# From Lipids to Micelles- A Tentative Analysis of Drug Delivery

Qi Gao *

Queen Mary University of London, UK

* Corresponding Author Email: gaoq_323@163.com

**Abstract.** Polymer micelles (PM) are core-shell nanostructures formed by the self-assembly of amphiphilic block copolymers. Due to its hollow form and biocompatibility, it is an excellent drug carrier and has a wide range of uses in the pharmaceutical field. This review summarizes the latest developments in PM development and its applications. First, I explained the basic structure and several types of micelles. This process introduces experiments and parameters to control the shape of the vesicles used for drug delivery. Next, we talked about various common synthetic methods such as the solvent conversion method and the solvent-free method. In addition, we introduce polymer micelles into conventional pharmacies and the difficulties of modern medicine. Finally, it summarizes the morphology, synthesis method and application of PM in the medical field, and provides insights into the future development of vesicle degradation and the biocompatibility of PM preparation and the resulting morphology. In addition to the above, this article also introduces different methods of PM targeting, imaging, and triggered release in pharmaceutical applications.

**Keywords:** Micelles, Morphology, Self-assembled, Drug Delivery.

## 1. Introduction

Polymeric micelles (PMs) are nanosized polymer capsules with membranes that are generally considered to have a hydrophobic bilayer structure to phospholipids [1]. In the past decades, PMs have experienced vigorous development. PMs have been synthesized and have found potential applications in target positioning and as drug carriers for cancer [2], gene therapy [3], catalysts [4], and building materials [5]. In this review, we summarize the recent progress of synthesis and applications of PMs. We first discuss the morphology of polymer vesicles. The morphology of polymer vesicles is very important. The key assembly parameters determine what form the polymer vesicles will exist in, such as spheres, cones, truncated cones, or the corresponding reverse vesicles. Testing methods of CMC (critical micelle concentration) will also be introduced which has a significant impact on the synthesis of polymeric micelles. Bilayer and liposome are like twin brothers of micelles. The morphology of bilayer and liposome will also be introduced, and the influence of hydrophobicity and hydrophilicity on the production of different polymer vesicles will be explained. Then we further introduce synthetic methods which are an important subject in the study of polymer vesicles. Among them, solvent-switching techniques and solvent-free techniques are the most widely used technologies [5], but they still have many shortcomings. Therefore, this article will also introduce some other new technologies that have emerged in recent years, such as PISA (Polymerization-induced self-assembly) [14-17]. In addition, complex or large vesicles are also been a hot topic in recent years. The synthesis mechanism and technology of some such vesicles will also be introduced [18, 19]. Finally, some mature or potential applications would be introduced. For PMs, the most important application is its various applications as drug carriers due to its high similarity with cells' membranes. However, after the drug enters the blood vessel, the cells that need to be released must be accurately located, otherwise serious side effects may occur. Therefore, some tumour targeting technologies and applications including passive targeting and active targeting will be introduced in this article. Additionally, PMs imaging methods include nuclear imaging, CT and MRI. After finally reaching the target cells, drug release is required. Some drug release response methods will also be introduced.

# 2. Morphology

## 2.1. Solvent-switch method

Block and graft copolymer micelles belong to a broad family of polymer colloids. This series covers self-associating, self-assembling, or self-organizing polymer systems with surfactant or colloidal properties. Improving the inherent pharmacodynamics or pharmacokinetics of drugs is considered an important step in the development of potential drug therapies. This section describes the latest achievements in the design and development of CPP-modified nanoscale pH-responsive micelles to provide controlled drug release in tumour cells. [14]

| Nanocarrier | Advantages | Disadvantages | Ref. |
|---|---|---|---|
| **Micelles** | Solubilization of anticancer drugs, safety, favorable modifications, rapid accumulation into tumors due to smaller dimension | Poor drug loading efficiency, poor stability, poor selectivity toward cancer | |
| **Liposomes** | Encapsulation of both hydrophilic and hydrophobic drugs, good biocompatibility, good biodegradability | Poor stability, requirement of special storage, | |
| **Dendrimers** | Multiple functional groups for drug delivery, solubility enhancer, | Expensive scale-up production, cellular toxicity | [7-12] |
| **Inorganic NPs** | Modification with a variety of groups, easy and simple synthesis, tunable characteristics | Agglomeration, toxicity, protein corona induction, interaction with healthy cells, poor biodegradability | |
| **Carbon-based NPs** | Potential drug carriers, tunable geometry, diameter, and functional groups, cost-effective | Toxicity, drug release, poor biodegradability, poor bioavailability, poor biocompatibility | |
| **Polymer NPs** | Control drug release, tunable physicochemical characteristics, existence of stimuli-responsive properties | Poor stability, degradation, difficulty with scale-up production | |

**Table 1.** Advantages and disadvantages of different kinds of nanocarriers in DDSs.[13]

## 2.2. The basic structure of lipid

As one of the six nutrients required for the normal functioning of the human body, lipids provide the energy and essential fatty acids needed by the body and are also a constituent of human cell tissues. Besides, lipids are also a component of human cell tissue. Taking phospholipids as an example, modern biology has proven that it plays an important role in the composition of biological membranes, that's all because phospholipids form a unique bilayer structure. Since the body fluid of the human body is an aqueous environment, the hydrophilic head of the phospholipid molecule contacts the body fluid outwards, separating the intracellular fluid from the internal environment.

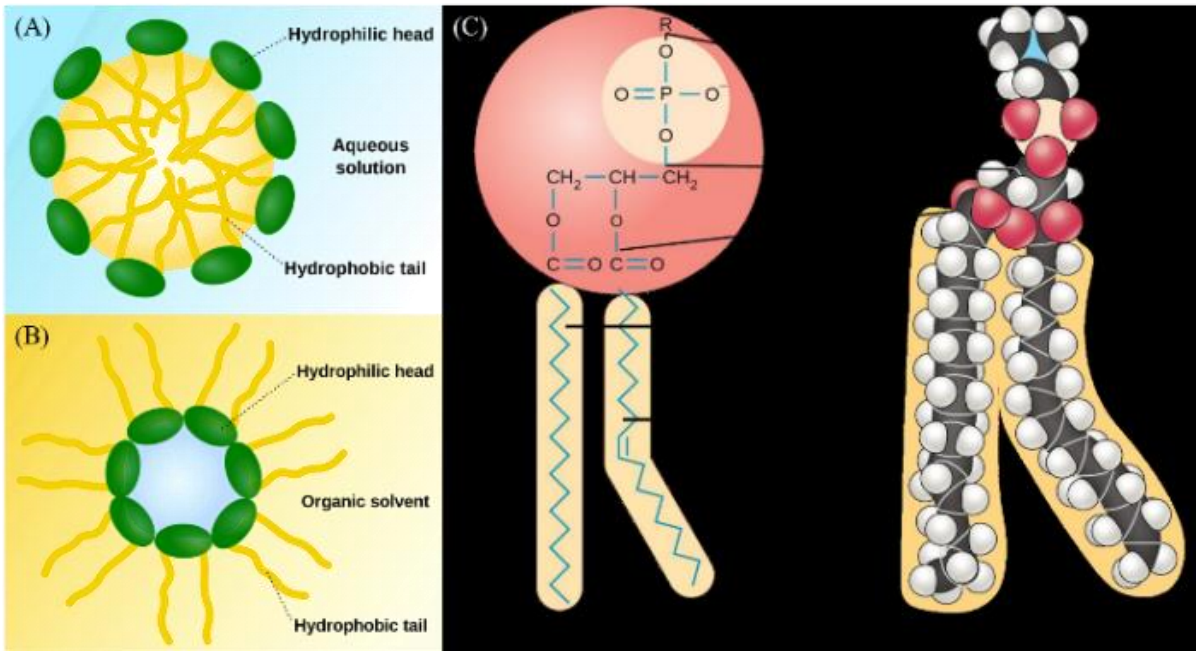



**Figure 1.** Different morphology of micelles [A] normal form [B] reverse form [C] microstructure

A detailed diagram of the phospholipid structure is shown in Figure 1(C) above. Biological membrane surfactants consist of phospholipids made up of glycerol esterified to two fatty acid chains plus a phosphate derivative polar head. The structure of it is RCH2-R'CH2-CH2-OPO3-X, where R and R' = alkyl-CO2-. The headgroups may contain a variety of different terminal groups X. For example, in phosphatidylcholine: X = -CH2CH2-N(CH3)3.

Due to the fluidity of the phospholipid bilayer, polymer micelles will easily serve as carriers to transport drugs to targeted organs or cells, which is undoubtedly a breakthrough for medical treatment.

### 2.3. Formation of micelles

Amphiphilic molecules (including phospholipids) can form micelles in both aqueous conditions and organic solvents. Micelles contain polar head groups that usually form the outside as the surface of micelles. They face the water because they are polar. The hydrophobic tails are inside and away from the water since they are nonpolar. The hydrophobic effect is the driving force for micelle formation. This is due to the strong hydrogen bond in water, which forces hydrophobic groups together to minimise their disruptive effect on the hydrogen-bonded water network. Hydrophobic groups arranged together in this way are sometimes said to be held by "hydrophobic bonds", even though their attraction is principally caused by repulsion from the water.

These amphiphilic molecules can structure themselves in a range of ways: micelle, liposome and bilayer sheet. A liposome consists of an aqueous core separated from the continuous aqueous phase by one or more spherical, bilayer membranes of surfactant molecules. They are simple models for biological cells, i.e., without proteins, and other cell contents, which will be a good drug carrier.

## 3. Testing

### 3.1. Testing

#### 3.1.1. Critical Micelle Concentration (CMC)

Critical micelle concentration is a concentration of surfactants (amphiphilic molecules) above which micelles are spontaneously formed. The CMC can be established by monitoring the change in the surface tension of water with increasing concentration of surfactant. When the addition of surfactant has no further impact on surface tension, the CMC has been reached.

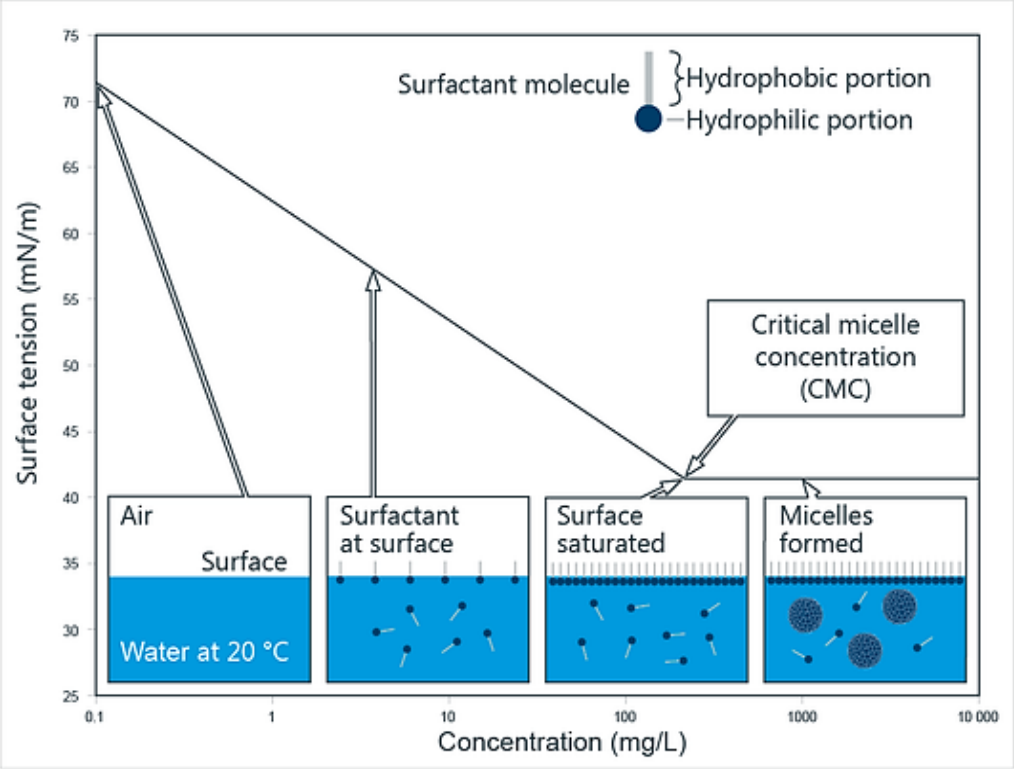



**Figure 2.** Surface tension vs concentration

The surface tension of water will reach its maximum when no surfactant molecule is added. After starting to add the surfactant, the micelles will not be formed immediately, but will first line up on the water surface with the hydrophilic head facing down the water and the hydrophobic tail facing the water surface. When the surface of the water is filled with surfactant molecules, that is, the surfactant concentration reaches CMC, the surface tension of the water reaches the minimum. At this time, continue to add surfactant molecules, the surface tension of the water does not change, and micelles begin to form.

It should be noted that the structure of micelles is determined by the surfactant (type, concentration and CMC) and the existing components (that is, completely water or hydrophobic solvent and salt concentration), therefore, a new parameter will be introduced to identify it, which will be explained in detail in the next section.

### 3.2. Critical Packing Parameter

#### 3.2.1. CPP formula

Micelle structures can be estimated visually by critical packing parameters. Critical packing parameter (CPP) shows a way on how surfactant molecular shape/interactions determine the aggregate geometry by using the formula below.

CPP=v/a0`lc (unitless)

Where, v = molecular volume of surfactant chain, a0 = area per surfactant head, lc = length of surfactant chain.

That is, if it is assumed that each surfactant molecule is a solid cone (cylinder), the parameter v is the volume of the chain, which can be calculated as the volume on a cone (cylinder); a0 is the area of the head, which could use the area formula of a circle to calculate; lc is the length of the chain, as shown in Figure 3.

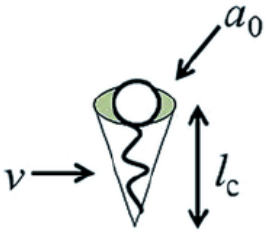



**Figure 3**. Away how assumes that the surfactant molecular as a cone (also can be a cylinder when CPP=1, which will be mentioned later)

### 3.2.2. CPP according to morphology

The value of CPP mainly divides the morphology of micelles into three stages. According to the size relationship with 1, the shape of each micelle is also different. To further distinguish the relationship between CPP and morphology is divided into the following five types, which represent different structures formed as micelles, bilayers and inverted micelles.

For drug transportation, CPP less than 1/2 or even 1/3 is the best choice, because the micelles can maintain a spherical structure to protect the internal targeted drugs. If the CPP increases to close to 1, the morphology of micelles is more like a phospholipid bilayer, which is the main morphology of biological membranes. For CPP greater than 1, this form of inverted hydrophilic and hydrophobic groups will not exist in the human body in a water environment, but in some solutions dominated by organic solvent environments, this form still plays a role in transmits the substance in the vesicle.

| Critical Packing Parameter ($v/a_0l_c$) | Critical Packing Shape | Structures Formed |
|---|---|---|
| < 1/3 | Cone | Spherical micelles |
| 1/3 – 1/2 | Truncated cone | Cylindrical micelles |
| 1/2 -1 | Truncated cone | Flexible bilayers, vesicles |
| ~1 | Cylinder | Planar bilayers |
| >1 | Inverted truncated cone or wedge | Inverted micelles |

**Table 2.** The corresponding morphology of different CPP

# 4. Self-assembly parameters

## 4.1. Formation mechanism

The formation of block copolymer micelles depends on the attraction of the hydrophobic end and the repulsion of the hydrophilic end. According to the law of thermodynamics, the micelles are more stable when the surface free energy of the core-shell interface is smaller. At this time, the micelles contract, the interfacial area decreases, and the space repulsion force of the hydrophilic end increases; The interfacial tension and spatial repulsion force restrict each other, so that the micelles cannot gather or relax indefinitely to form micelles with stable particle size.

## 4.2. Structure and proportion of copolymer block

When the hydrophobic block of the block copolymer is longer and the proportion of hydrophobic block is larger, it is beneficial to solubilization; For example, poloxamer, with the increase of PPO block ratio, the larger the solubilizable core, the higher the micelle aggregation number, which is conducive to solubilization. Zhang et al. [20] reported that after derivatization of hydroxycamptothecin to form 10,20-di-isobutyl dicarboxylic acid camptothecin, the drug loading in palla-peg-palla increased from 1% to 7%; According to the author's observation, the hydrophobic block has good crystallinity, small space for the drug in its core and poor solubilization. For example, PEG-PCL has less solubilization to HCPT than peg-pulla.

## 4.3. Solvent

The effect of different polarities of solvent on each block is different. The rule is that the closer the polarity of the hydrophilic block is to that of solvent, while the farther the polarity difference between hydrophobic block and the solvent is, the larger the aggregation number of micelles is, which is more conducive to solubilization [3]. Paschalis alexandrites [4] has shown that Pluronic acid can be produced by using formamide water and ethanol-water as mixed solvents dissolved inhomogeneous phase, which was not conducive to the formation of micelles; However, the effect of glycerol water cosolvent is just the opposite.

## 4.4. Temperature

Generally, in polar solvents such as water, the temperature increases to promote the formation of micelles, such as PEO-PPO-PEO aqueous dispersion system; However, the reverse micelles formed in a nonpolar solvent were not formed when the temperature was raised (6). Thermosensitive micelles such as PEO-PPO-PEO [2] micelles, pnippa-paa [7] micelles and peo-pla-peo micelles; When the temperature increases, the hydrophobicity of the core increases and CMC decreases, which is beneficial to the formation of micelles; Further increasing the temperature can make the micelles crosslinked and form gels. This temperature is called the lowest critical solution temperature (LCST). In vitro, the thermosensitive micelles are liquid when injected into the body, and gel can be formed after injection into the body, to release the drug [8].

# 5. Conclusion

In this review, we introduced the morphology, synthesis method of PMs as well as their applications in the medical field. From the initial hollow vesicles to the now complex and large smart vesicles, the technology of polymer vesicles is changing with each passing day. Therefore, further researches are emphasizing producing PMs that have a longer shelf life and better environmental adaptability.

# References

[1] JE House (2007) Principles of Chemical Kinetics, 2nd edition, Academic Press / ISBN: 978-0123567871.

[2] P Atkins (2009) Physical Chemistry, 11th Edition, Oxford University Press / ISBN: 978 - 0198769866.

[3] AW Adamson, AP Gast (1997) Physical Chemistry of Surfaces, 6th Edition, Wiley / ISBN:978-0471148739.

[4] K-Y Law & H Zhao (2016) Surface Wetting, Springer / ISBN: 978 - 3319252148.

[5] Y Leng (2013) Materials Characterization: Introduction to Microscopic and Spectroscopic Methods, 2nd Edition, Wiley-VCH / ISBN: 978 - 3527334636.

[6] G Attard, C Barnes (1998) Surfaces (Oxford Chemistry Primers), Oxford University Press / ISBN:978-0198556862.

[7] S. Biswas, P. Kumari, P.M. Lakhani, B. Ghosh. Recent advances in polymeric micelles for anti-cancer drug delivery. Eur. J. Pharm. Sci., 83 (2016), pp. 184 - 202.

[8] Y. Peng, Y. Zhao, Y. Chen, Z. Yang, L. Zhang, W. Xiao, J. Yang, L. Guo, Y. Wu. Dual-targeting for brain-specific liposomes drug delivery system: Synthesis and preliminary evaluation. Bioorg. Med. Chem., 26 (2018), pp. 4677 - 4686.

[9] A. Akbarzadeh, R. Khalilov, E. Mostafavi, N. Annabi, E. Abasi, T. Kafshdooz, R. Herizchi, T. Kavetskyy, S. Saghf, A. Nasibova. Role of dendrimers in advanced drug delivery and biomedical applications: a review. Exp. Oncol., 1 (2018), pp. 1 - 5.

[10] A. Pugazhendhi, T.N.J.I. Edison, I. Karuppusamy, B. Kathirvel. Inorganic nanoparticles: a potential cancer therapy for human welfare. Int. J. Pharm., 539 (2018), pp. 104 - 111.

[11] H. Wang, Q. Chen, S. Zhou. Carbon-based hybrid nanogels: A synergistic nanoplatform for combined biosensing, bioimaging, and responsive drug delivery. Chem. Soc. Rev., 47 (2018), pp. 4198 - 4232.

[12] S.S. Dunn, J.C. Luft, M.C. Parrott. Zapped assembly of polymeric (ZAP) nanoparticles for anti-cancer drug delivery. Nanoscale, 11 (2019), pp. 1847 - 1855.

[13] Suliman K, Yasaman V, Arif H, et al. Polymeric micelles functionalized with cell penetrating peptides as potential pH-sensitive platforms in drug delivery for cancer therapy: A review. Arabian Journal of Chemistry, Volume 14, Issue 8, August 2021, 103264.

[14] Kishimura A. Development of polyion complex vesicles (PICsomes) from block copolymers for biomedical applications [J]. Polymer Journal, 2013.

[15] Blanazs A, Madsen J, Battaglia G, Ryan AJ, Armes SP. Mechanisticinsights for block copolymer morphologies: how do worms formvesicles? J Am Chem Soc 2011; 133: 16581 – 7.

[16] Warren NJ, Mykhaylyk OO, Mahmood D, Ryan AJ, Armes SP. RAFTaqueous dispersion polymerization yields poly (ethylene glycol)-based diblock copolymer nano-objects with predictable singlephase morphologies. J Am Chem Soc 2014; 136: 1023 – 33.

[17] Warren NJ, Armes SP. Polymerization-induced self-assembly ofblock copolymer nano-objects via RAFT aqueous dispersion poly-merization. J. Am. Chem Soc 2014; 136: 10174 – 85.

[18] Marguet M, Edembe L, Lecommandoux S. Polymersomes in poly-mersomes: multiple loading and permeability control. AngewChem Int Ed 2012; 51: 1173 – 6.

[19] Shum HC, Kim JW, Weitz DA. Microfluidic fabrication ofmonodisperse biocompatible and biodegradable polymer-somes with controlled permeability. J Am Chem Soc 2008; 130: 9543 – 9.