.com

Received: 19-02-2021; **Revised:** 28-03-2021; **Accepted:** 06-04-2021; **Published on:** 20-04-2021.

ABSTRACT

Micelles have for decades been researched as carriers of drug delivery. Through the enhanced permeability and retention effect, their use can potentially result in high drug accumulation at the target site. Although micelles allow for a great depth of tissue penetration for the delivery of targeted drugs, they typically disintegrate into the body easily. Therefore, a challenge is continuous drug delivery from micellar nanocarriers. This article summarizes different main techniques and underlying concepts for the use of micellar nanocarriers for continuous drug delivery. Other competing delivery mechanisms, such as polymeric microparticles and nanoparticles, are contrasted. To form nanoscale micelles, amphiphilic molecules self-assemble in suitable liquid media. Prodrug application, drug polymer conjugates, novel polymers with low critical micellar concentration or reverse thermoresponsive nature, reverse micelles, multi-layer micelles with layer by layer assembly, polymeric films capable of forming micelles in vivo and micelle coats on a solid support are strategies for sustained release nanomicellar carriers. For sustained drug delivery, these new micellar systems are promising.

Keywords: Micelles, Nanocarrier, Microparticles, Prodrug, Sustained release.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2021.v67i02.020

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v67i02.020

INTRODUCTION

A molecule that has polar or hydrophilic groups as well as nonpolar or hydrophobic sections is known as an amphiphilic molecule. Amphiphilic molecules exhibit a strange self-assembling activity when exposed to a solvent. The polar part orientates itself towards the solvent in a hydrophilic solvent, while the hydrophobic part of the molecule orientates itself away from the solvent.

The molecules thus form clusters in which the hydrophobic components are clustered away from the solvent in the middle and the hydrophilic components are aligned with the solvent. Such aggregates of an amphiphilic molecule are classified as natural or regular micelles when formed in this orientation (figure 01). Amphiphilic molecules may form micelles with the opposite orientation when exposed to a hydrophobic solvent, that is, with the hydrophobic part on the outside and the hydrophilic portion on the inside. Efficient candidates for encapsulation and delivery of hydrophilic drugs are reverse micelles.[1] Tests were performed on reverse micelles such as lysozyme[2], trypan blue[3] and fluorescein, as well as other solutes. Additionally, these reverse self-assemblies can also be used to encapsulate polymeric microparticles.[4]

When treating certain infectious diseases and cancers, continuous drug delivery is also expected to be helpful. Drug synthesis, use of novel polymers, layer by layer assembly of micelles on solid support, creation of reverse micelles, and preparation of drug polymer conjugate micelles and production of polymer films that form micelles *in vivo* are the current approaches to achieving sustained drug release from micelles.

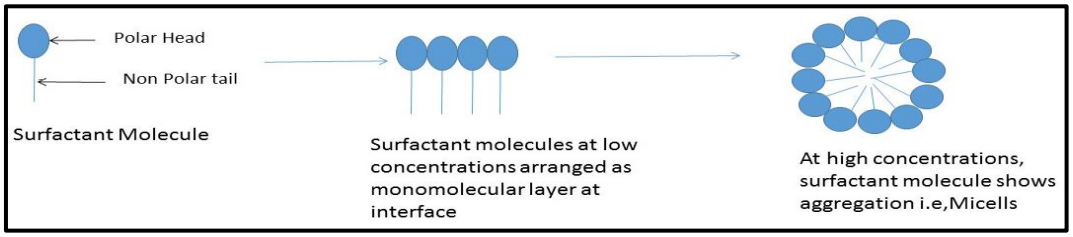

Figure 1: Structure of micells with polar and non-polar head

Increasing the solubility of poorly soluble drugs and targeting using pH-sensitive micelles are some of the other applications of micelles as well. However, these applications do not usually have an ongoing release and their discussion is thus beyond the reach of this article.

Sustain drug delivery from micelles

It is possible to identify approaches as those that use prodrugs, drug polymer conjugates, novel polymers with low essential micellar concentrations, reverse micelles, multilayer micelles, reverse thermoresponsive micelles, *in-vivo* micelle-forming polymer films and solid-support coated micelles.

Prodrugs

It is beneficial for preserving drug release to synthesize a prodrug of the drug of interest and encapsulate it in a micelle. A prodrug which is most compatible with the micelle-forming amphiphilic molecule is desirable in this approach. In this method, the two limiting mechanisms regulating drug release are prodrug release from the micelles and prodrug transfer to drugs. Paclitaxel palmitate, a prodrug of paclitaxel, synthesized by Forrest et al., is one such example.[9] and embedded in micelles of PEG-b-polycaprolactone (PEG-b-PCL) (Mw of PEG: 5000, Mw of PCL: 10,500). These micelles had a mean diameter of approximately 27-44 nm. Compared to 1 day release with the plain drug, the prodrug micelles released the prodrug over 14 days. This research did not, however, determine the release of the drug by itself from the prodrug.

In contrast with the unencapsulated prodrug or paclitaxel itself,[9] the prodrug micelles also showed stronger antiproliferative effects in breast cancer cells, although the changes were modest (~10-20 percent greater cell growth inhibition).

Encapsulation of paclitaxel in micelles increased the time from less than 10 to 25 h for the drug to be detected in the serum. For prodrug, as compared to approximately 11 h for plain prodrug, micelles maintained drug levels up to 50 h. Therefore, in combination with micelles, the prodrug strategy prolongs drug release and hence, theoretically, its effects as well.

This approach can, in addition to raising the release time and effect, contribute to an increase in drug tolerability among drug recipients. The encapsulated prodrug showed no signs of toxicity at a dose of 40 mg/kg for 24 hours, whereas the free prodrug showed signs of toxicity at a dose of 10 mg/kg and higher within 12 hours of administration.

Drug polymer conjugates

This is one of the most successful ways to sustain the release of drugs from a method of micellar delivery. Typically, this method involves forming a drug conjugate with the hydrophobic portion of an amphiphilic polymer and then forming micelles from this conjugate. Two phases will be applied to such a formulation for the release of the drug. First, by enzyme hydrolysis or other means of breakdown, the drug is released from the polymer, and second, the drug is released from the micelles by diffusion of the drug, with the former usually being the rate-limiting step. A significant benefit of this process is that, due to conjugation, the drug stays in the micelle for a long period of time. This process, however, involves some complicated chemistry to form a drug-polymer conjugate. Yoo and Park merged doxorub1icin (DOX) with the PLGA component of PLGA-PEG (Mn = 13000, Mw = 23000), where the molecular weight of the PEG used for copolymer preparation was 2000. [11]

PLGA-DOX formed the heart in this preparation and PEG formed the micelle's shell. The size of the micelles mentioned was roughly 61.4 nm. The CMC of the micelles with or without DOX was found to be 0.1 µg/ml, suggesting that the micelle-forming properties of the polymer were not affected by the conjugated DOX. The conjugate's drug-loading efficiency in micelles was approximately 99%, while that of the physically trapped drug was about 23%. In vitro drug release trials for conjugate micelles showed approximately 60% drug release over 16 days as compared to physical trapping micelles, which released the entire dose in around 4 days.[11] A comparison between drug-conjugated micelles and the plain drug showed that the micelles in HepG2 cells were 10 times more cytotoxic than the free drug. A conjugate of an oligodeoxynucleotide (ODN) and PLGA polymer was synthesised by Jeong and Park using carbodiimide chemistry. The ODN acted as the hydrophilic component and the hydrophobic portion of the conjugate acted as the PLGA. The micelles formulated with this conjugate had a mean diameter of about 65.2 nm and maintained up to 50 days of in vitro release of ODN. 7.5 µg/ml was found to be the CMC of the ODN conjugated micelles, which was higher than that of the PEG-PLA (100 µg/ml). [12] For the conjugated micellar formulation, the ODN uptake in mouse fibroblasts was higher compared to plain ODN [11, 12] Compared to 4 days when the drug is physically stuck in the micelles, a PLGA-DOX conjugate suggests an in vitro release for at least 16 days. In vitro drug release was maintained for up to 50 days by an oligodinucleotide-PLGA conjugate, on the other hand. The micelles prepared by the same strategy-polymer-drug conjugates are ODN-PLGA and PEG-PLGA-DOX. Therefore, comparing the in vitro release of both these forms of micelles is informative.

NK012 micelles

Kuroda et al. developed NK012 polymeric micelles with a diameter of 20 nm to encapsulate 7-ethyl 10-hydroxy camptothecin (SN38) and compared them with its prodrug irinotecan hydrochloride (CPT11). Five human glioblastoma cell lines were used to assess the formulation and the prodrug. The IC50 of the simple drug SN38 was found to be 0.052 µmol/l, while it was found to be 0.069 µmol/l for the micellar formulation. 13 µmol/l was found to be the IC50 of the prodrug CPT11, which is substantially higher than both the plain drug and the micellar formulation. In orthotopic glioblastoma xenografts in nude mice, both the micelle formulation and the simple drug were also tested.

Compared to the prodrug CPT11, the micellar formulation of SN-38 showed a substantial (almost six-fold) decrease in the relative volume of the tumour up to day 25. Until 80 days with the micellar formulation, the relative tumour volume was held near zero. The relative shift in body weight in mice during therapy was also approximately 10% lower for the micellar formulation than for the prodrug, suggesting that the micellar formulation was tolerated comparatively well than the prodrug.[13] Thus, it contributes to a sustained release of the drug by conjugating the drug with the polymer and then forming micelles from the conjugate.

Block copolymers with lipids one useful method in preparing micelles is to block copolymers between a polymer and a lipid. Increasing the length of a micelle's hydrophobic portion has been shown to lead to a decrease in its CMC.[14] Lipids are more hydrophobic than most polymers and, thus, the CMC could be reduced by a micelle made with a lipid as its hydrophobic portion. A useful solution may therefore be to use fatty acyl chains as hydrophobic segments in an amphiphilic copolymer. Distearoylphosphatidyl ethanolamine (DSPE) was used as the hydrophobic block to form 22 nm micelles in a diblock copolymer containing hydrophilic polyethylene oxide (PEO). These micelles maintained lipophilic beclomethasone dipropionate release for up to 6 days[15] (partition coefficient [logD] = 3.49). Micelles of polyethylene oxide-poly[N-(6-hexyl stearate-l-aspartamide)] (PEO-PHSA) were prepared by Lavasanifar et al. to encapsulate amphotericin B (an antifungal).[15] Within 10 minutes, the plain drug was released, while only 20 percent of the encapsulated drug was released in 1 h. The release was inversely dependent on the degree of substitution of fatty acids in the heart. A greater replacement contributes to a slower release of the drug from the micelles. The slow release was due to the beneficial interactions of fatty acids between the drug and the micellar heart. Red blood cells were also protected from hemolysis by slower release, a side effect of the drug. The continuous release was, however, only maintained for up to a few hours. [16]

Diblock copolymer micelles

It may result in drug retention and continuous release of the drug from such polymer micelles by using a polymer that physically interacts with the drug. If the drug can form hydrogen bonds with the micelle centre, so much more sustained would be the release obtained from the micelle. Yang et al., for instance, prepared PEG-b-poly-l-lactic acid (PEGb-PLLA; Mw: 8500 Da) and PEG-b-PCL (Mw: 10,050 Da) micelles to block copolymers and examined the in vitro release from these micelles of the hydrophobic drug quercetin. For approximately 160 h, the release of quercetin from PEG-PLLA and PEG-PCL micelles was preserved. The *in vitro* release experiments also showed that for the PEG-PCL micelles, the total amount of drug released in 160 h was less than for the PEG-PLLA micelles.[17] H-bonds formed between the drug and the hydrophobic centre of the micelle were due to the sustained release. A greater degree of H-bonding between quercetin and PCL than quercetin and PLLA was due to the lower quantity of drug released by the PEG-bPCL micelle. The release of the drug from the micelle can also be maintained by using a polymer which participates in hydrophobic interactions with the drug. If the polymer interacts with the drug hydrophobically, then the micelle's hydrophobic core resists the drug's migration from the core to the media, resulting in sustained drug release. This implies that not only the properties of the micelle, but also the properties of the polymer and drug influence the release. Xiangyang et al., who synthesised micelles of N-succinyl,N'-octyl chitosan (chitosan Mw: 100,000 Da) and loaded DOX, [18] made an attempt to shape such micelles. Depending on the percentage of octyl material, the mean diameter of the micelles was 100–200 nm and the CMC ranged from 2.4 to 5.9 µg/ml. The release inversely depended on the number of octyl chains, indicating that the octyl chain participates in the hydrophobic interactions with the drug.[19] The cytotoxicity of the micelles was tested on HepG2, A549, BGC and K562 cancer cell lines and was compared with free DOX. The IC50 for the drug and the micelles was compared and the IC50 for the micelles was found to be lower than the free drug by two- to six-fold. Polymeric micelles made from PEGpoly(benzyl aspartate) were used to encapsulate synthetic retinoids Am80 and LE540. In vitro phosphate buffered saline (PBS) release tests at 37°C showed that only 10 percent of the strongly hydrophobic retinoid LE540 was released in 4 days, while approximately 100 percent of the less hydrophobic retinoid Am80 was released in 4 days. This again demonstrates that hydrophobic drug-polymer interactions can play a role in preserving the release of the encapsulated drug. [20]

Multi-arm block copolymers

It can also be useful to synthesize multiarm block copolymers to solve the stability issue of normal micelles. For example, with an amphiphilic block copolymer with multiple hydrophilic blocks and a single hydrophobic block, star-shaped or multiarmed micelles can be produced. When the number of arms is high enough, these polymers will form micelles. H40–PLA–mPEG (Mn = 108,516 Da; Mw = 148,678 Da) is one such polymer. H40 is a polyol containing 64 groups of hydroxyl and is hydrophilic. This means that there are two hydrophilic portions of the multi-arm copolymer and one hydrophobic region. This polymer was used to shape 5-FU-containing micelles (5-fluorouracil). The micelles maintained a release of 5-FU for up to 80 h, unlike a single drug which was fully released within 4 h.[21] It was found that the CMC of this polymer was 4.5 µg/ml and 74 nm was the mean diameter of the micelles. In cultured human endothelial cells, neither polymer (400 µg/ml) nor micelle (up to 400 µg/ml) exposure up to 24 h demonstrated any cytotoxicity. Such a polymer can result in more prolonged release of the drug with some stabilizing strategies.

Graft polymers

Graft polymers have recently attracted significant attention in preparing micelles. Cellulose graft polymers can be used to form micelles for sustained drug release. The cellulose portion of the polymer can be the hydrophilic part, with any hydrophobic segment conjugated to it to form an amphiphilic graft polymer. Such polymers are claimed to be biodegradable. Cellulose-g-PLLA (Mn of cellulose = 1.2 × 105 g/mol; Mn of PLLA = 11,000 g/ mol) polymer has been used for the sustained delivery of prednisone acetate. [22] Delivery of prednisone acetate was sustained up to more than a week with the use of these micelles. However, drug release for plain drug was not reported. The polymer had a CMC of 47.1–58.1 µg/ml and the mean diameter of the micelles was 30–80 nm. [23] Similarly, graft polymer micelles of pthaloyl chitosan (Mw = 5.78 × 105 Da) and mPEG-2000 sustained the release of camptothecin for 96 h. Moreover, this polymer was synthesized in such a way that the release rate and the percentage yield depended on the degree of deacetylation of chitosan. The CMC of the polymer was 28 µg/ml and the mean diameters ranged from 100–250 nm. The diameter increased with an increase in the degree of deacetylation. Further, higher amounts of drug were incorporated with an increase in the degree of deacetylation of chitosan. The cytotoxicity in HeLa cells also increased with the degree of deacetylation, most likely due to a greater amount of drug incorporated in the micelles. [24]

Combination of polymer and polyamino acid

A combination of polymer and polyamino acid can form an amphiphilic polymer. PEG–polyglutamic acid copolymer was cast-off to prepare micelles for the delivery of cisplatin. The mean diameter of the micelles was 28 nm. The micelles showed a consistent and sustained release of the drug during a 150 h release study. Only 60% of the drug was released during 150 h. The micelles were injected in vivo in mice and compared with the free drug. After 25 h, approximately 10% of the injected dose was found in plasma with micelles compared with 0.1% with the plain drug. This increase was attributed to the decrease in clearance of the micelles compared with the plain drug. This corresponded to less accumulation of the drug in liver, kidney and spleen compared with the tumor with the micelles.[25] Wei et al. reported the synthesis of a polyglutamic acid–poly(propylene oxide) (PPO)–poly glutamic acid polymer (PPO-4000) that is pH sensitive. [26] At high pH, the polyglutamic acid residues form a coil conformation. But at low pH, it transforms to an alpha-helix conformation. Therefore, at low pH, the polyglutamic acid chain shrinks and creates a stress on the core and hence, results in the distortion of the core of the micelles, which causes the entrapped drug to leak out. DOX showed release up to 168 h with this system. Further, this system can be dispersed in a temperature-sensitive gel and hence, a much sustained release dual drug delivery system might be feasible. [27] However, using peptides to encapsulate drugs is relatively a new field and in vivo work needs to be done further on this delivery system to ensure that this system indeed works as it promises.

Reverse micelles

All the above mentioned approaches have been designed for the delivery of largely hydrophobic drugs. However, these approaches are not as useful for the delivery of hydrophilic drugs. Reverse micelles can be used for the delivery of hydrophilic drugs. Reverse micelles are especially useful for administration in oily vehicles. Usually the nutrients required for comatose patients are given as oily injections. Moreover, USP injections of steroids can also be made as oily injections. Reverse micelles can prove to be useful for the co-administration of hydrophilic drugs in such injections. Some biocompatible oils are also used as vehicles in oral delivery. Thus, reverse micelles may be useful in oral delivery of some drugs by dispersion of micelles in oily vehicles. Reverse micelles may be particularly useful for protein delivery. For instance, ovalbumin was encapsulated in poly caprolactone-poly(2-vinyl pyrrolidone (PCLb-P2VP; Mn PCL = 35,400 g/mol, Mn P2VP = 20,900 g/mol) reverse micelles and dispersed in an oily medium (oleic acid). [28] The mean hydrodynamic diameter of the ovalbumin loaded micelles was 157 nm. The protein was entrapped in the aqueous core and the micelles sustained protein release up to 200 h upon contact of the micelle containing oily medium with an aqueous medium. The release of hydrophilic dyes such as fluorescin sodium and trypan blue have been reported from this system up to 60 days. The dyes were dispersed in PLGA polymeric nanoparticles and the nanoparticles were encapsulated in micelles to provide a greater sustained release.[29]

Comparison with other delivery systems

Thus far, several strategies that are useful in achieving sustained release micelles have been discussed. Below, some competing alternative delivery systems for sustained drug delivery are briefly discussed. The discussion has been restricted to particulate delivery systems since these are more similar to micelles. However, it should be noted that implantable drug delivery systems are also clinically relevant for prolonged drug delivery. Polymeric microparticles Polymeric microparticles have been most successfully employed in the sustained delivery of drugs. Release profiles of drugs up to 6 months have been reported with polymeric microparticles (e.g., Lupron Depot®). Furthermore, sustained release up to 287 days has been shown in dogs with ivermectin in PLGA microparticles. [30] Such formulations are polymeric matrix formulations that are injected as suspensions. [31] These particles are micron size in diameter and hence, they exhibit low burst effects/release. However, such particles are large in size and hence, they are not suitable for applications where the particles need to pass through leaky blood vessels. Also, they are not as effective as micelles in solubilizing a poorly soluble drug. Hence, there is a need for better formulations that have both the solubilizing capacity of micelles and sustained release capacity of microparticles. Polymeric nanoparticles Polymeric nanoparticles have also been used

for targeted and sustained release of drugs. For instance, Singh et al. reported targeted gene delivery to the retina following intravenous administration of functionalized PLGA nanoparticles. [32] Furthermore, PLGA polymeric nanoparticles have been shown to sustain the release of tetanus toxoid in vivo for 4 months. [33] Nanoparticles increase the surface area of the formulation and hence, result in significant burst effects/release. [34] Moreover, drug loading can be limited in these nanoparticles. Further, they tend to aggregate more readily, resulting in larger particles compared with micelles less than 100 nm. Hence, polymeric nanoparticles do not completely alleviate the need for a better delivery system at the nanoscale.

Liposomes have also been used for sustained release of drugs. Liposomes are comprised of lipids that are largely endogenous in the human body. Hence, they avoid the toxicity issues. Although, release profiles up to a month have been reported with liposomes for anti-tubercular drugs [35], they are not the first choice delivery systems for prolonged drug delivery. Doxil, a pegylated liposomal formulation of DOX, demonstrates an in vitro release of 100% over 24 h. Atyabi et al. showed that 100% release of SN-38 occurs from pegylated liposomes in 25 days as compared with 60% from non-pegylated liposomes. [36]

Micelle stability and evaluation methods

When a micelle solution is diluted to a very low concentration (typically < 10^{-3} mM), the surfactant content is not sufficient to drive the self-assembly of micelles. Instead, they tend to distribute at the air-water or aqueous-organic solvent interface which leads to the disintegration of the micelles. Thus, a minimal concentration of surfactant, the CMC, is required to maintain the structure of micelles. [37] CMC is determined by the micelle inherent properties and is critical to evaluate the stability of micelles at diluted concentration.

In addition to dilution, the structural stability of micelles is influenced by the complicated physiological environment, such as salt concentration, solvents, temperature, and pH. For example, after injection/infusion into the bloodstream, micelles may undergo several environmental changes, including significant dilution, exposure to pH changes, and contact with numerous proteins, lipids, and cells. The hydrophilic and hydrophobic domains of certain micelles are linked via ester, amide and other functional groups. The micelle structure may potentially be disrupted due to the hydrolysis of linkers when facing significant pH changes. Other disruptors include protein absorption through non-specific binding or electrostatic interaction. The resulting premature release of the encapsulated therapeutic content may lead to the accumulation of the drug in healthy tissues or organs, which could cause severe side effects and a further decrease of the pharmaceutical activity of the drug. [38] The fundamental strategy to improve the stability of micelles is to enhance intra-micellar interactions, which are often reflected by a decreased CMC. Therefore, measuring the CMC value can directly evaluate the efficacy of these strategies.

The classical method to measure CMC is based on the observation of the concentration-mediated change in physical properties of micelles by measuring electrical conductivity [39], surface tension [40], chemical shifts detected by nuclear magnetic resonance (NMR) [41], absorption [42], determination of self-diffusion coefficients [43], and fluorescence intensity. [44] Transmission electron microscopy (TEM) and dynamic light scattering (DLS) are commonly used to show the overall morphology and size of micelles. The determination of aggregation number, which is the number of small molecules or polymer chains assembled to form a micelle, is another way to evaluate the assembly behavior. [45] The micelle aggregation number can be determined by isothermal titration calorimetry [45,46] or calculated from an apparent molecular mass of self-assembled micelle in a solvent obtained by static light scattering. In addition, fluorescence resonance energy transfer (FRET), which is sensitive to small changes in the distance between molecular groups, can be used to measure the integrity of micelles in solvents. [47–49] Typically, fluorescent energy donors and acceptors are encapsulated in the micelle hydrophobic domain, and the emission wavelength of the acceptors can be detected. Once a micelle dissociates upon dilution or other environmental changes, the resulting increased distance between donor and acceptor pair will lead to a decrease of the previous acceptor emission and an intensified emission of the donor.

CONCLUSION

Micelles have the distinct advantages of having a small size, less toxicity, solubilizing the drug and targetability. However, owing to their fragile structure and tendency to breakdown beyond CMC, preparation of long-circulating micelles and sustained-release micelles is a challenge. In the past few years, significant advances were made in overcoming these challenges. Currently, investigational micelle technologies are available for sustaining drug release from a few hours to a few months. However, the ease of preparation, shelf-stability and safety have to be factored prior to choosing a delivery system that is most appropriate in treating a particular disorder.

REFERENCES

1. Torchilin VP. Structure and design of polymeric surfactant-based drug delivery systems. Journal of controlled release. 2001 Jun 15;73(2-3):137-72.
2. Nishiyama N, Kataoka K. Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacology & therapeutics. 2006 Dec 1;112(3):630-48.
3. Determan MD, Cox JP, Mallapragada SK. Drug release from pH-responsive thermogelling pentablock copolymers. Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2007 May;81(2):326-33.
4. Qiu L, Zhang J, Yan M, Jin Y, Zhu K. Reverse self-assemblies based on amphiphilic polyphosphazenes for encapsulation

of water-soluble molecules. Nanotechnology. 2007 Oct 19;18(47):475602.

5. Forrest ML, Yáñez JA, Remsberg CM, Ohgami Y, Kwon GS, Davies NM. Paclitaxel prodrugs with sustained release and high solubility in poly (ethylene glycol)-b-poly (ε-caprolactone) micelle nanocarriers: pharmacokinetic disposition, tolerability, and cytotoxicity. Pharmaceutical research. 2008 Jan;25(1):194-206.

6. Yoo HS, Park TG. Biodegradable polymeric micelles composed of doxorubicin conjugated PLGA–PEG block copolymer. Journal of controlled Release. 2001 Jan 29;70(1-2):63-70.

7. Jeong JH, Park TG. Novel polymer− DNA hybrid polymeric micelles composed of hydrophobic poly (D, L-lactic-co-glycolic acid) and hydrophilic Oligonucleotides. Bioconjugate chemistry. 2001 Nov 21;12(6):917-23.

8. Kuroda JI, Kuratsu JI, Yasunaga M, Koga Y, Saito Y, Matsumura Y. Potent antitumor effect of SN-38-incorporating polymeric micelle, NK012, against malignant glioma. International journal of cancer. 2009 Jun 1;124(11):2505-11.

9. Zhang N, Guo SR, Li HQ, Liu L, Li ZH, Gu JR. Synthesis of Three Types of Amphiphilic Poly (ethylene glycol)-block-Poly (sebacic anhydride) Copolymers and Studies of their Micellar Solutions. Macromolecular Chemistry and Physics. 2006 Aug 2;207(15):1359-67.

10. Gaber NN, Darwis Y, Peh KK, Tan YT. Characterization of polymeric micelles for pulmonary delivery of beclomethasone dipropionate. Journal of Nanoscience and Nanotechnology. 2006 Sep 1;6(9-10):3095-101.

11. Lavasanifar A, Samuel J, Kwon GS. The effect of fatty acid substitution on the in vitro release of amphotericin B from micelles composed of poly (ethylene oxide)-block-poly (N-hexyl stearate-L-aspartamide). Journal of controlled release. 2002 Feb 19;79(1-3):165-72.

12. Yang X, Zhu B, Dong T, Pan P, Shuai X, Inoue Y. Interactions between an anticancer drug and polymeric micelles based on biodegradable polyesters. Macromolecular bioscience. 2008 Dec 8;8(12):1116-25.

13. Xiangyang X, Ling L, Jianping Z, Shiyue L, Jie Y, Xiaojin Y, Jinsheng R. Preparation and characterization of N-succinyl-N′-octyl chitosan micelles as doxorubicin carriers for effective anti-tumor activity. Colloids and Surfaces B: Biointerfaces. 2007 Apr 1;55(2):222-8.

14. Satoh T, Higuchi Y, Kawakami S, Hashida M, Kagechika H, Shudo K, Yokoyama M. Encapsulation of the synthetic retinoids Am80 and LE540 into polymeric micelles and the retinoids' release control. Journal of Controlled Release. 2009 Jun 19;136(3):187-95.

15. Prabaharan M, Grailer JJ, Pilla S, Steeber DA, Gong S. Amphiphilic Multi-Arm Block Copolymer Based on Hyperbranched Polyester, Poly (l-lactide) and Poly (ethylene glycol) as a Drug Delivery Carrier. Macromolecular bioscience. 2009 May 13;9(5):515-24.

16. Dong HQ, Xu Q, Li YY, Mo SB, Cai SJ, Liu LJ: The synthesis of biodegradable graft copolymer cellulose-graft-poly(l-lactide) and the study of its controlled drug release. Colloids Surf. B Biointerfaces 66(1), 26–33 (2008).

17. Opanasopit P, Ngawhirunpat T, Rojanarata T, Choochottiros C, Chirachanchai S. Camptothecin-incorporating N-phthaloylchitosan-g-mPEG self-assembly micellar system: effect of degree of deacetylation. Colloids and Surfaces B: Biointerfaces. 2007 Oct 15;60(1):117-24.

18. Nishiyama N, Okazaki S, Cabral H, Miyamoto M, Kato Y, Sugiyama Y, Nishio K, Matsumura Y, Kataoka K. Novel cisplatin-incorporated polymeric micelles can eradicate solid tumors in mice. Cancer research. 2003 Dec 15;63(24):8977-83.

19. Wei L, Cai C, Lin J, Chen T. Dual-drug delivery system based on hydrogel/micelle composites. Biomaterials. 2009 May 1;30(13):2606-13.

20. Miller AC, Bershteyn A, Tan W, Hammond PT, Cohen RE, Irvine DJ. Block copolymer micelles as nanocontainers for controlled release of proteins from biocompatible oil phases. Biomacromolecules. 2009 Apr 13;10(4):732-41.

21. Xu W, Ling P, Zhang T. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Journal of drug delivery. 2013;2013.

22. Topel Ö, Çakır BA, Budama L, Hoda N. Determination of critical micelle concentration of polybutadiene-block-poly (ethyleneoxide) diblock copolymer by fluorescence spectroscopy and dynamic light scattering. Journal of Molecular Liquids. 2013 Jan 1;177:40-3.

23. Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. Journal of pharmaceutical sciences. 2003 Jul 1;92(7):1343-55.

24. Avgoustakis K. Pegylated poly (lactide) and poly (lactide-co-glycolide) nanoparticles: preparation, properties and possible applications in drug delivery. Current drug delivery. 2004 Oct 1;1(4):321-33.

25. Cheng J, Teply BA, Sherifi I, Sung J, Luther G, Gu FX, Levy-Nissenbaum E, Radovic-Moreno AF, Langer R, Farokhzad OC. Formulation of functionalized PLGA–PEG nanoparticles for in vivo targeted drug delivery. Biomaterials. 2007 Feb 1;28(5):869-76.

26. Astete CE, Sabliov CM. Synthesis and characterization of PLGA nanoparticles. Journal of Biomaterials Science, Polymer Edition. 2006 Jan 1;17(3):247-89.

27. Dai Y, Wang H, Zhang X. Polyion complex micelles prepared by self-assembly of block-graft polycation and hyperbranched polyanion. Journal of Nanoparticle Research. 2017 Sep;19(9):1-8.

28. Kim S, Shi Y, Kim JY, Park K, Cheng JX. Overcoming the barriers in micellar drug delivery: loading efficiency, in vivo stability, and micelle–cell interaction. Expert opinion on drug delivery. 2010 Jan 1;7(1):49-62.

29. Talelli M, Barz M, Rijcken CJ, Kiessling F, Hennink WE, Lammers T. Core-crosslinked polymeric micelles: principles, preparation, biomedical applications and clinical translation. Nano today. 2015 Feb 1;10(1):93-117.

30. Domínguez A, Fernández A, González N, Iglesias E, Montenegro L. Determination of critical micelle concentration of some surfactants by three techniques. Journal of chemical education. 1997 Oct;74(10):1227.

31. Al-Soufi W, Piñeiro L, Novo M. A model for monomer and micellar concentrations in surfactant solutions: Application

to conductivity, NMR, diffusion, and surface tension data. Journal of colloid and interface science. 2012 Mar 15;370(1):102-10.

32. Moroi Y. Micelles: theoretical and applied aspects. Springer Science & Business Media; 1992 Mar 31.

33. Olesen NE, Westh P, Holm R. Determination of thermodynamic potentials and the aggregation number for micelles with the mass-action model by isothermal titration calorimetry: A case study on bile salts. Journal of colloid and interface science. 2015 Sep 1;453:79-89.

34. Bouchemal K, Agnely F, Koffi A, Djabourov M, Ponchel G. What can isothermal titration microcalorimetry experiments tell us about the self-organization of surfactants into micelles?. Journal of Molecular Recognition. 2010 Jul;23(4):335-42.

35. Lu J, Owen SC, Shoichet MS. Stability of self-assembled polymeric micelles in serum. Macromolecules. 2011 Aug 9;44(15):6002-8.

36. Chen H, Kim S, He W, Wang H, Low PS, Park K, Cheng JX. Fast release of lipophilic agents from circulating PEG-PDLLA micelles revealed by in vivo forster resonance energy transfer imaging. Langmuir. 2008 May 20;24(10):5213-7.

37. Chen H, Kim S, Li L, Wang S, Park K, Cheng JX. Release of hydrophobic molecules from polymer micelles into cell membranes revealed by Förster resonance energy transfer imaging. Proceedings of the National Academy of Sciences. 2008 May 6;105(18):6596-601.

Source of Support: None declared.

Conflict of Interest: None declared.