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# A Brief review on polymeric nanomicelles for anticancer drug delivery

**Mandeep Dahiya***

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India.

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***Corresponding author:**

**Email :** dahiyamandeep214@gmail.com
**Tel.:** +91-9255202785

**ABSTRACT**

Micelles are self-assembling, highly stable, biodegradable and biocompatible nanosized (5-200 nm) colloidal particles with amphiphilic copolymers (with a hydrophobic core and hydrophilic shell). These are currently used as pharmaceutical carriers for water-insoluble drugs and demonstrates a series of attractive properties as anticancer drug carriers. Among polymeric micelles, a special group is formed by lipid-core micelles, i.e., micelles formed by conjugates of soluble copolymers with lipids such as polyethylene glycol and phosphatidyl ethanolamine conjugate. Polymeric micelles, including lipid core micelles, carrying various contrast agents may become the imaging agents of choice in different imaging modalities and can also be used as targeted drug delivery systems. The targeting can be achieved via the enhanced permeability and retention effect (into the areas with the compromised vasculature), by making micelles of stimuli-responsive amphiphilic block-copolymers, or by attaching specific targeting ligand molecules to the micelle surface. Due to their hydrophilic shell and small size, they sometimes exhibit prolonged circulation times *in vivo* and can accumulate in tumoral tissues. This review will discuss some recent trends in using micelles as pharmaceutical carriers. Potential medical applications, especially in cancer chemotherapy, are described and discussed.

## INTRODUCTION

Micelles represent colloidal dispersions, belonging to the large family of dispersed systems consisting of particulate matter (termed dispersed phase), distributed within a continuous phase (termed dispersion medium). Polymeric micelles are characterized by core/shell structures and formed by amphiphilic block copolymers. The three most widely studied block copolymer classes are characterized by their hydrophobic blocks, and are poly(propylene oxide), poly(L-amino acid)s and poly(ester)s. Both the inherent and modifiable properties of polymeric micelles make them particularly well suited for drug delivery purposes. The polymeric micelles used for drug delivery have shown the abilities to attenuate toxicities, enhance delivery to desired biological sites and improve the therapeutic efficacy of active pharmaceutical ingredients [1].

Pharmaceutical research on polymeric micelles has been mainly focused on copolymers having an A-B diblock structure with A, the hydrophilic (shell) and B, the hydrophobic polymer (core), respectively. Multiblock copolymers such as poly(ethylene oxide)+ poly(propylene oxide)+poly(ethylene oxide) (PEO+PPO+PEO) (A+B+A) can also self - organize in micelles. Micelle formation occurs as a result of two forces. One is an attractive force that leads to the association of molecules while the other one, a repulsive force, prevents the unlimited growth of the micelles to a distinct macroscopic phase. Amphiphilic copolymers self-associate when placed in a solvent that is selective for either the hydrophilic or hydrophobic polymer. At very low concentrations, the polymers only exist as single chains. As the concentration increases to reach a critical value called the critical micelle concentration (CMC), polymer chains start to associate to form micelles in such a way that the hydrophobic part of the copolymer will avoid contact with the aqueous media in which the polymer is diluted. At the CMC, some amount of solvent can be found inside the micellar core and micelles are described as loose aggregates which exhibit larger size than micelles formed at higher concentrations [2].

The formation of micelles is driven by the decrease of free energy in the system because of the removal of hydrophobic fragments from the aqueous environment and the re-establishing of hydrogen bond network in water. Additional energy gain results from the formation of Van der Waals bonds between hydrophobic blocks in the core of the formed micelles. When used as drug carriers in aqueous media, micelles solubilize molecules

of poorly soluble nonpolar pharmaceuticals within the micelle core, while polar molecules could be adsorbed on the micelle surface and substances with intermediate polarity distributed along surfactant molecules in intermediate positions. If the length of a hydrophilic block is too high, copolymers exist in water as individual molecules, while molecules with very long hydrophobic block forms structure with non-micellar morphology, such as rods and lamellae [3].

Many amphiphilic copolymers have recently been synthesized as a novel promising micellar carriers for the delivery of poorly water-soluble anticancer drugs. It is recommended to take permeability, mucoadhesion, sustained release, and P-glycoprotein inhibition into consideration during copolymer preparation. Both, the copolymer structure and drug loading methods should be controlled in order to get micelles with appropriate particle size for better absorption [4].

Polymeric micelles can be developed with improved drug loading capabilities by modulating hydrophobicity and hydrophilicity of the micelle forming block co-polymers, they can also be successfully cancer targeted by surface modifying with tumor-homing ligands. However, maintenance of the integrity of the self-assembled system in the circulation and disassembly for drug release at the site of drug action remain a challenge. Therefore, stimuli-responsive polymeric micelles for 'on demand' drug delivery with minimal off-target effect has been developed and extensively investigated to assess their sensitivity [5].

Micelles allow a greater depth of tissue penetration for targeted drug delivery; they usually disintegrate rapidly in the body. Thus, sustained drug delivery from micellar nanocarriers is a challenge. Strategies for sustained release nanomicellar carriers include the use of prodrugs, drug polymer conjugates, novel polymers with low CMC or of a reverse thermoresponsive nature, multi-layer micelles with layer by layer assembly, polymeric films capable of forming micelles *in vivo* and micelle coats on a solid support. These new micellar systems are promising for sustained drug delivery [6].

The present work briefly reviews the potential applications of polymeric micelles as drug carriers for anticancer drug delivery.

## APPLICATIONS IN CANCER TREATMENT

Developing new drug carrier systems are of a great importance in the treatment approach for a wide range of diseases. The simulation techniques can be valuable for decreasing the time and cost of developing novel drug carriers. Among the simulation methods, there are a vast number of studies using the dissipative particle dynamics method for the prediction of different aspects of polymeric nano-micelles for encapsulating drugs [7].

Sustained release of drugs such as paclitaxel (PTX), doxorubicin and camptothecin using block copolymer micelles [PEG-*b*poly (dioxanone-*co*-methyl dioxanone)] have been obtained. Copolymers with variable lengths of hydrophobic and hydrophilic blocks have been synthesized and successfully loaded with paclitaxel, doxorubicin and camptothecin, with micelles size in the range 130-300 nm. Drug encapsulation efficiencies varied between 15-70%, depending on the drug and copolymer composition [8].

Nonaqueous vehicle containing Cremophor EL is associated with serious clinical side effects. The ability of polymeric micelles to solubilize PTX without Cremophor EL and to be used as an effective delivery system for PTX was evaluated by developing a novel self-assembling poly(ethylene glycol)(750)-block - poly(epsilon-caprolactone-co-trimethylenecarbonate) polymeric micelles. The solubility of PTX increased up to three orders of magnitude. The PTX-loaded micelles showed a slow release of PTX with no burst effect. The HeLa cells viability assessed by the MTT test was lower for PTX-loaded micelles than for Taxol. The maximum tolerated doses of PTX-loaded micelles and Taxol in mice were 80 mg/kg and 13.5 mg/kg, respectively, after intraperitoneal administration; and 45 mg/kg and 13.5 mg/kg, respectively, after intravenous administration. These results demonstrated that PTX-loaded self-assembling micelles reduced the toxicity, allowing the increase in the dose for better therapeutic response [9].

Polymeric nanoscale drug-delivery system (nano-DDS) for PTX was developed from poly(□-caprolactone)-poly(ethylene glycol)-poly(□-caprolactone) copolymers, intended to be intravenously administered, able to improve the therapeutic efficacy of the drug and devoid of the adverse effects of Cremophor EL. PTX-loaded micelles exhibited core-shell morphology with a satisfactory size of 93 nm, and were favorable for intravenous injection. *In vitro* cytotoxicity demonstrated that the cytotoxic effect of PTX-loaded micelles was lower than that of Taxol. Pharmacokinetics results indicated that the PTX-loaded micelles had longer systemic circulation time and slower plasma elimination rate than those of Taxol. Furthermore, PTX-loaded micelles showed greater tumor growth-inhibition effect *in vivo* on EMT6 breast tumor, in comparison with Taxol. Therefore, the prepared polymeric micelles might be potential nano-DDS for PTX delivery in cancer chemotherapy [10].

A paclitaxel/MPEG-PLA block copolymer conjugate was prepared in three steps. Hydroxyl-terminated diblock copolymer of monomethoxy-poly(ethylene glycol)-b-poly(lactide) (MPEG-PLA) was synthesized by ring-opening polymerization of L-lactide using MPEG as a macroinitiator. It was converted to carboxyl-terminated MPEG-PLA by reacting with mono-t-butyl ester of diglycolic acid and subsequent deprotecting the t-butyl group with trifluoroacetic acid, and the latter was reacted with paclitaxel in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. Structures of the polymers synthesized were confirmed by $^{1}$H NMR, and their molecular weights were determined by gel permeation chromatography. The antitumor activity of the conjugate against human liver cancer H7402 cells was evaluated by MTT method. The results showed that paclitaxel can be released from the conjugate without losing cytotoxicity [11].

PTX loaded nanoparticles were developed using biodegradable methoxy poly (ethylene glycol)-poly (ε-caprolactone) (MPEG-PCL) diblock copolymer by solid dispersion technique without toxic organic solvent. The lyophilized powder has been stored at room temperature for more than six months and still unchanged. PTX-loaded MPEG-PCL nanoparticles (PTX-NPs) displayed that the highest drug loading of PTX was about 25.6% and entrapment efficiency was over 98%, and the optimized average diameter and polydispersity index were about 27.6±0.1 nm and 0.05, respectively. PTX-NPs had sustained-release effects and its curve fitting followed the Higuchi model. The maximum tolerated dose of PTX-NPs after single dose in Balb/c mice was above 80 mg PTX/kg body weight [12].

Polymeric micelles were constructed from poly(l-lactic acid)

(PLA; M(n) 3K)-b-poly(ethylene glycol) (PEG; M(n) 2K)-b-poly(l-histidine) (polyHis; M(n) 5K) as a tumor pH-specific anticancer drug carrier. Micelles (diameter 80 nm; CMC 2 μg/ml) formed by dialysis of the polymer solution in dimethylsulfoxide against pH 8.0 aqueous solutions, is assumed to have a flower-like assembly of PLA and polyHis blocks in the core and a PEG block as the shell. The pH-sensitivity of the micelles originates from the deformation of the micellar core due to the ionization of polyHis at a slightly acidic pH. However, the co-presence of pH-insensitive lipophilic PLA block in the core prevented the disintegration of the micelles and caused the aggregation. A fluorescence probe study showed that the polarity of pyrene retained in the micelles increased as pH was decreased from 7.4 to 6.6, indicating a change to a more hydrophilic environment in the micelles. Considering that the size increased up to 580 nm at pH 6.6 from 80 nm at pH 7.4 and that the transmittance of a micellar solution increased with decreasing pH, the micelles were not dissociated but rather aggregated [13].

To design the pH-responsive polymeric micelles, hydrophilic methyl ether poly(ethylene glycol) (MPEG) and pH-responsive/biodegradable poly(beta-amino ester) (PAE) were copolymerized using a Michael-type step polymerization, resulting in an MEPG-PAE block copolymer. The amphiphilic MPEG-PAE block copolymer formed polymeric micelles with nano-sized diameter by self-assembly, which showed a sharp pH-dependant micellization/demicellization transition at the tumoral acidic pH value (pH 6.4). For the cancer imaging and therapy, fluorescence dye, tetramethylrhodamine isothiocyanate (TRITC), and camptothecin (CPT), was efficiently encapsulated into the pH-responsive polymeric micelles (pH-PMs) by a simple solvent casting method. The TRITC or CPT encapsulated pH-PMs (TRITC-pH-PMs or CPT-pH-PMs) showed a rapid release of TRITC or CPT in weakly acidic aqueous (pH 6.4) because they still presented a sharp tumoral acid pH-responsive micellization/demicellization transition [14].

Multidrug resistance remains a major obstacle to successful cancer chemotherapy. Some chemical multidrug resistance inhibitors, such as ciclosporin and verapamil, have been reported to reverse resistance in tumor cells. However, the accompanying side effects have limited their clinical application. A novel drug delivery system has been developed by using, polyethylene glycol-polycaprolactone (PEG-PCL) copolymer micelle encapsulating doxorubicin, in order to circumvent drug resistance in adriamycin-resistant K562 tumor cells. Doxorubicin-loaded diblock copolymer PEG-PCL micelles were developed by using a solvent evaporation method, and the physicochemical properties of these micelles and accumulation and cytotoxicity of doxorubicin in adriamycin-resistant K562 tumor cells were studied. The diameter of prepared micelles was 36 nm with a zeta potential of +13.8 mV. The entrapment efficiency of doxorubicin was 48.6%±2.3%. The micelles showed sustained release, increased uptake, and cellular cytotoxicity, as well as decreased efflux of doxorubicin in adriamycin-resistant K562 tumor cells [15].

The triblock copolymer composed of two identical hydrophilic segments: Monomethoxy poly(ethylene glycol) (mPEG) and one hydrophobic segment poly(ε-caprolactone) (PCL); which is synthesized by coupling of mPEG-PCL-OH and mPEG-COOH in a mild condition using dicyclohexyl-carbodiimide and 4-dimethylamino pyridine. The amphiphilic block copolymer can self-assemble into nanoscopic micelles to accommodate doxorubicin (DOX) in the hydrophobic core. In this study, DOX was encapsulated into micelles with a drug loading content of 8.5%. Confocal microscopy indicated that DOX was internalized into the cytoplasm via endocytosis. A dose-finding scheme of the polymeric micelle (placebo) showed a safe dose of PEG-PCL-PEG micelles was 71.4 mg/kg in mice. The circulation time of DOX-loaded micelles in the plasma significantly increased compared to that of free DOX in rats. A biodistribution study displayed that plasma extravasation of DOX in liver and spleen occurred in the first four hours. The tumor growth of human breast cancer cells in nude mice was suppressed by multiple injections (5 mg/kg, three times daily on day 0, 7 and 14) of DOX-loaded micelles as compared to multiple administrations of free DOX [16].

Redox-responsive micelles based on amphiphilic polyethylene glycol-polymethyl methacrylate with the introduction of disulfide containing cross-linked agent (mPEG-PMMA-SS) were developed for intracellular drug release. mPEG-PMMA-SS could self-assembled into core cross-linked micelles in an aqueous medium with tunable sizes (85-151 nm), zeta potential (−24.8 mV), and desirable CMC (0.18 mg/mL). Doxorubicin could efficiently load into the micelles with satisfactory entrapment efficiency. *In vitro* release studies displayed that DOX release from mPEG-PMMA-SS micelles were about 75% within 10 h under the tumor-relevant reductive condition, whereas only about 25% DOX was released in the non-reductive medium. Fluorescence microscopy showed that DOX was delivered by micelles to the cytoplasm, released in the cytoplasm under reductive environment, and then accumulated in the cell nucleus. These results suggest that such redox-responsive micelles may develop into an efficient cytoplasmic delivery of hydrophobic anticancer drugs [17].

Zhao *et al*., (2012) demonstrated the loading of curcumin in mixed micelles composed of Pluronic P123 and F68. They observed high drug entrapment and loading, 86.93% and 6.99% respectively. *In vitro* cytotoxic assay demonstrated a marked reduction in IC50 values for curcumin in MCF-7 cells [18]. Sahu *et al*., (2011) demonstrated curcumin delivery by using Pluronic F127 and F68 as micelles-forming polymers. Both the micelles demonstrated long-term stability. Moreover, Pluronic F127 exhibited higher entrapment efficiency compared to F68 due to the better hydrophobic interaction and prolonged drug release [19].

Park *et al*., (2014) formulated singlet-oxygen producible polymeric micelles of Pluronic F127 conjugated to chlorin e6. Doxorubicin was loaded into micelles, which further enhanced the anti-cancer activity of chlorin e6. Resistance to doxorubicin was reduced without any adverse effect, thereby enhancing the efficiency of the therapy [20].

In a recent study, a micelle-like structure of poloxamer-methotrexate (MTX) conjugate as a nanocarrier for methotrexate delivery has been developed. MTX was physically entrapped and chemically conjugated to the same drug delivery system. Poloxamer-MTX (p-MTX) conjugate was synthesized, where MTX was conjugated to poloxamer via an ester bond. Due to the hydrophobicity, MTX formed the inner core of the p-MTX micelles, which could also physically encapsulate free MTX. The pharmacokinetic study revealed that the formulation delayed the MTX elimination from the bloodstream and prolonged *in vivo* residence time compared to free MTX [21].

PEG-PLA micelles have been attempted to deliver the potent chemotherapeutic agents to the brain. Brain delivery of PEG-PLA

micelles was achieved by applying microbubble-enhanced unfocused ultrasound. PEG-PLA signal was distributed deeply into the parenchyma after the ultrasound treatment [22].

Potent chemotherapeutic drug Gemcitabine, the first line treatment option for pancreatic cancer has been delivered to the Gemcitabine-resistant cells by synthesizing a hydrophobic prodrug and loading it in the PEG-PLA micelles. Gemcitabine was modified with a stearyl group to form a lipophilic pro-drug, GemC18, which was loaded into PEG-PLA polymeric micelles. GemC18-loaded micelles could effectively reduce the cell viability of Gemcitabine-resistant AsPC-1 cells [23].

PEG-PLA has also been utilized for co-delivery of two potent chemotherapeutic agents to achieve the synergistic anticancer activity. In a study, Crizotinib, an antitumoral drug approved for the treatment of non-small cell lung cancer in humans, and Sildenafil (Viagra®) were loaded in PEG-PLA micelles and their synergistic drug action were evaluated in breast cancer cells. High drug loading was achieved by using PEG-PLA micelles. The result demonstrated that delivery of both the drugs led to 2.7 fold increase in the anti-tumoral effect even after administering half the concentration of the free drugs producing the effect [24].

PEG-PCL micellar nanoparticles were actively targeted to the tumor by the surface anchorage of cancer targeting ligands. Star-shape Folate-PEG-PCL copolymer in which doxorubicin is encapsulated for targeted delivery in breast cancer was synthesized. The distal end of the PEG chain was modified by conjugating a folic acid. Folate receptors are overexpressed in tumors of the breast and ovarian cancer. Therefore, targeted delivery of the drug would be possible by conjugation of folic acid to the micellar carrier, PEG-PLA [25].

Gao *et al.,* (2002) performed various studies on loading photo dynamic therapeutic (PDT) agent called chlorin e6 trimethyl ester (modified porphyrin, m-porphyrin) and two anticancer agents tamoxifen and paclitaxel. The major problem associated with porphyrins is their poor water solubility [26]. Porphyrin loaded PEG2000-PE micelles are prepared by vortexing mporphyrin PEG2000-PE film in an aqueous buffer. Encapsulating porphyrins in micelles overcame that problem [27].

Antinuclear antibodies (ANAs) are natural auto antibodies which will selectively recognize tumor cell surface [28]. These antibodies target nucleosomes. The targeted nucleosomes are released from the apoptotically dying tumor cells and bind to the neighboring live tumor cells through certain nucleosome binding sites/receptors present on the surface of tumor cells thus converting these cells into the targets for the nucleosome-specific ANAs. As a result, some ANAs were found to be reactive against the surfaces of many transformed cells but not normal cells. Elbayoumi *et al.,* (2007) prepared Meso-tetraphenylporphine (TPP) loaded lipid-core micelles from PEG2000-PE and PEG5000-PE in 1:1 molar ratio. Nucleosome-specific monoclonal antinuclear autoantibody (ANA) 2C5 (mAb 2C5) is conjugated to the micelles which recognize a broad variety of cancers [29]. Results showed that TPP-containing PEG-PE micelles resulted in approx 65% cancer cell death, while the use of TPP in 2C5-immunomicelles resulted in the killing of 95% of cancer cells [30].

Phase changing behavior was observed in the case of azobenzene chromophore incorporated worm-like micellar structure. The micelles were developed by using sodium oleate and a cationic azobenzene dye, 1-[2-(4-phenylazo-phenoxy)-ethyl]-3-methylimidazolium bromide. The gel-like fluidic state was observed at certain azo dye to sodium oleate ratio (35/100) due to the formation of long, entangled worm-like micelles. However, the structural integrity reversibly collapsed upon irradiation, which causes photoisomerization (trans to cis) of azo dye leading to the disruption of the worm-like micellar structure resulting in the drop in viscosity of the solution [31].

The magnetic field has been utilized as an extrinsic stimulus to develop stimuli-sensitive multifunctional polymeric micelles. Application of magnetic field fulfils two different purposes. Magnetic guidance under a permanent magnetic field is typically obtained by focusing an extracorporeal magnetic field on the biological target during the injection of the magnetically responsive nanocarriers, which caused increased accumulation of nanocarriers to the tumor. Application of alternating magnetic field causes an increase in the temperature, which is exploited for deformation of the nanocarriers for quick drug release. There is a possibility to utilize the ferric oxide loaded nanocarriers for magnetic resonance imaging for their application as a diagnostic agent in image-guided therapy [32].

Magnetic nanoparticles were included into the block co-polymeric micelles to develop a poly(ethylene glycol-*b*-caprolactone)-based magnetically triggered micellar drug delivery system. Magnetic nanoparticles in the core of the micelles melted at temperatures above the physiological condition and caused thermo-responsive drug release [33].

Ultrasound triggered drug delivery by using polymeric micelles is an effective method to attain spatiotemporal control over the drug release at the desired site. Facile control over tissue penetration depth by tuning frequency and the time of exposure of ultrasound along with the non-invasiveness nature makes this delivery system suitable for the biological application, especially in the treatment of complex diseases, including cancer. Application of ultrasound does not require radiation, which is also advantageous in terms of toxicities to the cells associated with radiation. Ultrasound waves produce thermal and mechanical effects generated by cavitational phenomena and as a result, induce nanocarrier destabilization and drug release. The ultrasound causes nanocarrier permeability leading to increased cellular uptake [34].

An effective ultrasound responsive polymeric micelles composed of polyethylene glycol-poly(caprolactone) was developed that loaded anticancer drug, curcumin, and ultrasound imaging contrast agent, perfluorocarbon. At 37°C, the droplets of perfluorocarbon (boiling point 29°C) were converted to nanodroplets, which were further cavitated and collapsed by the application of ultrasound resulting in rapid drug release [35].

The amphiphilic chitosan derivatives, *N*-naphthyl-*N*,*O*-succinyl chitosan (NSCS), *N*-octyl-*N*-*O*-succinyl chitosan (OSCS) and *N*-benzyl-*N*,*O*-succinyl chitosan (BSCS), were synthesized. Meloxicam (MX) was loaded into polymeric micelles (PMs), and the effects of hydrophobic moieties of the inner core segment, on the loading efficiency, the stability of MX-loaded PMs, cytotoxicity, drug release, and porcine small intestine permeation were investigated. Among the hydrophobic cores, the *N*-octyl moiety revealed the highest MX loading efficiency and most stable MX-loaded PMs compared to the other hydrophobic cores. All PMs were spherically shaped (213-282 nm) and had low toxicity against Caco-2 cells [36].

Despite the direct access to the lung offered by the inhalation

route, drug penetration into lung tumors could remain an important issue. Folate-polyethylene glycol-hydrophobically-modified dextran (F-PEG-HMD) micelles were developed as an effective pulmonary drug delivery system to reach and penetrate lung tumors and cancer cells. The F-PEG-HMD micelles were able to enter HeLa and M109-HiFR, two folate receptor-expressing cancer cell lines, *in vitro*, and *in vivo* after administration by inhalation to orthotopic M109-HiFR lung tumor grafted mice. Paclitaxel-loaded F-PEG-HMD micelles characterized in phosphate buffer saline by an average diameter of 50 nm and a zeta potential of −4 mV were prepared with an encapsulation efficiency of approximately 100%. The loaded micelles reduced HeLa and M109-HiFR cell growth, with half maximal inhibitory concentrations of 37 and 150 nM, respectively. Dry powders embedding the paclitaxel-loaded F-PEG-HMD micelles were developed by spray-drying. *In vitro*, good deposition profiles were obtained, with a fine particle fraction of up to 50% and good ability to re-disperse the micelles in physiological buffer. A polymeric micelle-based dry powder without paclitaxel was well-tolerated *in vivo*, as assessed in healthy mice by determination of total protein content, cell count, and cytokine IL-1β, IL-6, and TNF-α concentrations in bronchoalveolar lavage fluids [37].

Clinical application of Cabazitaxel was restricted due to its high hydrophobicity and severe side effects. To overcome these problems, self-assembled micelle loading cabazitaxel (CBZ-PM) for therapy of lung cancer was developed. The CBZ-PM has high drug loading (10.52%) and encapsulation efficiency (99.30%) with a particle size of 28.77±0.52 nm and a polydispersity index of 0.114±0.012. *In vitro* release profile showed CBZ-PM has a sustained-release behavior. The result of cell proliferation assays proved that CBZ-PM could induce the Lewis lung carcinoma (LLC) cells death through $G_2$/M arrest more effectively than free CBZ. *In vivo* anti-tumor activity of CBZ-PM was further studied in mice model of LLC. The tumor inhibitory rate of CBZ-PM was more than 50% and the survival time of LLC bearing mice was efficiently prolonged following administration of CBZ-PM. In addition, the immunohistochemical study showed that more apoptosis cells were detected in the tumor tissue of CBZ-PM group than that of the positive control group. All these indicated that CBZ-PM served as a potential anti-lung cancer agent [38].

## CONCLUSION

Polymeric micelles possess an excellent ability to solubilize poorly water-soluble anticancer drugs and increase their bioavailability, due to their small size, high solubility, simple sterilization and controlled release of drugs. In addition, they show enhanced permeability and retention effect in pathological areas with compromised vasculature. Micelle specific targeting to required areas can be also achieved by attaching specific targeting ligand molecules (such as target-specific antibodies, transferrin or folate) to the micelle surface. Varying micelle composition and the sizes of hydrophilic and hydrophobic blocks of the micelle-forming material can easily control properties of micelles, such as size, loading capacity, longevity in the blood. Another interesting option may be provided by stimuli-responsive micelles, whose degradation and subsequent drug release should proceed at abnormal pH values and temperatures characteristic for many pathological zones. It will be necessary to systematically investigate the influence of micelle composition, structure and zeta potential on the pharmacokinetics, biodistribution and activity of the carried drug. The wide variety of block-copolymers available, as well as the ability to derivatize the core-forming blocks, provides the opportunity to incorporate virtually any molecule with high compatibility and solubilization potential. Owing to their fragile structure and tendency to breakdown beyond CMC, preparation of long-circulating micelles and sustained-release micelles is a challenge. The article covered the immense progress that has recently been made in developing the micellar systems for cancer therapy. Many of the micellar system have paved their way in clinical trials. However, challenges still remain for developing polymeric micelles that are sensitive to the stimuli suitable for clinical application.

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