WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 6, 610-626 Review Article SSN 2277– 7105

A COMPREHENSIVE REVIEW OF POLYMERIC MICELLES

Samra Khan*, Maria Saifee

India.

Article Received on
03 March 2023,

Revised on 23 March 2023,
Accepted on 13 April 2023

DOI: 10.20959/wjpr20236-27913

***Corresponding Author**
Samra Khan
India.

1. ABSTRACT

One of the most widely studied subjects in nanoscience technology is related to the creation of supramolecular architectures with well-defined structures and functionalities. These supramolecular structures are generated as a result of the self-assemblage of amphiphilic block polymers. Self-assembly of block polymers via hydrophobic and hydrophilic effects, electrostatic interactions, hydrogen bonding, and metal complexation has shown tremendous potential for creating such supramolecular structures with a wide array of applications. Polymeric micelles have gathered considerable attention in the field of drug and gene delivery due to their excellent biocompatibility, low toxicity, enhanced blood circulation time, and ability to solubilize a large number of drugs in their micellar core. In this article, we have reviewed several aspects of polymeric micelles concerning their general properties, preparation and characterization techniques, and their applications in the areas of drug delivery. Polymeric micelles can be used as 'smart drug carriers' for targeting certain areas of the body by making them stimuli-sensitive or by attachment of a specific ligand molecule onto their surface.

KEYWORDS: Micellization, polymeric micelles, solubilization, targeting, stimuli-sensitivity, polymers.

2. INTRODUCTION

The versatility of micelles produced from amphiphilic copolymers as self-assembled nanostructures (≈10 to 200 nm) has signaled significant advances in the biomedical area due to their varying functions and clinical success.[1] The enormous progress in polymer science has enabled the design of these colloidal systems that can selectively accumulate in solid tumors, and have improved loading capability, better therapeutic efficacy, and superior targeting ability by surface modification with tumor homing ligands and aptamers. Polymeric micelles that can form above the critical micellar concentration (CMC) are composed of

solvophilic and solvophobic portions. In aqueous media, the solvophobic portion forms the core, while the solvophillic portion forms the shell, also called corona. Both these portions are covalently attached to each other as blocks (block copolymers) or grafts (graft or brush type copolymers).[2] The core of polymeric micelles acts as a reservoir for hydrophobic bioactives, while the shell provides required colloidal stability. The shell plays an important role in preventing opsonization, protein adsorption, and together with the small size of polymeric micelles when accumulated in tissues with leaky vasculature through enhanced permeation and retention effect (EPR). Long circulation of these carriers can be prevented by glomerular filtration.[3]

The micelle-based delivery systems have unique versatility to deliver a variety of payloads including, but not limited to drugs, proteins, peptides, DNA, SiRNA etc. These nano or submicron delivery systems have mostly a spherical structure, thereby giving the most physical stability due to lowest surface energy. Block copolymers have been tailor-made based on their physic-chemical properties of the drug, thereby achieving cellular, tissue, or organ level targeting. In this review, we have described how a micelle can be prepared and how its properties can be manipulated to offer better bioavailability or localized delivery. Modification of micelle components can be done to achieve biological target specificity, leading to better safety due to dose reduction of drugs. Stimuli responsiveness of the micelle determines the target specificity and thereby multiple targeting approaches are possible.[4]

The design and refinement of drug-polymeric micelle solubility parameters, biocompatibility, drug disposition in various tissues and release profile with localized delivery option have been identified as the critical parameters for successful micelle-based delivery. In this regard, we have discussed the micelles in achieving desired characteristics required in clinical and preclinical testing. The preclinical and clinical findings of such micellar systems would reach the market. In these aspects, this review gives a clear understanding of the overall scenario of these micellar systems.[4]

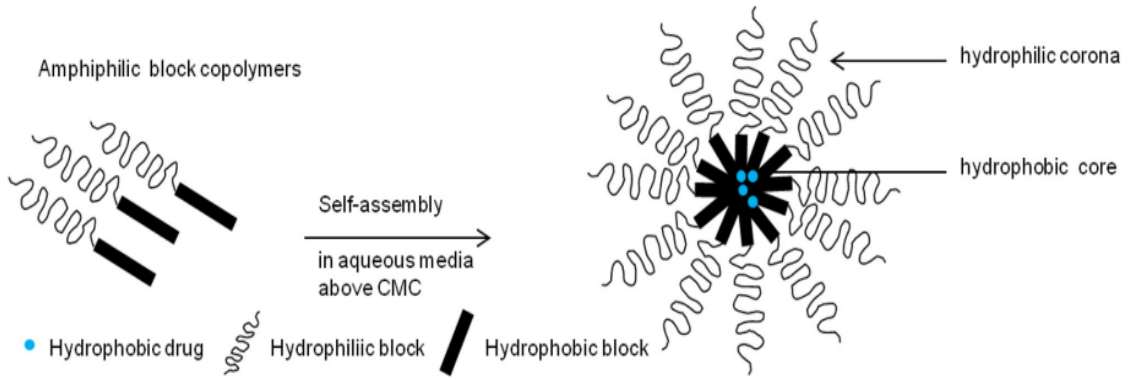

FIGURE 1 | Micelle formation. Drug-loaded polymeric micelle formed from self -assembly of amphiphilic block copolymers in aqueous media. [7]

3. POLYMERIC MICELLES: BACKGROUND AND RELEVANCE

Polymeric micelles are spherical, colloidal, supramolecular nanoconstructs (10–100 nm) usually formed from the self-assembly of amphiphilic block copolymers which consist of both hydrophilic and hydrophobic units in an aqueous environment.[5] This self-assembly of amphiphilic monomers is entropically favoured and occurs above their critical micelle concentration (CMC) to result in the formation of micelles with a core-shell structure.[6] The hydrophobic portion of the block copolymer forms the core of micelles, while the hydrophilic portion forms the shell or the corona. Generally, micelles of amphiphilic copolymers with low CMC values exhibit greater stability even at low concentrations of the amphiphile in the medium. Increasing the hydrophobicity of the copolymer reduces the CMC which in turn, increases the micelle stability.[6] Non-polar molecules are solubilized within the hydrophobic core of micelles; polar molecules get adsorbed on the micelle surface, whereas molecules with intermediate polarity distribute along the surfactant molecules in intermediate positions.[7]

Micelles are dynamic structures that are in continuous equilibrium with free monomers, wherein monomers are constantly exchanged between micelles and intermicellar solution. Due to this to and fro motion of molecules or the exchange phenomenon, surfactant molecules reside in the micelle form for a definite time called the surfactant residence time.[8] An average number of monomers forming micelle at any given time is termed as the aggregation number. Micelles are generally made up of 50–200 monomers. The radius of a spherical micelle is almost the same as the length of a fully extended surfactant monomer, which mostly is 1– 3 nm, and thus micelles lie in the colloidal range. Molecular size and geometrical features of the surfactants determine the size of the micelle.[9] Micelle formation in aqueous solution is mainly governed by the effective interaction between the hydrophobic

parts of the surfactants. The major driving force behind self-association is the decrease of free energy in the system. The decrease in energy of the system is a result of the removal of hydrophobic fragments from the aqueous surroundings with the formation of a micelle core stabilized with hydrophilic blocks exposed to water. The change in free energy for the micellization process is described as:

$$\Delta G^{\circ}_{\text{mic}} = RT \ln(\text{CMC})$$

Where R is the gas constant, T is the temperature of the system and CMC is the critical micelle concentration.[10]

4. TYPES OF POLYMERIC MICELLES

Polymeric micelles can be classified based on the intermolecular forces that apart the core segment interacting with the aqueous environment. They are classified into three groups.

- Conventional
- Poly-ion complex micelles
- Non-covalently connected polymeric micelles

4.1 Conventional

These micelles are formed by hydrophobic interactions between the core segment and the corona region in the aqueous environment. One of the simplest amphiphilic block copolymer, poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide), forms micelles as a result of hydrophobic interactions.[12]

4.2 Poly-ion complex micelles (PICMs)

Poly-ion complex micelles are formed by means of electrostatic interaction between two oppositely charged moieties. The structure and size of the charged micelles coronas are controlled by electrostatic and the Vander Waals force of interactions. The simple synthetic route, high drug loading capacity, structural stability, prolonged circulation in the blood, and self-assembly in aqueous medium are some features of poly-ion complex micelles. Micelles are prepared in aqueous media without using organic solvent. This will allow to remove the side effects, that may be caused due to residual organic solvent. The core polyion complex micelles can trap many therapeutic agents through electrostatic, hydrophobic hydrogen bonding interactions. These therapeutic agents are released from the core by a suitable trigger. Polyion complex micelles can be used for the delivery of charged drugs, antisense oligonucleotides, DNA, and enzymes.[13]

4.3 Non-covalently connected polymeric micelles

Polymeric micelles are obtained via self-assemblage of homopolymer, random copolymer, graft copolymer, or oligomer for which interpolymer hydrogen bonding complexation serves as the driving force. Core and shell are non-covalently connected at their homopolymer chain end by specific intermolecular interactions such as H-bonding or metal-ligand interactions in the resultant structures and hence these are termed non-covalently connected micelles.[14]

5. METHODS OF PREPARATION

- Direct dissolution method
- Solvent evaporation method
- Dialysis method
- Oil in water emulsion
- Solid dispersion
- Freeze drying

5.1 Direct dissolution method

In this simple preparation method, the amphiphilic copolymer and the drug, added in excess, are dissolved in an aqueous solvent. At or above CMC, the copolymer and drug self-assemble, creating a loaded PM. This technique presupposes that both the drug and the copolymer are water-soluble and it is associated with a low drug loading, although increasing the temperature of the system might reduce this disadvantage.[15]

5.2 Solvent evaporation method

Also known as film hydration method, solvent evaporation process demonstrates a high incorporation efficiency in copolymers with less water solubility, being only selected for copolymers with low HLB values. This method consists in dissolving the drug and copolymers in a volatile organic solvent or a mixture, that is afterwards evaporated, forming a thin polymeric film at the recipient's bottom. The film is then hydrated with water by sonication or stirring.

5.3 Dialysis method

If the selected copolymers have low water solubility, the dissolution of copolymer and drug can be executed in a water-miscible organic solvent, that posteriorly is replaced with deionized water through a semipermeable membrane, inducing micelle formation. The

solvent removal is a slow process that often requires up to 36 hours, and the IE and size of the particles are dependent of this phase.[15]

5.4 Oil-in-water emulsion method

In this method, the hydrophobic drug and polymer are co-dissolved in a volatile solvent, for example, acetone, chloroform, etc. either alone or combined with ethanol. The solution is added to water and accompanied by sonication to form an oil-in-water type emulsion. This emulsion is kept overnight for complete evaporation of the organic solvent which results in formation of the drug–micelle conjugate. Sometimes surfactants such as polyvinyl alcohol or pluronic-85 can also be added in the aqueous solution to increase the stability of the emulsion.[16]

5.5 Solid dispersion method

In this method the polymer and the hydrophobic drug are dissolved in an organic solvent followed by the removal of the organic solvent under decreased pressure to form a polymer/drug solid dispersion. The polymer matrix is heated and then hot water is added to the preheated matrix to form the drug-loaded micelles.[17]

5.6 Freeze-drying method

In the simple freeze-drying method, the drug(s) and polymers are co-dissolved in a mixture of water and tert-butanol and freeze-dried. Drug-loaded polymeric micelles form spontaneously upon rehydration of this freeze-dried cake in an injectable vehicle.

6. Polymeric micelles: an intelligent drug delivery system

As per the literature reviews, it has been found that polymeric micelles have been gaining importance as Smart drug delivery Carrier:

6.1 Mucoadhesive polymeric micelles

The mucosal retention can be used to increase the transit time in the GI tract resulting in the extended time window for the payload release. The mucoadhesive polymeric micelles swell and fill the mucous membranes crevices, contributing to the active surface area in contact with the intestinal mucosa and yielding a high local concentration of the drug.[21] The muco adhesion process can also localize the polymeric micelles at the target site. The process can be achieved by building either nonspecific interactions with the mucosal surface such as covalent bonds or specific interactions by functionalizing polymers with targeting ligands

like lectins or reactive thiols.[22], the surface charges of PMs seem to play an important role in particle uptake. On one hand, the negatively charged intestinal mucosa, due to the existence of glycocalyx, attracts more positively charged PMs. Therefore, a considerable number of studies have been conducted using positively charged polymers such as chitosan to increase residence time in the GI tract.[40,41]

Crater and Carrier demonstrated a 20– 30 times faster diffusion for anionic particles in comparison with cationic ones[42] Polymers such as cross-linked polyacrylic acids (PAA)[43–45], carboxy polymethylene, carboxymethyl cellulose, alginate, chitosan (CS), and their derivatives[46–48] are commonly accepted as mucoadhesive and safe polymers. chitosan is an ideal candidate for oral DNA and protein delivery[49] due to its mucoadhesive properties and its ability to induce a transient opening of the tight junctions.[50] Phenylboronic acid (PBA) is a synthetic molecule that has been extensively used in glucose sensing and insulin delivery systems due to its ability to form high-affinity complexes with 1,2- cis-diols.[35] This affinity between boronic acids and diols has also been utilized in other mucoadhesive drug delivery systems such as vaginal delivery of interferon[36], nasal delivery of insulin[37,38], and ocular delivery of cyclosporine A (CycA).[39]

6.2 Temperature-sensitive polymeric micelles

It is used to prepare intelligent systems that are hydrophilic below their critical temperature of dissolution. When the temperature is above Lower Critical Solution Temperature, the polymer becomes hydrophobic, and its conformation changes from soluble to insoluble state. Amphiphilic copolymers containing poly(N-isopropyl acrylamide)one of its derivatives can be used to obtain temperature-sensitive micelles.[24] Above this temperature, the micelle destabilizes, and the drug is released. The most common example is Doxorubicin, the micelles of this copolymer slowly release the drug at 37ºC, but the release becomes faster when the temperature rises to 42ºC.[25] The micelles could be useful for developing intelligent systems that release the drug when hyperthermia occurs either at a systemic level or a specific region. The release could also be triggered by an external source of heat applied to a delimited area of the body.[26] A drug delivery system with an upper critical solution temperature (UCST) of 438 degrees celsius based on an amphiphilic polymer poly(AAm-co-AN)-g-PEG, whose UCST relies on hydrogen bonding and its UCST behavior was independent of solvent, ionic strength, and polymer concentration was developed.[51] it could encapsulate hydrophobic antitumor drugs and give long systemic circulation.

6.3 Light-sensitive polymeric micelles

Light-sensitive micelles are generally composed of a hydrophilic shell and a responsive hydrophobic core with tunable solubility that depends on the wavelength of light with which it is irradiated.[8] In these systems, the core-forming block plays a crucial role in the formation and dissociation of the micelles. The block copolymers initially aggregate spontaneously to form micelles with a hydrophobic core. After UV irradiation, the hydrophobic core becomes hydrophilic and the copolymer can dissolve in water.

Recently, photoreversible morphological changes of block copolymer micelles based on azobenzene have been reported.[52] Azobenzene units undergo cis-trans isomerization on alternating irradiation with UV and visible light, which induces changes in the polarity of the units; the cis isomer of azobenzene is more polar and therefore less hydrophobic than the trans isomer.

In a typical example, Matyjaszewski and coworkers reported a poly(ethylene oxide)-block-poly- (methacrylate) whose methacrylate block had spiropyran side-chains (PEO-b-PMSP).[53]

6.4 Ultrasound-sensitive polymeric micelles

Polymeric micelles can be destabilized by applying ultrasounds for pulsatile drug delivery in tumors.[26] Once IV is injected, polymeric micelles accumulate in tumor tissues via the EPR effect. The ultrasounds should be used when maximum micelle accumulation in the tumor is reached; the waiting period depends on the kinetics of the micellar system's distribution. The amount of drug released can be modulated by controlling the frequency, power density, pulse length, and inter-pulse intervals.[26]

Nelson et al. introduced a colon carcinogen tumor cell into the hind limbs of rats which were treated weekly with stabilized micelles or free doxorubicin by i.v. administration.[59] Application of 20 and 70 kHz low-frequency ultrasound significantly reduced the tumor size as compared to noninsonated controls.

The group of Husseini has been engaged in the development of ultrasound-based polymeric micelles and their characterization to optimize the effects of drug for better efficiency. Polymeric micelles incorporating doxorubicin have been prepared that released the drug after ultrasonication.[60] They showed that the DNA damage induced by doxorubicin delivered to

human leukemia cells (HL-60) from Pluronic P105 micelles was at an optimum after cells were exposed to ultrasound, when comparatively studied with and without the application of ultrasound.

6.5 Acid-Sensitive Polymeric Micelles

There are a number of pH gradients that exist in normal and pathophysiological states inside the body. Acid-sensitive or pH-sensitive polymeric micelles exploit these differences in pH for drug targeting. In tumors and inflammatory tissues a mildly acidic pH is encountered (pH approx. 6.8). This is a slightly low value as compared with the pH of the blood and normal tissues (pH approx. 7.4).

Polypyridines like poly(2-vinylpyridine) (P2VP) and poly(4-vinylpyridine) (P4VP) are water-insoluble at neutral or alkalic pH, but become protonated and thus soluble at $pH < 5$. A recently developed micellar formulation containing P2VP has been described by Karanikolas *et al.*[54] A triblock copolymer of PEO-*b*-P2VP-*b*-PEO was used to demonstrate pH-triggered micelle destabilization. No drug release studies concerning this micelle formulation, however, have been reported yet.

Bae *et al.* prepared micelles based on mPEG-*b*-poly (aspartate hydrazone doxorubicin) where doxorubicin was conjugated to the hydrophobic segments through acid-sensitive hydrazone linkers. Selective release of the drug at endosomal pH and suppressed tumor growth in mice with enhanced therapeutic efficacy and decreased systemic toxicity compared to free doxorubicin was reported.[55]

Chen *et al.* prepared micelles with PEG and an acid-labile polycarbonate[56], and demonstrated that the acetal groups of the polycarbonate were hydrolyzed, resulting in paclitaxel or doxorubicin release of 60–70% after exposure to mildly acidic conditions (pH 5.0–4.0) for 10 h.

Huang *et al.* prepared PEG-*b*-P*t*NEA micelles based on the orthoester-containing monomer poly(*trans*-*N*-(2-ethoxy-1,3-dioxan-5-yl)acrylamide) (P*t*NEA) containing Nile Red dye. The micelles remained stable at pH 7.4 but destabilized in mildly acidic media due to the acid-triggered hydrolysis of the orthoester groups, which increased the hydrophilicity of P*t*NEA, resulting in Nile Red release.[57]

Tang *et al.* used polymethacrylamide derivative (PMYM)-bearing orthoester side chains as a pH-sensitive hydrophobic block to prepare PEG-*b*-PMYM micelles capable of drug release after exposure to mildly acidic conditions.[58]

7. CHARACTERIZATION OF POLYMERIC MICELLES

7.1 Critical Micellar Concentration (CMC)

In aqueous media, amphiphilic polymers can exist in the form of micelles when the concentration is higher than CMC, and when diluted below this concentration, the micelles may collapse. Hence, CMC is the key parameter for the formation and the static stability of polymeric micelles. Some of the methods used for the determination of CMC in aqueous dispersions of micelles include surface tension measurements, chromatography, light scattering, small angle neutron scattering, small angle X-ray scattering, differential scanning calorimetry, viscometry, and utilization of fluorescent probes. For easy practical determination, CMC is obtained from plots of the surface tension as a function of the logarithm of the concentration. The CMC is said to be attained when the surface tension stops decreasing and reaches a plateau value. Most of the researchers have relied upon the use of pyrene as a fluorescent probe for estimating CMC.[27]

7.2 Size and Shape Determination

After the preparation of the micelles, useful information regarding the polydispersity index of the prepared structures is obtained by examining the micellar solution with the quasielastic light scattering technique. Monodisperse micelles produce blue color from light scattering which indicates good micellar preparation, as contrasted with the white color shown by aggregates.[32] Size of polymeric micelles usually falls in the colloidal range. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques have been widely used for many years for the direct visualization, size, and shape determination of block copolymer micelles. The more recently developed cryo-TEM technique has increasingly started gaining importance for the characterization of block copolymer micelles in the aqueous medium. SEM or atomic force microscopy (AFM) reveals information regarding size distribution when chemically attached micelles to surfaces are presented. Direct visualization of block copolymer micelles either in the dried state or directly “in situ” within a liquid cell can be achieved by AFM. Hydrodynamic diameters and polydispersity indices of micelles are obtained using photon correlation spectroscopy. Recently size characterization of drug-loaded polymeric micelles was done using asymmetrical flow field-

flow fractionation and the structure of assemblies was determined by small angle neutron scattering.[28,29]

7.3 In Vitro Drug Release Behavior

In-vitro drug release behavior from micelles is easily studied by placing the micellar solution in a dialysis tube. The dialysis bag is immersed in a flask containing a release medium and kept at a constant temperature. At predetermined time intervals, aliquots of the release medium are taken and replaced by fresh medium. The content of the drug released in the medium can be measured by spectroscopic or other suitable methods.[30]

8. CONCLUSION

Polymeric micelles have emerged as important pharmaceutical carriers because of their attractive properties. The preparation of polymeric micelles appears to be relatively simple as compared with the other novel drug delivery systems. Polymeric micelles can be easily loaded with a wide variety of poorly soluble drugs, thus resulting in enhanced bioavailability of these drugs. In this review article, we have illustrated the potential of polymeric micelles for the delivery of poorly water-soluble drugs, especially in the areas of oral delivery. A required field that verifies the effectiveness of micellar drug carriers is controlling the location and time over which drug release occurs. The pH-sensitive polymeric micelles, light-sensitive, ultrasound-sensitive, and temperature-sensitive polymeric micelles have emerged as fascinating drug carriers that can be easily applied for programmed drug delivery. Different methods to characterize polymeric micelles have also been highlighted in the study. Thus, polymeric micelles have proved a promising drug delivery carrier to fulfill targeted and localized drug delivery

9. REFERENCES

1. Kataoka, K., Harada, A., Nagasaki, Y., Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv. Drug Deliv. Rev., 2001; 47: 113–131.
2. Tuzar, Z., Kratochvil, P., Block and graft copolymer micelles in solution. Adv. Coll. Interface Sci., 1976; 6: 201-232.
3. Kang, N., Perron, M., Prudhomme, R., Zhang, Y., Gaucher, G., Leroux, J.C., Stereocomplex block copolymer micelles: core-shell nanostructures with enhanced stability. Nano. Lett., 2005; 5: 315–319.

4. Deshmukh, Anand S., Chauhan, Pratik N., Noolvi, Malleshappa N., Chaturvedi, Kiran, Ganguly, Kuntal, Shukla, Shyam S., Nadagouda, Mallikarjuna N., Aminabhavi, Tejraj M., Polymeric micelles: Basic research to clinical practice. International Journal of Pharmaceutics http://dx.doi.org/10.1016/j.ijpharm.2017.09.005
5. Yokoyama, M., Satoh, A., Sakurai, Y., Okano, T., Matsumura, Y., Kakizoe, T., et al. Incorporation of water-insoluble anticancer drug into polymeric micelles and control of their particle size. J. Control. Release, 1998; 55: 219–229. doi: 10.1016/S0168-3659(98)00054-6
6. Torchilin, V. P. Structure and design of polymeric surfactant-based drug delivery systems. J. Control. Release, 2001; 73: 137–172. doi: 10.1016/S0168- 3659(01)00299-1
7. Jhaveri Aditi M., Torchilin Vladimir P.vol5(2014) Multifunctional polymeric micelles for delivery of drugs and siRNA, Frontiers in Pharmacology DOI=10.3389/fphar.2014.00077 https://www.frontiersin.org/articles/10.3389/fphar.2014.00077
8. Zana R. Introduction to surfactants and surfactant self-assemblies. In: Dynamics of surfactant selfassemblies – micelles, microemulsions, vesicles, and lyotropic phases. Zana R, editors. Boca Raton, FL: Taylor & Francis, 2005; 2–36.
9. Rangel-Yagui CO, Pessoa JA, Tavares LC. Micellar solubilization of drugs. Journal of Pharmacy and Pharmaceutical Sciences, 2005; 8: 147–63.
10. Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. Journal of Pharmaceutical Sciences, 2003; 92: 1343–55.
11. Shukla A, Tiwari S, Singh MP, et al. A comprehensive review on polymeric micelles: a promising drug delivery carrier. *J Anal Pharm Res*., 2021; 10(3): 102-107. DOI: 10.15406/japlr.2021.10.00372 *From <https://medcraveonline.com/JAPLR/a-comprehensive-review-on-polymeric-micelles-a-promising-drug-delivery-carrier.html>*
12. Bouchemal K, Agnely F, Koffi A, Ponchel G. A concise analysis of the effect of temperature and propanediol1, 2 on Pluronic F127 micellization using isothermal titration microcalorimetry. J Colloid Interface Sci., 2009; 338: 169-76.
13. Ranger M, Jones MC, Yessine MA, Leroux JC. From well-defined diblock copolymers prepared by a versatile atom transfer radical polymerization method to supramolecular assemblies. J Polym Sci Part A: Polym Chem., 2001; 39: 3861-74. Zhang J, Ma PX. Hostguest interaction mediated polymeric core-shell assemblies: Versatile nanocarriers for drug delivery. Angew Chem Int Ed Engl, 2009; 48: 964-68.

14. Kwon GS, Polymeric micelles for delivery of poorly water-soluble compounds. Crit Rev Ther Drug Carrier Syst., 2003; 20: 357-403.
15. Vesicular and particulate drug delivery system edited by, R.S.R. Murthy, 297.
16. Grande R, Carvalho AJ. Compatible ternary blends of chitosan/poly (vinyl alcohol)/poly (lactic acid) produced by oil-in-water emulsion processing. Biomacromolecules, 2011; 12(4): 907–914.
17. Yang M, Wang P, Huang C-Y, Ku MS, Liu H, Gogos C. Solid dispersion of acetaminophen and poly (ethylene oxide) prepared by hot-melt mixing. International J. Pharmaceut, 2010; 395(1): 53–61.
18. LL Fu. Plant lectins: Targeting programmed cell death pathways as antitumor agents. International Journal of Biochemistry and Cell Biology, 2011; 43(10): 1442–1449.
19. N Yamazaki. Endogenous lectins as targets for drug delivery. Advanced Drug Delivery Reviews, 2000; 43(2): 225–244. ES Lee, HJ Shin. Poly(L-histidine)PEG block copolymer micelles and pH-induced de-stabilization. Journal of Controlled Release, 2003; 90(3): 363–374.
20. ES Lee, K Na, YH Bae. Polymeric micelle for tumor pH and folatemediated targeting. Journal of Controlled Release, 2003; 91(1–2): 103–113.
21. Fukushima S, Miyata. A PEG-based biocompatible block catiomer with high buffering capacity for the construction of polyplex micelles showing efficient gene transfer toward primary cells. Chem Med Chem., 2006; 1(4): 439–444.
22. Chris Oerlemans. Polymeric Micelles in Anticancer Therapy: Targeting, Imaging and Triggered Release. Pharm Res., 2010; 27(12): 2569–2589.
23. Hamidreza Montazeri. Polymeric Micelles for Drug Delivery. Journal Expert Opinion on Drug Delivery, 2005; 3(1): 139–162. A comprehensive review on polymeric micelles: a promising drug delivery carrier 107 Copyright: ©2021 Shukla et al. Citation: Shukla A, Tiwari S, Singh MP, et al. A comprehensive review on polymeric micelles: a promising drug delivery carrier. J Anal Pharm Res., 2021; 10(3): 102–107. DOI: 10.15406/japlr.2021.10.00372
24. Ren-XiZhuo. Thermo-sensitive polymeric micelles based on poly(Nisopropylacrylamide) as drug carriers. Progress in Polymer Science., 2009; 34(9): 893–910.
25. Rijcken CJ. Triggered de-stabilization of polymeric micelles and vesicles by changing polymers polarity: an attractive tool for drug delivery. J Control Release, 2007; 120: 131–148.

26. Satturwar P. pH-responsive polymeric micelles of poly(ethylene glycol)- b-poly(alkyl(meth) acrylate-co-methacrylic acid): influence of the copolymer composition on self-assembling properties and release of candesartan cilexetil. Eur J Pharm Biopharm, 2007; 65: 379-87.
27. Kabanov AV, Batrakova EV, Alakhov VY. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J Control Release, 2002; 82: 189-12.
28. Kang DY, Kim MJ, Kim ST, Oh KS, Yuk SH, Lee S. Size characterization of drug-loaded polymeric core/shell nanoparticles using asymmetrical flow field-flow fractionation. Anal Bioanal Chem., 2008; 390: 2183-88.
29. Ramzi A, Rijcken CJF, Veldhuis T, Schwahn D, Hennink WE, Nostrum CF. Core-shell structure of degradable, thermosensitive polymeric micelles studied by smallangle neutron scattering. J Phys Chem B., 2008; 112: 784-92.
30. Dong PW, Wang XH, Gu YC et al. Self-assembled biodegradable micelles based on star-shaped PCL-bPEG copolymers for chemotherapeutic drug delivery. Colloids Surf A: Physicochem Eng Aspects, 2010; 358: 128-34.
31. Webber SE. Polymer micelles: An example of selfassembling polymers. J Phys Chem B., 1998; 102: 2618- 26.
32. Horacio Cabral, Kanjiro Miyata, Kensuke Osada, and Kazunori Kataoka Chemical Reviews, 2018; 118(14): 6844-6892 Block Copolymer Micelles in Nanomedicine Applications DOI: 10.1021/acs.chemrev.8b00199
33. Zhang Y, Jiang M. New approaches to stimuliresponsive polymeric micelles and hollow spheres. Front Chem., 2006; 4: 364-68.
34. Nishiyama N, Kataoka K. Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacol Therap., 2006; 112: 630-48.
35. Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. Adv Drug Del Rev., 2006; 58: 1655-70.
36. Springsteen, G.; Wang, B. A Detailed Examination of Boronic Acid-Diol Complexation. Tetrahedron, 2002; 58(26): 5291–5300.
37. Li, C.; Liu, Z.; Yan, X.; Lu, W.; Liu, Y. Mucin-Controlled Drug Release from Mucoadhesive Phenylboronic Acid-Rich Nanoparticles. Int. J. Pharm., 2015; 479(1): 261–264.
38. Cheng, C.; Zhang, X.; Xiang, J.; Wang, Y.; Zheng, C.; Lu, Z.; Li, C. Development of Novel Self-Assembled poly(3-Acrylamidophenylboronic acid)/poly(2-

Lactobionamidoethyl Methacrylate) Hybrid Nanoparticles for Improving Nasal Adsorption of Insulin. Soft Matter, 2012; 8(3): 765.

39. Jachowicz, R.; Czech, A. Preparation and Evaluation of Piroxicam-HPMCAS Solid Dispersions for Ocular Use. Pharm. Dev. Technol., 2008; 13(6): 495–504.
40. Liu, S.; Jones, L.; Gu, F. X. Development of Mucoadhesive Drug Delivery System Using Phenylboronic Acid Functionalized poly(D,L-Lactide)-B-Dextran Nanoparticles. Macromol. Biosci, 2012; 12(12): 1622–1626.
41. J. H. Park, G. Saravanakumar, K. Kim, and I. C. Kwon, "Targeted delivery of low molecular drugs using chitosan and its derivatives," Advanced Drug Delivery Reviews, 2010; 62(1): 28–41.
42. H. Takeuchi, J. Thongborisute, Y. Matsui, H. Sugihara, H. Yamamoto, and Y. Kawashima, "Novel mucoadhesion tests for polymers and polymer-coated particles to design optimal mucoadhesive drug delivery systems," Advanced Drug Delivery Reviews, 2005; 57(11): 1583–1594.
43. J. S. Crater and R. L. Carrier, "Barrier properties of gastrointestinal mucus to nanoparticle transport," Macromolecular Bioscience, 2010; 10(12): 1473–1483.
44. L. Bromberg, M. Temchenko, V. Alakhov, and T. A. Hatton, "Bioadhesive properties and rheology of polyether-modified poly(acrylic acid) hydrogels," International Journal of Pharmaceutics, 282(1-2): 45–60, 20.
45. J. Blanchette and N. A. Peppas, "Cellular evaluation of oral chemotherapy carriers," Journal of Biomedical Materials Research A, 2005; 72(4): 381–388.
46. J. Blanchette and N. A. Peppas, "Oral chemotherapeutic delivery: design and cellular response," Annals of Biomedical Engineering, 2005; 33(2): 142–149.
47. S. Dunnhaupt, J. Barthelmes, J. Hombach, D. Sakloetsakun, ¨ V. Arkhipova, and A. Bernkop-Schnurch, "Distribution of ¨ thiolated mucoadhesive nanoparticles on intestinal mucosa," International Journal of Pharmaceutics, 2011; 408(1-2): 191– 199.
48. A. Makhlof, M. Werle, Y. Tozuka, and H. Takeuchi, "A mucoadhesive nanoparticulate system for the simultaneous delivery of macromolecules and permeation enhancers to the intestinal mucosa," Journal of Controlled Release, 2011; 149(1): 81–88.
49. V. V. Khutoryanskiy, "Advances in mucoadhesion and mucoadhesive polymers," Macromolecular Bioscience, 2011; 11(6): 748–764.
50. W. Guang Liu and K. De Yao, "Chitosan and its derivatives— a promising non-viral vector for gene transfection," Journal of Controlled Release, 2002; 83(1): 1–11.

51. I. M. Van Der Lubben, J. C. Verhoef, A. C. Van Aelst, G. Borchard, and H. E. Junginger, "Chitosan microparticles for oral vaccination: preparation, characterization and preliminary in vivo uptake studies in murine Peyer's patches," Biomaterials, 2001; 22(7): 687–694.
52. Li, W., Huang, L., Ying, X., Jian, Y., Hong, Y., Hu, F., & Du, Y. Antitumor Drug Delivery Modulated by A Polymeric Micelle with an Upper Critical Solution Temperature. Angewandte Chemie International Edition, 2015, 54(10): 3126–3131. doi:10.1002/anie.201411524
53. Guang Wang, Xia Tong, and Yue Zhao Preparation of Azobenzene-Containing Amphiphilic Diblock Copolymers for Light-Responsive Micellar Aggregates *Macromolecules,* **2004;** *37*(24): 8911-8917.
54. Lee, H., Wu, W., Oh, J. K., Mueller, L., Sherwood, G., Peteanu, L., … Matyjaszewski, K. *Light-Induced Reversible Formation of Polymeric Micelles. Angewandte Chemie International Edition,* 2007; *46(14): 2453–2457.* doi:10.1002/anie.200604278
55. Karanikolas A, Tsolakis P, Bokias G, Tsitsilianis C. Stimuliresponsive poly(ethylene oxide)-b-poly(2-vinylpyridine)-b-poly (ethylene oxide) triblock copolymers and complexation with poly(acrylic acid) at low p H. Eur Phys J E Soft Matter, 2008.
56. Bae Y, Nishiyama N, Fukushima S, Koyama H, Yasuhiro M, Kataoka K. Preparation and biological characterization of polymeric micelle drug carriers with intracellular pH-triggered drug release property: tumor permeability, controlled subcellular drug distribution, and enhanced in vivo antitumor efficacy. Bioconjug Chem., 2005; 16: 122–30.
57. Chen W, Meng F, Li F, Ji SJ, Zhong Z. pH-responsive biodegradable micelles based on acid-labile polycarbonate hydrophobe: synthesis and triggered drug release. Biomacromolecules, 2009.
58. Huang XN, Du FS, Cheng J, Dong YQ, Liang DH, Ji SP, et al. Acid-sensitive polymeric micelles based on thermoresponsive block copolymers with pendent cyclic orthoester groups. Macromolecules, 2009; 42: 783–90.
59. Tang RP, Ji WH, Wang C. Amphiphilic block copolymers bearing ortho ester side-chains: pH-dependent hydrolysis and self-assembly in water. Macromol Biosci, 2010; 10: 192–201.
60. Nelson JL, Roeder BL, Carmen JC, Roloff F, Pitt WG. Ultrasonically activated chemotherapeutic drug delivery in a rat model. Cancer Res., 2002; 62: 7280–3.

61. Husseini GA, Diaz de la Rosa MA, Gabuji T, Zeng Y, Christensen DA, Pitt WG. Release of doxorubicin from unstabilized and stabilized micelles under the action of ultrasound. Journal of Nanoscience and Nanotechnology, 2007; 7: 1–6.