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A review on polymer micelles as drug carriers

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Abstract
It is recognized that by intrinsic boost to the activity of absorption, distribution, metabolism and excretion i.e. (ADME) properties results into increase in therapeutic effect of the drug. By altering distribution of drug by conjugating toxic drug to antibodies having high affinity towards cancer cell specified antigens in order to increase both therapeutic efficiency of cancer and decreasing to toxicity towards it. By directly altering intrinsic absorption, distribution, metabolism and excretion i.e. (ADME) through modifications of the drug which is limited or precluded by structural requirements for activity Polymeric micelles have recently gained attention as a promising colloidal delivery system for targeting poorly soluble and amphiphilic medications. They are regarded as more stable in comparison to surfactant micelles and can encapsulate significant quantities of hydrophobic substances within their inner core. Several numbers of polymer related therapies are presently in the market and they are undergoing clinical evaluation for the treatment of cancer and other diseases. Many of them are low molecular weight drug molecules or therapeutic proteins which are chemically linked to water-soluble polymers for increasing the drug solubility and drug stability or enable to target tumors.

Keywords: Critical micelle concentration, amphiphilic polymer, dendrimers, blocks copolymers, passive targeting, blood brain barrier, carrier, hydrophobic compounds

Introduction
Polymeric micelles have become a novel and promising colloidal delivery system for targeting drugs that are poorly soluble in water and amphiphilic [1]. They are regarded as more stable in comparison to surfactant micelles and have the capacity to solubilize significant quantities of hydrophobic compounds within their inner core [2]. Due to their hydrophilic shell and diminutive size, these particles may demonstrate extended circulation times in vivo and may influence tumor tissues [3]. This review examines the structural characteristics, drug loading capacities, pharmacokinetics, and biodistribution of various formulations, along with clinical trials and the methodologies employed to characterize these aspects in relation to drug delivery systems [4]. It explores the multifaceted role of polymer micelles in drug delivery, highlighting their unique properties, such as stability, biocompatibility, and tunable drug release kinetics [5]. By harnessing the advantages of polymer micelles, researchers aim to overcome longstanding challenges in drug delivery, including poor solubility, low bioavailability, and off-target effects [6]. Through a comprehensive examination of recent advancements, applications, and future prospects, this review aims to shed light on the transformative potential of polymer micelles as innovative drug carriers, paving the way for enhanced therapeutic outcomes and improved patient care [7].

Structure of polymeric micelles
Self-assembled micelles: This type of micelles is made from amphiphilic polymers which is spontaneously form of Nano sized aggregates [8]. When individual polymer chains i.e. Unimers, which are directly dissolved in aqueous solution as a dissolution medium and the threshold concentration is call critical micelle concentration [9]. Amphiphilic polymers which have very low water solubility that can alternatively dissolved in volatile organic solvent, and then dialyzed against an aqueous
The self-assembly of amphiphilic copolymers is reversible as well as thermodynamic process which is entropic-ally driven by release of water from hydrophobic blocks and is stabilized or destabilized by hydrophilic shell interaction with solvents [10]. Such as, the structural potential of amphiphilic copolymer unimers by forming micelles which is determined by mass ratio of hydrophilic to hydrophobic blocks, this may also affects subsequent morphology if aggregates are formed. Important consideration for drug delivery that relate to thermo-dynamic and kinetic stability i.e. potential for disassembly and rate of disassembly of the polymer micelle

complexes after Intra-venous and subsequent extreme dilution in the vascular compartment [11]. The stability of polymer micelles is essential to prevent the premature release of the drug into the systemic circulation. This stability allows the micelles to persist as nanoparticles for an adequate duration, facilitating their accumulation in sufficient concentrations at the intended target site [12].

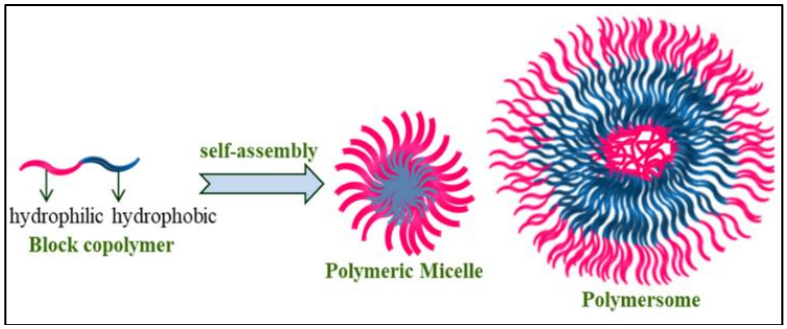

Figure 1. Self-assembly of block copolymer micelles.

Uni-molecular micelles

This type of micelles are same as the self-assembled micelles but here presence of single polymer molecule with presence of covalently bonded amphiphilic chains [13]. Depending on the structure and composition the copolymers with star-like architecture i.e. dendritic can aggregate onto multiple micelles [14]. Dendrimers are widely used as building blocks to prepare uni-molecular micelles because they are highly-branched, have well-defined globular shape and controlled surface functionality [15]. For example, uni-molecular micelles were prepared by coupling dendritic hyper-cores of different generations with PEO chains [16].

Cross-linked micelles

In this the multi-molecular micelles structure can be reinforce by formation of the cross linkage between the polymeric chains [17]. The resulting cross linkage micelles are essence single molecules of nano-scale size which is stable during dilution, shear forces and environmental variations such as ionic strength, solvents, changes in pH etc [18]. Cross-linking has resulted in stabilization reports concerning polymeric micelles, including linkages within the core domain and throughout the shell layer. In these instances, the core-shell morphology of the cross-linked micelles, along with their small size, was consistently maintained, effectively suppressing their dissociation. Stable nano-spheres were produced from PEO-b-polylactide micelles through the incorporation of a polymerizable group in the core segment [19].

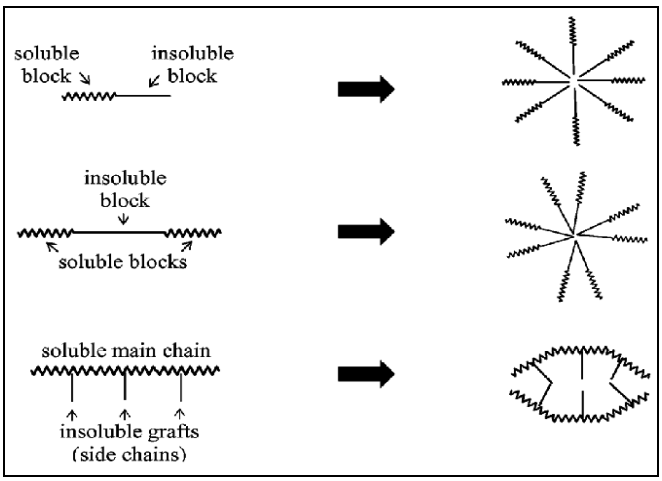

Figure 2. Polymer micelle structures.

Drug loading and release of polymer micelles

In detail, here we study three major types of drug loading and release into polymer micelle core, they are classified as follows

Poly-ionic complexation, Chemical conjugate, Physical solubilization [20].

Poly-ionic complexation

Through electrostatic interaction, charged therapeutic agents can incorporated in block copolymer by opposite charged ionic segment of block copolymer [21]. This method is commonly employed for integrating various polynucleic acids into block ionomer complexes, facilitating the advancement of non-viral gene delivery systems [22]. The sensitivity of these block ionomer micelles to both salt and pH facilitates the regulated release of the active therapeutic agent [23]. Block ionomer complexes may participate in polyion interchange reactions, which are thought to facilitate the release of the therapeutic agent and DNA in their active forms within cells [24]. Multiple ionic block lengths, the charge density, and the ionic strength of the solution all influence the development of the stable block ionomer complex, which in turn controls the amount of medicine that can be incorporated within the micelles [25].

Chemical conjugate

It was first proposed by Rings-dorf's group in 1984, by this approach, a drug is conjugated chemically to form a core by block copolymer i.e. by designed pH sensitive linker or enzyme linker that may be cleaved for release of drug into active form within the cell [26]. This drug-polymer conjugate allows acting as a polymer pro-drug, this gives self assembles into a core structure formation [27]. By this choice, conjugate bond depend on the specified applications. For the effectiveness of the pro-drug, the nature of drug-polymer linkage and stability can be control to influence drug release [28]. By using doxorubicin conjugated to poly-aspartic acid chain of PEO-b-poly block copolymer though an amide bond, by composition of this block copolymer and conjugate doxorubicin, it improves the efficacy as by eliminating the tumors that was implanted in mice, it was then concluded that doxorubicin was physically encapsulated by micellar core which shows anti-tumor activity. This helps in use of PEO-b-poly conjugates as nano-containers for physically entrapped doxorubicin [29].

Physical solubilization

This method is mainly preferred over the drug-polymer conjugation, especially for the hydrophobic molecules. Instead many of the polymer-drug molecules didn't consist of reactive functional groups for the chemical conjugation, thus, specified block copolymers have been designed for this types of drugs [30]. A diverse range of drugs can be physically integrated into the core of micelles through the re-engineering of the core structure formed by segments. This process, along with the molecular characteristics, composition, and the presence of functional groups for active targeting within the homo-copolymer series, can enhance the drug's performance [31]. This concept came into existence in late 1980 and was known as 'micelle micro-container' and nowadays it is known as 'micellar nano-container' and from last 25 years, large variety of amphiphilic block copolymer are explore as nano containers for many drugs [32].

Pharmacokinetics and bio-distribution of polymeric micelles

Introducing a drug having low molecular mass in polymer micelles, this alters pharmacokinetics and bio-distribution of drug in body, which is important for drug action [33]. By using low molecular mass drug, after administration it releases rapidly to various tissues and affect almost all of them indiscriminately and thus rapid excretion from the body [34]. By this we may observe the toxicity to kidneys due to renal clearance. Here, most of the drugs have low stability and may get degraded in systemic circulation, and can lead to toxic metabolites [35]. For an example, let us consider doxorubinol, it is a metabolite of doxorubicin, this can lead to cardiac toxicity. By using encapsulated drugs in polymer micelles for the drugs having low molecular mass to therapeutic action, here the drug molecules are protected within the micelles from the enzymatic degradation by the outer shell [36]. The miceller incorporated drugs for pharmacokinetic and bio-distribution is mainly determined by the surface properties, sixe and micelles stability and this is not more affected by the property of loaded drug [37]. The surface property of micelles are determined by micelle shell, the shell from PEO masks the drug molecule and thus prevents in the interaction with serum proteins and cell, this helps in prolong activity in the systemic circulation. Here it's clear that degradation of micelles must result to decrease in related to the size and drug release [38]. It results in formation of copolymer unimer which could be an important route for the removal of polymeric material from body. Most of unimer are less in molecular mass as the renal excretion limit i.e. less than 20 to 40 KDa, While some micelles which consist of hundreds of unimers is above the limit, hence, unimers are small and are easily removed by renal excretion but micelles cannot [39].

Application of polymeric micelles as a drug delivery

In this, polymeric micelles as drug have focus on several areas which are elaborated as follows,

- Drug delivery to the brain to treat neuro-degenerative disease
- Delivery of anti-cancer agent to treat tumors
- Delivery of polynucleotide therapeutics
- Delivery of antifungal agents

These areas are considered below

Drug delivery to the brain to treat neuro-degenerative disease

By restriction to the drug transport to the brain i.e. blood brain barrier, plays important role in treatment in tumors and neuro-degenerative disease, such as HIV, stroke, Parkinson's and Alzheimer. Here we look for two study by using polymer micelles, which have been evaluated to enhance drug delivery of biologically active agents to the brain [40].

Now, the first study is based on polymer micelle modification by including antibodies which are capable of transport across brain, from micro-vessels comprising the blood brain barrier [41].

The second study is based on use of Pluronic block copolymers for inhibition of drug reflux systems, here selectively Pgp increase permeation of blood brain barrier to its substrate, an early study state that micelles of Pluronic block copolymer for the delivery of CNS drug to the brain [42]. By these studies, the group came into existence that selected Pluronic block copolymer for example Pluronic P85 which are potential inhibitors of Pgp and increase the entry of Pgp substrate to brain across blood brain barrier [43].

Delivery of anti-cancer agent to treat tumors

It is also called as chemotherapy of cancer, to enhance chemotherapy using polymer micelles, four major approaches were employed as,

- Sensitization of drug resistance tumors by block copolymers
- Targeting of polymer micelles to specific antigens over-expressed at the surface of tumor cell
- Passive targeting of polymer micelles to tumor due to ERP effect
- Enhanced drug release at the tumors site having low pH

Here, molecular markers expressed at the surface of cancer cell by tumor specific targeting of polymeric micelles, and it has developed to eradicate tumor cell [44]. For an example, a study from Gaos foundation, develop a polymer micelle carrier for the delivery of doxorubicin to tumor cell with more expressed ingredients with it [44]. In this cyclic penta-peptide, cRGD is use as targeting ligand and which is capable for selective high affinity binding for integrin, micelles of PEO-b-poly-caprolactone is loaded with the doxorubicin, which is covalently bounded with cRGD, by this modification the uptake of doxorubicin containing micelles in, *in-vitro* endothelial model of human derived from Kaposi's sarcoma was found to be increased [45]. As a result, folate receptor were taken into consideration and overexpressed in cancer cell, which is been evaluated for the targeting of various drug carriers to tumors, and this is also evaluated for the targeted polymer micelle delivery [46].

Delivery of polynucleotide therapeutics

Here, for improving the stability of polynucleotide i.e. poly-cation based delivery complexes in related with dispersion block and graft copolymer which consist of segments by poly-cation and non-ionic water soluble polymer i.e. PEO, poly-ion complex micelles consist of hydrophobic sites that are formed by the poly-cation neutralize DNA and PEOchains which are formed by the hydrophobic sites, thus this complex don't interact with the serum proteins, hence this is used as an intra-viteral delivery for an anti-sense oligonucleotide and suppression of gene expression in retina, this were experimented on the rats [47].

Delivery of antifungal agents

The necessity for efficient and safe methods for administering chemotherapeutic agents in the treatment of systemic fungal infections, particularly in patients with AIDS, those

undergoing surgery, transplant recipients, or individuals who are sensitive to cancer treatment agents, is evident. To address this, the application of low solubility hydrophobic core polymeric micelles, which are standard block copolymers, is proposed [48]. But to increase solubility of amphotericin B, the core blocks methoxy-PEO-b-poly-L-aspartate, which is derived from stearate chains, As a result block copolymer form micelles. Here, amphotericin B interact more with stearate side chains in micelles core, thus solubility of amphotericin B in micelles are hemolytic activity of the drug to erythrocytes and is then relative to that of free drug [49]. Using a neutropenia murine model of disseminated candida, it was shown that micelle-incorporated amphotericin B retained potent in vivo activity [50]. Pluronic block copolymers were used by the same group to encapsulate another poorly soluble antifungal agent, NY statin [51]. As the drug is available commercially that shows potential for systemic action, but never been approved for that specific purpose because of its toxic reports [52]. Thus to use pluronic block copolymer has been demonstrated to overcome the resistance at certain antifungal agents [53].

Clinical trials of polymeric micelles formulations

Clinical trials report the study of three polymer micelle formulations of anti-cancer drug. Doxorubicin conjugate was recently studied at the Phase I trial at the National cancer hospital at Tokyo, Japan. Pluronic micelle formulation of doxorubicin was most advanced in clinical studies [54]. After the Animal study for toxicity, it was reported safe and trials have been successfully completed [55]. Finally, the phase II study of this formulation to treat inoperable metastatic adenocarcinoma of the esophagus is close to completion, during trials no hypersensitivity reaction was observed in any patient but some common toxicities such as myalgia and Neuropathy were observed [56].

Table 1: Patent Citation

S. No	Publication number	Publication date	Assignee	Title
1.	DK1631313T3	2015-06-15	Genentech Inc	Combination therapy for b cell disorder
2.	AT440117T	2009-09-15	Intezyne Tech Inc	Polymer micelles for drug supply
3.	EP1871343A2	2008-01-02	Wiscosin Alumni Research Foundation	Micelle composition of polymer and passenger drug
4.	US20070005927A1	2007-01-04	Khosravi Hormuzd M	System and methods for remote triggering of page faults
5.	AU2003230761A1	2003-10-13	Abbott Laboratories	Polymeric micelles formulations of hydrophobic compounds and methods
6.	WO1999043736A1	1999-09-02	Ono Pharma-ceutical Co. Ltd	Carrier polymer migrating into target organs and drug containing polymers
7.	FR2692578B1	1995-06-30	Sanofi Elf	Indolizin derivative, process for the preparation thereof and use thereof for the preparation of aminoalkoxybenzenesulfonyl -indolizine compounds with pharmaceutical activity

Conclusion

- It was observed that the polymer micelles play a vital role in the delivery of the drug which are poor water soluble, especially to the delivery of the oral preparation Polymeric micelles are believed to enhance the bioavailability of drugs by influencing their pharmacokinetic properties and thermodynamic stability. Their primary function is to facilitate the controlled delivery of active ingredients while safeguarding the drug from adverse environmental conditions [57].
- There is achievement for the consideration in advance process of polymer micelle delivery in tumor by vector targeting and passive targeting, it also include overall possibilities to overcome multiple drug therapy toward cancer and to increase delivery of drug to brain by using several block copolymer micelle system. In future, novel drug may get developed and it can be applicable to various other disease for human development and safety [58].
- Looking ahead, the future of Polymer micelles utilized as carriers for pharmaceuticals appears promising, with ongoing efforts focused on optimizing their design, functionality, and clinical utility. By leveraging emerging technologies, such as stimuli-responsive materials and targeted delivery strategies, polymer micelles are poised to play a pivotal role in the development of next-generation therapeutics, ushering in a new era of precision medicine [59].
- In summary, the comprehensive understanding of Polymer micelles utilized as carriers for pharmaceuticals presented in this review underscores their significant impact on the field of pharmaceutical sciences and highlights the exciting opportunities they offer for advancing drug delivery and improving patient outcomes [60].

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