Highlights on polymeric micelles as versatile nanocarriers for drug transporting

***Hussein A. Abdul Hussein, *Nidhal K. Maraie**
***Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq**

Article Info:

Received 3 Mar 2021
Accepted 24 Jun 2021
Published Jun 2021

Corresponding Author email:
pharm.dr.nidhal.khazaal@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0001-5628-1479

Abstract

Polymeric micelles are nanoscale core-shell structures formed by amphiphilic (block or graft) copolymers, that can self-aggregate in an aqueous medium. PMs characterized by small size, spherical shape, lower critical micellar concentration, which gave higher stability for PMs over conventional surfactant micelles. The core/shell structure permits polymeric micelle to entrap poor soluble drugs and can improve their solubility and permeability. The preparation of PMs tends to be relatively easy as compared to other novel drug delivery systems. This review focus on the general properties, types, types of copolymer utilized, formation mechanism, preparation methods, characterization techniques, and the applications on PMs.

Key words: amphiphilic copolymers, critical micelle concentration, solubilization, drug delivery, drug targeting and polymeric micelles.

تسليط الاضواء على المذيلات البوليمرية كحاملات نانوية متعددة الاستخدامات لنقل الأدوية

حسين علي عبد الحسين* ، نضال خزعل مرعي*
***قسم الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق**

الخلاصة:

المذيلات البولمرية وهي تراكيب نانوية ذات قشرة - لب مكونة من بوليمرات مشتركة الآلفة و التي لها القابلية على التجمع الذاتي في الوسط المائي . المذيلات البولمرية تمتاز بحجمها الصغير، شكلها الكروي و قلة التركيزالمذيلات الحرج ، هذة الماصفات جعلت الثباتية عالية على حساب المذيلات التقليدية. تركيب اللب و القشرة يسمح للمذيلات البولمرية لاحتواء الادوية ضعيفة الذوبان و تحسين ذوبانيتها و نفاذيتها . طريقة تحضيرها سهلة نسبيا مقارنة بأنظمة توصيل الأدوية الجديدة الاخرى . هذة المراجعة تركز على الخصاص العامة ، الانواع ، انواع البولمرات المستخدمة، ميكانيكية التكوين، طرق التحضير، تقتيات التوصيف و التطبيقات على المذيلات البولمرية.

الكلمات المفتاحية: البوليمرات المشتركة مزدوجة الالفة ، تركيز الميسيل الحرج ، الذوبان ، توصيل الدواء ، استهداف الدواء والمذيلات البوليمري.

Introduction

Micelles are nano-sized, spherical, self-associated colloidal-sized clusters that have a hydrophobic core–hydrophilic shell architecture that forms when surfactant monomers or amphiphilic molecules self-aggregated. Aqueous exposure of the amphiphiles that have a hydrophilic head and a hydrophobic tail causes the hydrophilic and hydrophobic segments to orient and interact to form a core-shell

structure. The polar region of monomers forms the micelle's shell on the outside, while the non-polar of monomers forms the micelle's core on the inside. Micelles normally have particles of 50-100nm range. An important property of micelles with particular significance in pharmacy is their ability to increase the solubility of poorly soluble drugs in water, thus increasing their bioavailability (1).

Hypothetically, the micelles are created when the decrease in the system's free energy occurs, which results from the removal of hydrophobic domains from the aqueous phase and re-forming the H-bonds. The small concentration range over which sudden physicochemical changes occur is referred to as the critical micelle concentration (CMC) (2). Below this concentration, the amphiphilic molecules have a clear propensity to be adsorbed at the interface between air and water. As the overall concentration is raised to the point that both the interface and the bulk of the solvent (water) are filled with monomeric amphiphiles, any addition of amphiphilic more than CMC results in the formation of aggregation and micelle (3). the certain temperature under which amphiphilic molecules appear as unimers and above that temperature, they appear as micelles this temperature is known as the critical micellization temperature (CMT) (4).

Polymeric micelle (PMs)

Polymeric micelles are nanoscopic core-shell structures produced in an aqueous medium by the self-aggregation of di-block(hydrophilic-hydrophobic), tri-block (hydrophilic-hydrophobic-hydrophilic), and graft copolymers are shown in (Figure 1) (5). The inner core is hydrophobic in nature, while the outer shell, which is hydrophilic, that clarified in (Figure 2) (6). The inner core acts as a pool, encapsulating the water-insoluble drug. The outer layer, or corona, protects the drug in the aqueous environment from the biological invasion by the reticuloendothelial system in vivo (RES), which phagocyte PMs, and this due to stealth properties of shell, where polyethylene glycol or polyethylene oxide mostly used in shell formation, that prevent interaction with portions (provide steric stability), thus decrease the possibility to phagocyte by macrophages. PMs have a diameter in the range of 10-100 nm (7), which is essential to prevent the filtration by kidneys, that filtered particles less than 10 nm in size, while the size lower than 100 nm decrease the detection by liver and spleen, where they destroy and cleared any partial larger than 100 nm, thus the size of PMs in this range gave the advantage of prolonging time circulation in the body (8). Also, small size gave the advantage of drug targeting by improving permeability and retention effect (EPR) of tumor tissues (9), which enhance drug accumulation at target tumor sites. Polymeric micelles are mainly used for targeting anticancer drugs given parentally or orally for example; paclitaxel undue trade name (NK-105), which is under clinical trials, was loaded in PMs prepared from PEG-(aspartate) and the purpose was targeting for advanced stomach cancer. Size of polymeric micelles controlled mainly by the length of the hydrophobic chain the increase in length of hydrophobic block decrease in size (10).

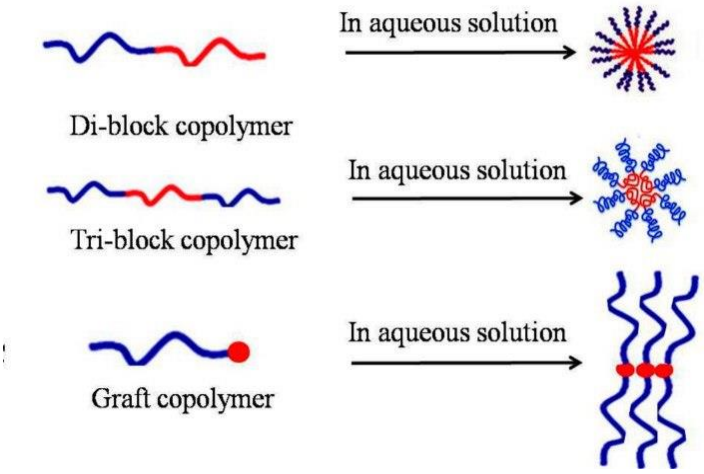

Figure (1): The different types of copolymers used in PMs fabrication, the blue part represents hydrophilic chain, while red part represents hydrophobic chain [5].

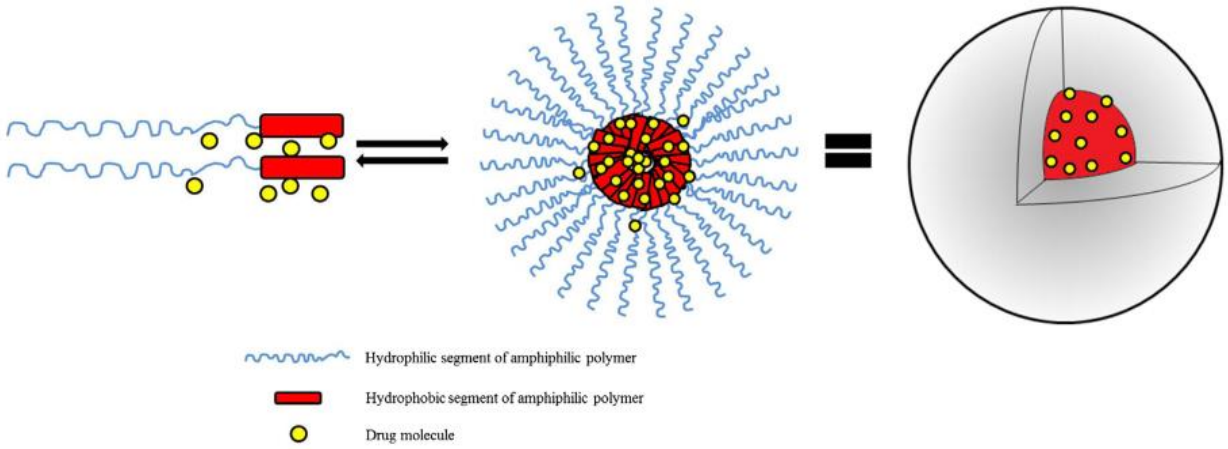

Figure (2): Schema showing the structure and formation of the polymeric micelles [6].

Polymeric micelles types

Conventional Micelles

These micelles are also known as block copolymer micelles, which are formed from the block copolymers that have two homo-polymeric blocks or more with different hydrophilicity that linked to one another. These amphiphilic block copolymers when dissolved in an aqueous medium they self-assembled to form the PMs with the hydrophilic segment forms the outer shell and the hydrophobic segment forms the inner core. The core can entrap lipophilic drugs physically, or the hydrophobic domain could be chemically conjugated with the drug before the PMs formation. An example on conventional polymeric micelles like pluronics (poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide)) (11, 12).

Polyion complex micelles (PICM)

These types of micelles arise when the two or more opposite charged ionic polymers, for example, polyelectrolytes, interact electrostatically. When these polymers are added to the solution, they can penetrate the micelle's shell to form certain PMs. The Van-der Waals interaction forces and the electrostatic force determined the structure and size of the charged micelle coronas. These micelles are easily self-assembled in an aqueous solution, structurally stable, and have a high drug

cargo potential. The core formed in PICMs is used for the encapsulation of various therapeutic agents such as hydrophobic drug molecules, charged macromolecules, and metal complexation through hydrogen bonding, as well as hydrophobic and electrostatic interactions (13, 14). Methoxy polyethylene glycol-grafted chitosan is an example of a copolymer used to prepare polyion complex micelle (15).

non-covalently connected polymeric micelles

This type of PMs is characterized by the presence of a non-covalent bond that connects the core with the shell, for example; hydrogen bond and metal-ligand bond, the graft copolymers mainly used in the preparation of this type, where the backbone and side grafted chains connected non-covalently by H-bond (16). An example, poly (4-vinyl pyridine) with carboxyl-terminated polybutadiene forming polymeric micelles (17).

Polymers used in polymeric micelle preparation

The majority of PMs are made with amphiphilic di- or triblock copolymers and graft copolymers. Block copolymers are usually linear polymers, di-block consists of two parts hydrophilic and hydrophobic block, while triblock consists of three parts. In graft copolymers, the parts of the polymer on the side chain are grafted to the main polymer chain (18). The hydrophilic part of these copolymers mainly made by polyethylene glycol or polyethylene oxide, while other hydrophilic shells made up of Poly(vinylpyrrolidone) (19), while a hydrophobic chain of block copolymers are made of different types of hydrophilic blocks, for example; poly (L-amino acids), poly (Poly-ε-caprolactone) and polypropylene oxide (20). An example on diblock copolymers like poly (ethylene glycol)-poly (D, L-lactic acid) (21), while pluronics (poly (ethylene oxide)-poly (propylene oxide)- poly (ethylene oxide)) are a common example on triblock copolymer (22), and for graft copolymers the polyethylene-g-poly (n-butyl acrylate) is a good example (23). When the length of the hydrophilic chain exceeds, to a certain degree, the length of the hydrophobic chain, spherical micelles are formed from amphiphilic di-block or tri-block copolymers which are self-assembled in an aqueous medium. While the length of the hydrophilic chain is too long, copolymers appear as unimers in the aqueous medium, and molecules with long hydrophobic blocks have different shapes (24).

Micelle formation mechanism

Amphiphilic block copolymers having a difference in solubility between hydrophilic and hydrophobic segments, which is the main force that derives polymeric micelle formation (25). When the concentration of block copolymer below the critical concentration need to form micelles, the block copolymers adsorbed at the interface between water and air, and when concentration increase gradually until reaching CMC, the saturation in this air/water interface occur and reduction in surface tension and the system free energy, that is responsible for removal of hydrophobic parts of copolymers, which could encapsulate hydrophobic drugs in a form of the polymeric micelle (26, 27).

Preparation of polymeric micelle

Drug-loaded in PMs can primarily be prepared using three common approaches:

Direct dissolution method

In this preparation process, both an amphiphilic copolymer and a drug are dissolved in an aqueous solvent. This process is mainly used for hydrophobic copolymers such as poly (ethylene oxide) and poly (propylene oxide) block copolymers. However, this technique is characterized by lower drug loading. The combination of the solution with stirring, thermal, or ultrasound treatment will increase the drug loading and solubility (28). Polylactide /poly (ethylene glycol)

(PLA/PEG) polymeric micelles of paclitaxel were prepared by direct dissolution method (29).

Dialysis Method

In this process, the dissolution of drug and amphiphilic copolymer in a water-miscible organic solvent such as dimethylformamide (DMF), then placed in a dialysis bag with a certain molecular cut-off then dialyzed against water. In this process, water replaces the organic solvent gradually inside the bag to form PMs progressively due to aggregation of the amphiphilic copolymer in response to a decrease in the solubility. The micelles remain in a dialysis bag with the help of a semipermeable membrane, and the only unloaded drug is removed from micelles during the dialysis. The method described here is well suited to the laboratory setting rather than feasible to the large-scale industry. Another limitation for this type of incorporation is the incomplete elimination of the free drug from the polymeric micellar composition (30). For example, camptothecin (CPT), which is an anticancer agent was loaded in polyethylene glycol–di-stearoyl phospha-tidylethanolamine (PEG–DSPE) polymeric micelles by this method (31).

Solvent evaporation

In this method, the water-miscible organic solvent used in dissolving the drug and block copolymer, then the removal of this solvent is done by evaporation to form a thin film on the wall of the round flask, then the reconstitution of the film with water result in the formation of PMs loaded with the drug, this method also called thin-film hydration technique. The PMs that result from this method had more potential for solubilizing large amounts of hydrophobic drugs (32, 33). Dexibuprofen was loaded in pluronics (Pluronic F127 and/or P123) to form polymeric micelles by this method (34).

Polymeric micellar characterization

Determination of CMC of PMs

The main factor that affects the formation of micelles and the static stability of PMs is the CMC. Several methods used to estimate the CMC in aqueous dispersions include surface tension measurements, light scattering, dye solubilization, and utilization of fluorescent probes. The fluorescent probes method is extensively used because it's a more precise and sensitive method. Pyrene is the most widely used molecule in fluorescent probes. Pyrene is a polyaromatic molecule, preferred partition inside the hydrophobic core of PMs. Pyrene was placed with different concentrations of amphiphilic copolymer at a constant dilution. The increase in pyrene partitioning in PMs cores led to increasing pyrene fluorescence intensity which increases proportionally with increasing concentration of copolymer. This phenomenon is used for CMC estimation (35-37).

Size and morphological surface determination of PMs

For the size determination of PMs, two parameters are measured to calculate the size of PMs, which are the hydrodynamic diameter and the size distribution of PMs also called (size poly-dispersity). The broadly used technique for the determination of the two parameters is the dynamic light scattering technique (DLS). In addition, PMs size can be calculated using microscopic techniques such as scanning electron microscopy, transmission light microscopy, or atomic force microscopy. Furthermore, these microscopic techniques can be used to investigate the morphology of the PMs surface as well as the size. There are different methods available for the investigation of micellar morphology, but the most useful and reliable are the microscopic techniques and the small-angle scattering techniques (38).

Drug release

Estimation of in vitro drug release can be done by placing the micellar solution in dialysis tube which dipped into flask including the release medium, kept at unchanged stirring about 100 rpm and heating (about 37 °C). At different predetermined periods, a certain volume of the medium is drawn out and then substitution with a fresh medium is done to provide sink condition. The drugs released in the medium are measured by the spectroscopic method or other suitable methods (39).

Polymeric micelles applications

Solubilization of water-insoluble drugs

The non-polar core of PMs acts as a reservoir where the lipophilic drug can be entrapped inside the core. The increment in the solubility of poorly soluble drugs leads to enhancement in their bioavailability. The degree of solubilization is determined by the compatibility between the core of PMs and the drug entrapped, method of preparation of micelles, the length of the hydrophobic segment, the concentration of the polymer used, and temperature. The solubility of the poorly soluble drug increases as the concentration of polymer becomes higher than the CMC. As the core of PMs become larger and more space in the core allow the entrapment of more drug (40-42). For example, solubility of lyophilized lacidipine, polymeric micelles were approximately 450 times that of raw lacidipine and 300 times that of lyophilized lacidipine suspension in both water and 0.1 M HCl (43).

Using PMs for sustained drug release

The water-insoluble drug encapsulated inside the core region of the PMs can be released in a sustained manner when the hydrophobic domain of the block copolymer is modified to increase lipophilicity and rigidity of the cores, thus decrease drug loss from the core and the desired sustained drug release (44). Ibuprofen was loaded in amphiphilic diblock copolymers forming polymeric micelles was released in sustained fashion (45), additionally, the in-vitro release of nimodipine from polymeric micelles formed from Pluronics P85, F127, and F68 were in sustained fashion (46).

Polymeric micelles for drug targeting

When the drug is delivered to a particular site in the human body like cells, tissues, and organs this process is called drug targeting which can be either passive or active targeting of the drug.

A-passive targeting

This process of drug targeting takes advantage of the pathological abnormalities at the targeted region. PMs also can be passively targeted to solid tumors due to enhanced permeability and retention effect (EPR), which is the superior possible mechanism for PMs to be targeted passively to the solid tumor. The EPR effect could be seen in nearly all cancer tissue in the human body. The leaky blood vessels to the tumor area also the lymphatic drainage is weak in the tumors, thus the drug that reaches the tumor cells has a long residence time as compared to the healthy tissue thus decrease in side effects (47, 48). Doxorubicin-loaded Poly (acrylic acid)-graft-poly (ethylene glycol) (PAA-g-PEG) polymeric micelles showed accumulation in tumors as a result of passive targeting and the EPR effect (49).

B- Active targeting

The active targeting aims to achieve the specific drug delivery to the selective sites by employing the heat (Temperature-sensitive micelles), pH changes (pH-responsive micelles), ultrasounds (Ultrasound-responsive micelles), and specific interactions or binding such as binding to a specific ligand, antibody receptor-mediated or stimuli-responsive micelles (47, 48). Docetaxel loaded Poly(N-isopropylacrylamideco-acrylamide)-b-poly (D, L-lactide) copolymer micelles; it was found that

hyperthermia increased the accumulation of drug at the targeted tumor site (50). An example of pH-sensitive polymeric micelles was docetaxel after encapsulation in poly (lactic acid) (PLA)–polyethylene glycol (PEG) folate block copolymer (51). Curcumin-loaded pluronic P123/F127 polymeric micelles showed the established ultrasound at site-specific chemotherapy significantly inhibited tumor growth and the decrease in tumor weight was approximately 6.5-fold more than without exposure to ultrasound irradiation (52).

Conclusion

This review emphasizes that polymeric micelles are a promising drug delivery vehicle for drugs, due to their various advantages like structure stability, very small size, controlled drug release, water solubility, and high drug loading. The polymeric micelles can be applied successfully to obtain the required release profile, solubility enhancement, and targeting of the loaded drug leading to bioavailability and therapeutic improvement.

Acknowledgment

The authors would like to acknowledge the support of Mustansiriyah University (www.uomustansiriyh.edu.iq) Baghdad-Iraq.

References

1- Torchilin VP. Micellar nanocarriers: pharmaceutical perspectives. Drug Delivery Strategies for Poorly Water-Soluble Drugs. 2007;24(1):1-16.
2- Torchilin VPJJocr. Structure and design of polymeric surfactant-based drug delivery systems. 2001;73(2-3):137-72.
3- Imran M, Shah MR. Amphiphilic block copolymers–based micelles for drug delivery. Design and Development of New Nanocarriers: Elsevier; 2018. p. 365-400.
4- Mourya V, Inamdar N, Nawale R, Kulthe SJIJPER. Polymeric micelles: general considerations and their applications. 2011;45(2):128-38.
5- Hanafy NA, El-Kemary M, Leporatti S. Micelles structure development as a strategy to improve smart cancer therapy. Cancers. 2018;10(7):238.
6- Lu Y, Park K. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. International journal of pharmaceutics. 2013;453(1):198-214.
7- Yokoyama M. Polymeric micelles as drug carriers: their lights and shadows. Journal of drug targeting. 2014;22(7):576-83.
8- Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. Journal of pharmaceutical sciences. 2003;92(7):1343-55.
9- Kapare H, Metkar S. Micellar drug delivery system: A review. 2020; 2:21-6.
10- Deepak P, Nagaich U, Sharma A, Gulati N, Chaudhary A. Polymeric micelles: potential drug delivery devices. Indonesian Journal of Pharmacy. 2013:222-37.
11- Bai S, Ma X, Zhang T, Gao Y-E, Wang Y, Gao Y, et al. 12 - Polymeric micelles as delivery systems. In: Mozafari M, editor. Nanoengineered Biomaterials for Advanced Drug Delivery: Elsevier; 2020. p. 261-78.
12- Kapse A, Anup N, Patel V, Saraogi GK, Mishra DK, Tekade RK. Polymeric micelles: a ray of hope among new drug delivery systems. Drug Delivery Systems: Elsevier; 2020. p. 235-89.
13- Reddy B, Yadav HK, Nagesha DK, Raizaday A, Karim A. Polymeric micelles as novel carriers for poorly soluble drugs. Journal of nanoscience nanotechnology for Cancer Therapy 2015;15(6):4009-18.
14- Ahmad Z, Shah A, Siddiq M, Kraatz H-B. Polymeric micelles as drug delivery vehicles. Rsc Advances. 2014;4(33):17028-38.

15- Jeong Y-I, Seo D-H, Kim D-G, Choi C, Jang M-K, Nah J-W, et al. Methotrexate-incorporated polymeric micelles composed of methoxy poly (ethylene glycol)-grafted chitosan. Macromolecular research. 2009;17(7):538-43.
16- Yuan X, Jiang M, Zhao H, Wang M, Zhao Y, Wu C. Noncovalently connected polymeric micelles in aqueous medium. Langmuir. 2001;17(20):6122-6.
17- Chen D, Jiang M. Strategies for constructing polymeric micelles and hollow spheres in solution via specific intermolecular interactions. Accounts of chemical research. 2005;38(6):494-502.
18- Kulthe SS, Choudhari YM, Inamdar NN, Mourya VJDM, Polymers. Polymeric micelles: authoritative aspects for drug delivery. 2012;15(5):465-521.
19- Torchilin VP, Trubetskoy VS, Whiteman KR, Ferruti P, Veronese FM, Caliceti PJJops. New synthetic amphiphilic polymers for steric protection of liposomes in vivo. 1995;84(9):1049-53.
20- Kozlov MY, Melik-Nubarov NS, Batrakova EV, Kabanov AV. Relationship between pluronic block copolymer structure, critical micellization concentration and partitioning coefficients of low molecular mass solutes. Macromolecules. 2000;33(9):3305-13.
21- Kwon GS, Okano TJPr. Soluble self-assembled block copolymers for drug delivery. 1999;16(5):597.
22- Kabanov AV, Alakhov VY. Pluronic® block copolymers in drug delivery: From micellar nanocontainers to biological response modifiers. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2002;19(1).
23- Guerrero-Santos R. Synthesis of graft copolymers. III. Polystyrene-g-poly (butyl acrylate). Journal of Applied Polymer Science. 2002; 83:19-26.
24- Kulthe SS, Choudhari YM, Inamdar NN, Mourya V. Polymeric micelles: authoritative aspects for drug delivery. Designed Monomers Polymers for Advanced Technologies. 2012;15(5):465-521.
25- Deshmukh AS, Chauhan PN, Noolvi MN, Chaturvedi K, Ganguly K, Shukla SS, et al. Polymeric micelles: Basic research to clinical practice. International Journal of Pharmaceutics. 2017;532(1):249-68.
26- Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;6(6):714-29.
27- Gaucher G, Dufresne M-H, Sant VP, Kang N, Maysinger D, Leroux J-C. Block copolymer micelles: preparation, characterization and application in drug delivery. Journal of controlled release. 2005;109(1-3):169-88.
28- Gohy J-F. Block copolymer micelles. Block copolymers II. 2005:65-136.
29- Yang L, Wu X, Liu F, Duan Y, Li S-M. Novel Biodegradable Polylactide/poly (ethylene glycol) Micelles Prepared by Direct Dissolution Method for Controlled Delivery of Anticancer Drugs. Pharmaceutical research. 2009; 26:2332-42.
30- Aliabadi HM, Lavasanifar A. Polymeric micelles for drug delivery. Expert Opinion on Drug Delivery. 2006;3(1):139-62.
31- Sezgin Z, Yüksel N, Baykara T. Preparation and characterization of polymeric micelles for solubilization of poorly soluble anticancer drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2006;64(3):261-8.
32- Jette KK, Law D, Schmitt EA, Kwon GS. Preparation and drug loading of

poly (ethylene glycol)-block-poly (ε-caprolactone) micelles through the evaporation of a cosolvent azeotrope. Pharmaceutical research. 2004;21(7):1184-91.
33- Chaithanya A, Kulkarni PK, Gowda D, Joshi KH, Shruthi N, Selvam RP, et al. Formulation and Evaluation of Rosuvastatin Calcium Polymeric Micelles. 2017; 14:18.
34- Abdelbary G, Makhlouf A. Adoption of polymeric micelles to enhance the oral bioavailability of dexibuprofen: formulation, in-vitro evaluation and in-vivo pharmacokinetic study in healthy human volunteers. Pharmaceutical development technology. 2014;19(6):717-27.
35- Ding H, Wang X, Zhang S, Liu XJJoNR. Applications of polymeric micelles with tumor targeted in chemotherapy. 2012;14(11):1-13.
36- Moretton MA, Taira C, Flor S, Bernabeu E, Lucangioli S, Höcht C, et al. Novel nelfinavir mesylate loaded d-α-tocopheryl polyethylene glycol 1000 succinate micelles for enhanced pediatric anti-HIV therapy: in vitro characterization and in vivo evaluation. Colloids Surfaces B: Biointerfaces 2014; 123:302-10.
37- Peterson AM, Tan Z, Kimbrough EM, Heemstra JMJAM. 3, 3′-Dioctadecyloxacarbocyanine perchlorates (DiO) as a fluorogenic probe for measurement of critical micelle concentration. 2015;7 (16):6877-82.
38- Bussche EV, De Deene Y, Dubruel P, Vergote K, Schacht E, De Wagter C, editors. The use of static light scattering for the structure analysis of radiosensitive polymer gels: a literature survey. Journal of Physics: Conference Series; 2004: IOP Publishing.
39- Dong P, Wang X, Gu Y, Wang Y, Wang Y, Gong C, et al. Self-assembled biodegradable micelles based on star-shaped PCL-b-PEG copolymers for chemotherapeutic drug delivery. Colloids Surfaces A: Physicochemical Engineering Aspects. 2010;358(1-3):128-34.
40- Sezgin Z, Yüksel N, Baykara T. Preparation and characterization of polymeric micelles for solubilization of poorly soluble anticancer drugs. European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2006;64(3):261-8.
41- Lee H, Zeng F, Dunne M, Allen C. Methoxy poly (ethylene glycol)-block-poly (δ-valerolactone) copolymer micelles for formulation of hydrophobic drugs. Biomacromolecules. 2005;6(6):3119-28.
42- Sang-Cheol C, Dae-II Y, Sung-Chul K, Eun-Seok P. A polymeric micellar carrier for the solubilization of biphenyl dimethyl dicarboxylate. Archives of pharmacal research. 2003;26(2):173-81.
43- Fares AR, ElMeshad AN, Kassem MA. Enhancement of dissolution and oral bioavailability of lacidipine via pluronic P123/F127 mixed polymeric micelles: formulation, optimization using central composite design and in vivo bioavailability study. Drug delivery. 2018;25(1):132-42.
44- Trivedi R, Kompella UB. Nanomicellar formulations for sustained drug delivery: strategies and underlying principles. Nanomedicine (Lond). 2010;5(3):485-505.
45- Zhang Y, Chen J, Zhang G, Lu J, Yan H, Liu K. Sustained release of ibuprofen from polymeric micelles with a high loading capacity of ibuprofen in media simulating gastrointestinal tract fluids. Reactive Functional Polymers. 2012;72(6):359-64.
46- Sotoudegan F, Amini M, Faizi M, Aboofazeli R. Nimodipine-loaded Pluronic® block copolymer micelles:

preparation, characterization, in-vitro and in-vivo studies. Iranian journal of pharmaceutical research: IJPR. 2016;15(4):641.

47- Yokoyama M. Polymeric micelles for the targeting of hydrophobic drugs. Polymeric drug delivery systems. 2005; 148:533-76.

48- Amin MCIM, Butt AM, Amjad MW, Kesharwani P. Polymeric micelles for drug targeting and delivery. Nanotechnology-Based Approaches for Targeting and Delivery of Drugs and Genes: Elsevier; 2017. p. 167-202.

49- Sun Y, Zou W, Bian S, Huang Y, Tan Y, Liang J, et al. Bioreducible PAA-g-PEG graft micelles with high doxorubicin loading for targeted antitumor effect against mouse breast carcinoma. Biomaterials. 2013;34(28):6818-28.

50- Mourya V, Inamdar N, Nawale R, Kulthe S. Polymeric micelles: general considerations and their applications. Indian J Pharm Educ Res. 2011;45(2):128-38.

51- Hami Z, Amini M, Ghazi-Khansari M, Rezayat SM, Gilani K. Synthesis and in vitro evaluation of a pH-sensitive PLA–PEG–folate based polymeric micelle for controlled delivery of docetaxel. Colloids Surfaces B: Biointerfaces. 2014; 116:309-17.

52- Wu P, Jia Y, Qu F, Sun Y, Wang P, Zhang K, et al. Ultrasound-Responsive Polymeric Micelles for Sonoporation-Assisted Site-Specific Therapeutic Action. ACS Applied Materials & Interfaces. 2017;9.