Review Article

Recent Updates on Polymeric Micelles: A Review

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ABSTRACT

Polymeric micelles are a promising method for drug delivery and drug targeting research. Polymeric micelles are nano-sized colloid particles that self-assemble from amphiphilic block co-polymers and they are more stable than surfactant micelles, and their inner core can solubilize large amounts of hydrophobic substances. In this article we have reviewed several aspects related to polymeric micelles like fundamental of polymeric micelles such as general feature, main properties, size, shape, structure analysis and chemistry of polymeric micelles, mechanism of micelles formation. The types of polymeric micelles also highlighted. Here, we have especially emphasized recent advancement of polymeric micelles application like treatment of cancer, treatment of Covid-19 and oral drug delivery, cutaneous drug delivery, polynucleotide delivery and delivery to brain by using polymeric micelles as a nanocarrier.

Keywords: Polymers, Polymeric Micelles, Drug Delivery, Nanocarrier.

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INTRODUCTION

Polymeric micelles are self-assembly nanoparticles made out of amphiphilic block polymers (polymers that contain both hydrophilic and hydrophobic blocks). The behaviour of amphiphilic block polymers is similar to that of ordinary amphiphiles, and these polymers form polymeric micelles in aqueous solution above CMC. Unlike traditional surfactant monomer micelles, polymeric micelles have a covalent bond between individual surfactant molecules within the hydrophobic core. The dynamic interchange of monomers between free solution and the micellar pseudo-phase is prevented by this connection. This validates the polymeric micelles' stiffness and stability. This polymeric micelle has particles that are 10-10 nm in size, which is smaller than phospholipid vesicles.[1,2] The molecular weight of the amphiphilic block copolymer, the aggregation number of the amphiphiles, and the relative percentage of hydrophilic and hydrophobic chains are all factors that influence the size of the polymeric micelles. Polymeric micelles are more stable and have lower cytotoxicity than surfactant micelles. Because of the substantial drug loading capacity of the inner core and the unique disposition features in the body due to their size, polymeric micelles allow access to targeting. Using stimuli responsive (pH, temperature sensitive) copolymer, polymeric micelles led to the construction of an "intelligent vehicle." Polymeric micelles have recently gotten a lot of attention as a viable delivery system for poorly soluble medicines. [3-4]

Amphiphilic block copolymers can self-assemble into spherical micelles, worm-like or cylindrical micelles, and polymer vesicles in an aqueous media. The hydrophilic–hydrophobic balance of the block copolymer, described by the hydrophilic volume fraction, f, is the most important factor determining micelle shape. Polymer vesicles are created from amphiphilic block copolymers with a value of approximately 35 percent, whereas spherical micelles are formed from self-assembled amphiphilic block copolymers with a value of more than 45 percent. In contrast to surfactants, which have a molecular mass of 100–500 Da, amphiphilic diblock polymers have a molecular mass of 5000–30,000 Da. Amphiphilic block copolymers have complicated structures in addition to larger molecular weights. More complex morphologies such as crew-cut micelles, multicompartment micelles, toroid, and others can be obtained by using amphiphiles with more complicated molecular designs, such as star copolymers, or by varying the experimental conditions for self-assembly. These morphologies can have a significant impact on their application performance in terms of interfacial activity, viscosity, and emulsification. [5]

Advantages of Polymeric Micelles:

- Polymeric micelles are extremely structurally stable.
- Polymeric micelles are very small, with a diameter ranging from 10nm to 100nm, and are effective in the long-term circulation of the carrier system in the bloodstream.
- Polymeric micelles have a high-water solubility due to the huge number of hydrophobic drug molecules in the inner core.

- Biocompatibility of polymeric micelles is excellent.
- Toxicity of polymeric micelles is minimal.[6-9]

Disadvantages of Polymeric Micelles:

- Polymeric micelles are expensive.
- In an aqueous solution, a drug or copolymer undergoes hydrolytic cleavage, posing a stability issue.
- Polymeric micelles employ a high level of polymer chemistry.[6-9]

FUNDAMENTALS OF POLYMERIC MICELLES

General Features: Polymeric micelles are nano-sized drug delivery systems with a core-shell structure formed by the self-assembly of amphiphilic block copolymers in aqueous solution. Amphiphilic molecules exist separately in diluted aqueous solution, and amphiphiles act as surfactants, lowering surface tension at the air-water interface. As more chains are added to the system, the adsorption at the interface increases until unimers aggregation occurs due to bulk solution saturation. The Critical Micellar Concentration (CMC) is reached at this point. As a result, the parameter is defined as the minimum concentration of polymers in solution that causes micelles to form. According to this, micelles are stable at polymeric chain concentrations greater than the CMC, whereas the system disassembles after dilution below the CMC. [10-13]

Main Properties: Polymeric micelles are interesting carriers for various administration routes due to their small size, ease of preparation, and good solubilization properties. They can increase drug bioavailability and produce controlled and targeted drug release, which is beneficial for reducing side effects. [14,15] The most studied micelle administration route is intravenous (i.v.) injection/infusion (primarily used for chemotherapy), but very interesting results in terms of improved drug bioavailability have also been reported following oral and topical (ocular, nasal, buccal) administration. [16-19]

Size: These micelles range in size from 10 to 200 nm. This small size provides numerous benefits, including avoiding phagocytic scavenging in the liver and avoiding filtration by interendothelial cells in the spleen. These two benefits result in longer circulation times and micelle accumulation at tissue sites with vascular abnormalities (which may be useful in delivering anticancer drugs). [20]

Shape: Although micelles are commonly depicted as spherical systems, rod-like, worm-like, or even disk-like structures can be observed in some cases. [21] The differences in micellar shape are primarily due to the structure of the polymers used, as well as the surrounding environment's temperature, pH, and composition. [22,23]

Structure analysis and Chemistry of polymeric micelles: A core-shell structure distinguishes polymeric micelles. Pharmaceutical research on polymeric micelles has primarily concentrated on copolymers with an A-B diblock structure, with A representing the hydrophilic (shell) and B representing the hydrophobic (core). [24,25] Multiblock copolymers, such as poly (ethylene oxide) ± poly (propylene oxide) ± poly (ethylene oxide) ± poly (ethylene oxide) ± poly (ethylene oxide) ±poly (ethylene oxide), can self-organize in micelles and have been described as potential drug carriers. [26]

Because of their unique core-shell structure, PMs have great potential as a drug delivery system for hydrophobic compounds with low bioavailability. The inner hydrophobic core allows for the incorporation of drugs that are poorly water soluble, improving their stability and bioavailability. Typically, the inner core of the PMs was formed by hydrophobic interaction between the copolymer's hydrophobic blocks. Furthermore, it can be formed through electrostatic interactions between charged block copolymers of oppositely charged macromolecules, resulting in the formation of polyion complex (PIC) micelles. [27,28] There have also been reports of PMs formed by complexation via hydrogen bonding and metal-ligand coordination interactions, both of which are referred to as noncovalently connected micelles. [29-31] The use of polymeric micelles as carrier systems has the advantage of being able to undergo dynamic physicochemical changes during drug entrapment and release in molecular form, as well as dissociate between different block copolymer components. [32]

Mechanism of micelle formation: PMs are amphiphilic block copolymer-based self-assembled core-shell nanostructures formed in an aqueous solution. [33,34] Micelles form in aqueous solution when the concentration of the block copolymer exceeds a certain concentration known as the critical aggregation concentration (CAC) or critical micelle concentration (CMC). Hydrophobic segments of block copolymers begin to associate at the CAC or CMC to minimize contact with water molecules, resulting in the formation of a vesicular or core-shell micellar structure. In theory, the formation of micelles is caused by a decrease in free energy. The removal of hydrophobic fragments from the aqueous environment and the reestablishment of the hydrogen bond network in water reduce the system's free energy and, eventually, form the micelles. [35-37]

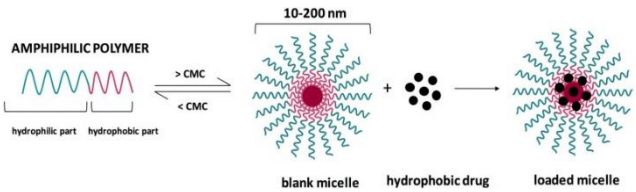

Figure 1: Schematic representation of Polymeric micelles[38]

Why did Polymeric Micelles Function as an Intelligent Drug Delivery Carrier?

From the unique research, it's been observed that Polymeric Micelles served the Intelligent Drug Delivery System's purpose. They are the result of the affiliation of polymeric chains which are touchy to stimuli. The polymers are stored collectively through vulnerable interactions

with inside the polymeric micelles. Polymeric Micelles are nano-sized shell shape shaped with the aid of using amphiphilic block copolymers. From the findings, it has been discovered that the Polymeric Micelles have significant advantages due to next subsequent properties:[39]

They have the capability for the solubilization of poorly soluble drugs.

1. Small in length.
2. Capable of sustainable transport of lively drug molecules.
3. Low molecular weights pills may be without problems administered.
4. Protect encapsulated cloth from degradation and metabolism.
5. Nano-sized aggregates of micelles form spontaneously in aqueous solutions, increasing a drug's half-lifestyle. [40]

The have a look at targets to complicated records concerning the position of Polymeric micelles for the smart transport of pills. The polymeric micelles include a centre-shell shape with a flexible drug-loading hydrophobic centre and biocompatible hydrophilic shell and are nanometers in length. Due to the improvement of various nanotechnology-primarily based methods, polymeric therapeutics has been a rising factor of drug carrying and genes. [40,41]

TYPES OF POLYMERIC MICELLES

Polymeric micelles may be categorized primarily based totally at the intermolecular forces which aside the centre section interacting with the aqueous surroundings. They are categorized into 3 groups i.e.

1. Conventional

In the aqueous surroundings the centre and the shell engage hydrophobically forming micelles. An instance for amphiphilic block co-polymer shaped by means of hydrophobic interaction is poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide). [42]

2. Polyion complicated micelles (PICMs)

Polyion complicated micelles are fashioned by way of electrostatic interplay among oppositely charged moieties. The shape and length of the charged micelles coronas are managed through electrostatic and the Vander Waals pressure of interactions. Simple artificial route, excessive drug loading capacity, structural stability, extended movement withinside the blood, self-meeting in aqueous medium are a few capabilities of polyion complicated micelles. Micelles are organized in aqueous media without the use of natural solvent. This will permit to take away the aspect effects, that can be induced because of residual natural solvent. The centre polyion complicated micelles can lure many healing sellers thru electrostatic, hydrophobic hydrogen bonding interactions. These healing retailers are launched from the middle by means of appropriate trigger. Polyion complicated micelles may be used for the shipping of charged pills, antisense oligonucleotides, DNA and enzymes. [43]

3. Non-covalently related polymeric micelles

In the non-covalently related polymeric micelles, polymeric micelles may be organized withinside the absence of block co-polymer have the riding pressure used is inter polymer hydrogen bonding complexation. Core and the corona are non-covalently related at homopolymer chain stop through hydrogen bonding or metallic ligand interactions, as a result the call non-covalently linked polymeric micelles. [44]

APPLICATIONS OF POLYMERIC MICELES

1. Polymeric Micelles in Treatment of Cancer

The most frequent cancers are lung, breast, colorectal, prostate, skin, and stomach cancers, which are ranked from highest to lowest in terms of the number of cancer cases.[45] In the recent years, polymeric micelles have gained interest and have become one of the well-studied nanocarriers in the diagnosis and pharmacotherapy of cancer. Polymeric micelles can be easily functionalized to target certain types and could be useful for cancer. The USFDA has approved a number of anticancer medications, both as monotherapy and as combination treatment for cancer. The majority of small molecule medicines utilised in clinical trials to treat a variety of malignancies are highly hydrophobic and bioavailable. Due to their limited pharmacokinetics (PK) and biodistribution profiles, chemotherapeutic medications are challenging to give in vivo. As a result, it's vital to design delivery systems that can precisely target sick areas. Polymeric micelles (PM) are good systems for encapsulating hydrophobic compounds because their hydrophobic core can accommodate these types of drugs and their hydrophilic corona, usually poly (ethylene glycol), allows PM to circulate for extended periods of time in the bloodstream, allowing them to reach tumour tissues via the enhanced permeability and retention (EPR) effect. The first generation of PMs were unstable, and they were mostly used to solubilize hydrophobic medications for intravenous distribution. Following an i.v. injection, next-generation PMs have been engineered to provide high drug encapsulation and retention while preserving prolonged circulation. [46] This technology allows for both passive and active delivery targeting.

Polymeric micelles with passive targeting: With the exception of hypo vascular tumours like prostate cancer and pancreatic cancer, the enhanced permeability and retention effect (EPR effect) can be employed to passively target polymeric micelles on solid tumours. PMs must circulate in the blood for long periods of time in order to pass by the target site multiple times for passive targeting to work. Their size is thought to have a significant impact in passive targeting and biological fate determination. [47]

Polymeric micelles with active targeting: The goal of active targeting is to use biologically specific interactions or other strategies to increase pharmaceutical delivery to target locations. Signals that are applied locally using heating and sonication procedures. Active targeting can be performed by ligand receptor or antigen-antibody interactions, or by using polymeric micelles overexpressed at the sick site to molecularly identify diseased cells. When a ligand is linked to the polymeric micelles' surface, the interaction between the ligand and its receptors, which are over-expressed at the malignant cell surface, enhances cellular absorption. The ligand includes polymeric micelles, polymeric immune micelles, epidermal growth factor (EGF), and the folate receptor. [47]

One of the most commonly utilised carriers for the solubilization of hydrophobic medicines is cremophor. [48-49] Cremophor is used to make the drugs more soluble. The drugs are delivered intravenously, but they are swiftly carried to blood proteins and then eliminated from circulation. [50-52] The first generation of PMs was created with the goal of dissolving hydrophobic materials. The block copolymer PEG-b-poly (D, L-lactic acid) (PEG-PLA) can be used to dissolve hydrophobic. Paclitaxel loaded in PEG-PLA (GenexolTM- PM) is a micellar formulation that can solubilize paclitaxel in its core, lowering the amount of paclitaxel in the body, which are Cremophor adverse effects. [53-56] In vivo stability and drug retention following intravenous administration, both of which are necessary for EPR effect mediated passive drug delivery, are the key challenges in the PM sector.

Anticancer medication delivery using polymeric micelles: In 2007, the first micellar formulation was approved in South Korea for the treatment of breast and non-small cell lung cancer (NSCL). [57] GenexolTM-PM is a paclitaxel-encapsulated micelle formulation based on the mPEG-b-poly (D, L-lactic acid) block copolymer. Following the approval of GenexolTM-PM, a number of PMs are currently being tested in clinical trials. PM Formulation might include poly (ethylene glycol)-block-poly (aspartic acid) (PEG-b-pAsp) entrapped with doxorubicin (NK911) or paclitaxel (NK105), as well as poly (ethylene glycol)-block-poly(glutamic-acid) (PEG-b-pGlu) entrapped with cisplatin (NC-6004), SN-38 (NK012). [58]

Oral delivery of anticancer medicines with polymeric micelles: We shall concentrate on the specifics of oral chemotherapeutic medication administration via polymeric micellar carriers in drug delivery. unlike intravenous infusions, oral formulations can contain large molecular weight, nondegradable polymers and gels, as long as they are excretable and do not enter the systemic circulation. [59] To increase the formulation's residence period, the oral polymer formulations should be mucoadhesive, with better adhesion to the intestinal walls. [60] Oral delivery devices that include the chemotherapy medication bleomycin include hydrogel nanospheres composed of PMAA acid and PEG and loaded with the chemotherapeutic agent bleomycin.[61-63] The permeability of a cell epithelial model was improved by these PMAA-PEG nanogel particles, potentially increasing medicine administration into the circulation. Oral delivery of hydrophobic medicinal chemicals by pH-sensitive polymeric micelles may be a viable option.[64]

In clinical trials with polymeric micelles: Several drug-loaded polymeric micelles for cancer treatment are being studied in preclinical studies to improve medication efficacy. Five micellar formulations have been tested in clinical trials. [65]

Table 1: Polymeric micelles in clinical trials [78]

Polymeric micelles	Block polymer	Drug	Diameter	Indication	Clinical phase	References
NK012	PEG-PGlu (SN-38)	SN-38	20 nm	Breast cancer	II	66
NK105	PEG-P(aspartate)	Paclitaxel	85nm	Advanced stomach cancer	II	67,68
SP1049C	Pluronic L61 and F127	Doxorubicin	22-27nm	Adenocarcinoma of oesophagus, gastroesophageal junction and stomach	III	69,70
NC-6004	PEG-PGlu (cisplatin)	Cisplatin	30nm	Solid tumour	I/II	71,72
Genexol-PM	PEG-P (D, L-lactide)	Paclitaxel	20-50nm	Breast cancer Pancreatic cancer Non-small-cell lung cancer in combination with carboplatin Pancreatic cancer in combination with gemcitabine Ovarian cancer in combination with carboplatin	IV II II I/II II/III	73,74 75,76 77 78 78

Polymeric micelles in multi-drug delivery in cancer

The major goals of anticancer medication combinations are to overcome tumour heterogeneity, minimise chemoresistance, and create additive or more desirable synergistic anticancer activity without causing overlapping toxicity. Synergism, optimum dosing regimen (concurrent versus sequential), pharmacokinetics (PK), multi-drug toxicity, and safety, such as drug precipitation and vehicle toxicity, are all important factors to consider when delivering drug combinations.[79] One of the most effective treatment choices for metastatic breast cancer is a combination of doxorubicin (DOX), taxanes, and platinum-derivatives. [80] Anticancer drugs that are poorly water soluble can be chemically or physically incorporated into polymeric micelles for simultaneous multi-drug administration. Many anticancer drugs that are poorly water soluble are injected sequentially or orally and then infused separately in clinical trials. Concurrent delivery using polymeric micelles simplifies multi-drug delivery, increases safety, and may allow anticancer medicines to act on solid tumours at the same time, resulting in a synergistic drug interaction.[81-84]

Imaging system of cancer based on polymeric micelles

Imaging Modalities: Nuclear imaging, magnetic resonance imaging (MRI), and X-ray computed tomography (CT) are all used to diagnose cancer and assess treatment response. The use of contrast chemicals to enhance the specificity of certain imaging modalities by highlighting the area of interest.

Polymeric micelles for nuclear imaging: Nuclear imaging allows for the visualization of minute amounts of gamma-emitting isotopes, nuclear imaging is the most sensitive imaging technique, requiring a concentration of isotopes of roughly 10^{-10} M at the target spot. ^{99m}Tc and ^{111}In are often utilised nuclides for this purpose because they are readily available, require simple labelling processes, and have half-lives that allow for prolonged in vivo imaging.[85] A selective N-(N-(3-diphenylphosphinopropionyl) glycyl) cysteine linker can be used to couple ^{99m}Tc. [86] Chelating compounds conjugated to the polymers, such as diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane1,4,7,10-tetraacetic acid (DOTA), can be used to couple ^{111}In to micelles.

Polymeric micelles for MRI: MRI is a technique that uses radiofrequency pulses to detect changes in the magnetization of hydrogen nuclei (1 H) in the body in a high magnetic field Fluorine-19 (^{19}F)-containing contrast agents are a relatively recent type of MRI contrast agents. In a magnetic field, ^{19}F nuclei behave similarly to 1 H nuclei and can be seen on clinical MRI systems.[87] In recent years, the use of ^{19}F-loaded particulate devices for MRI contrast enhancement has gained popularity. Perfluorocarbons such as perfluorooctyl bromide and perfluoropolyether are currently the most widely utilised ^{19}F contrast agents. [88-89]These chemicals, on the other hand, have a low water solubility and must be given as emulsions. Self-assembling fluorinated block copolymers have been developed as an alternative. These block copolymers, which are made up of a hydrophilic PEG and a hydrophobic block containing ^{19}F, produce micelles in aqueous solution and have shown encouraging imaging results in vitro, but more research in vivo is needed.[90-91]

Polymeric micelles for CT- imaging: CT imaging uses changes in X-ray absorption between different tissues in the body to distinguish between body structures. Heavy metals like iodine, bromine, and barium are employed as contrast agents in CT. CT imaging is less suitable for molecular imaging due to the comparatively high contrast agent concentration required. Micelle-based CT iodine-containing micelles (mPEG-b-indolizine, indolizine is iodine-substituted poly-L-lysine) that were utilised as a so-called blood pool agent. [92] CT is especially ideal for merging with SPECT or PET pictures. This combines the specificity of nuclear medicine with anatomical information from CT, resulting in a significant increase in nuclear imaging's applicability.[93]

Role of pH-Sensitive Micelles in cancer: The pH of the tumour is acidic when compared to the pH of healthy tissue, which serves as a differentiating feature for cancer cells. The pH of the tumour varies from 5.7 to 7.8, with a mean of 6.0. [94]The development of pH sensitive medication delivery devices is based on the acidic pH of tumour cells. pH-sensitive N-naphthyl-N, O-succinyl chitosan (NSCS) and N-octyl-N, O-succinyl chitosan (OSCS) polymeric micelles loaded with curcumin. There was a considerable increase in medication release when exposed to the pH of simulated intestinal fluid and simulated colonic fluid**.** Curcumin loaded pH sensitive polymeric micelles have much better anticancer activity in HT-29 cells.[95] recently example of pH-sensitive polymeric micelle for anticancer medication delivery and controlled release given by Luo. Self-assembly of two amphiphilic diblock copolymers (poly(ethylene glycol) methyl ether-b-poly(-amino esters) (mPEG-b-PAE) and poly(ethylene glycol) methyl ether-grafted disulphide-poly(-amino esters) (PAE-ss-mPEG) loaded with doxorubicin resulted in dual pH/redox-responsive.[96]

Role of Thermoresponsive polymeric micelles in cancer: The thermosensitive micelles are based on the thermosensitive block of the block copolymer creating micelle's lower critical solution temperature (LCST) or cloud point (CP). When placed in high-temperature conditions, Thermoresponsive polymeric micelles undergo structural changes, which could be used to force medication deposition at the target spot. In this type of micellar system, the most important parameter is LCST.[97] Using a thermo-responsive star-blockco-polymer poly(-caprolactone)-blockpoly(2-(2-methoxyethoxy)ethyl methacrylate-co-oligo(ethylene glycol- methacrylate) and Mn, Zn-doped ferrite magnetic micelles (MZF-MNPs) with the LCST controlled at 43°C. magneto thermally responsive drug loaded micelles were prepared by combining the principles An external magnet stimulus was used to locate the micelles, which was followed by a rise in temperature,

which resulted in drug release from the thermo-responsive micelles.[98]

Role of Ultra-sound sensitive polymeric micelles in cancer: Ultrasound focusing is a relatively novel method of delivering medications to tumour sites, and ultrasound-responsive micelles are gaining popularity as stimuli-triggered drug delivery systems. Adjusting the ultrasound time, intensity, and placement fine-tunes the high-intensity focused ultrasound (HIFU) stimuli. By reducing the pH as a trigger, Wang created a novel therapeutic formulation that induces a transition core-shell type micelle to form an ultrasonic sensitive polymeric nanosphere. The researchers enclosed the medicine doxorubicin (DOX) in micelles made of the triblock polymer PEG-PAAPBA-PAsp (DMA), which has dual pH sensitivity. External ultrasonography with a low frequency was employed in this study.[99]

Using polymeric micelles to overcome multiple medication resistance in cancer: In cancer, multidrug resistance (MDR) is common. MDR will demand significant improvements in present chemotherapy medication delivery systems. Polymeric micelles with multifunctional properties offer a promising approach to combating MDR processes. Developing stimuli sensitive cross-linked micelles for on demand drug delivery against treatment resistant malignancies takes advantage of a single or several stimuli present in the tumour cell microenvironment. The goal of developing folate-mediated pH sensitive doxorubicin micelles is to reduce the drug's systemic toxicity while boosting its anticancer activity in multidrug-resistant malignancies.[100]

Polymeric micellar cancer vaccines: Vaccines have been shown to prevent some of the deadliest diseases of the twentieth century, saving hundreds of millions of lives worldwide. Prophylactic vaccines and therapeutic vaccines are the two forms of vaccine therapeutics. [101] In the case of a cancer vaccine, the situation is significantly more convoluted, making the development of preventative and therapeutic cancer vaccines more difficult.[102] Viruses and bacteria appear to be foreign to our immune system, yet malignant cells have a lot in common with healthy cells in our bodies. Preventative cancer vaccinations that target this can help to reduce the number of cases. The human papillomavirus (HPV), for example, can cause cervical, head, and neck cancer, while the hepatitis B virus can cause liver cancer (HBV). Cervarix®, Gardasil®, Gardasil-9®, and HEPLISAV-B® are four vaccines that have been licenced by the US Food and Drug Administration (FDA) for preventing HPV and HBV infection and reducing the risks of cervical cancer (HPV vaccine) and hepatocellular carcinoma (HBV vaccine) in high-risk groups.[103]

There are four forms of therapeutic vaccinations under investigation, including DC vaccines, nucleic acids, tumour cell lysates (TCLs), and neoantigens in addition to preventative vaccines. DCs are primarily responsible for the presentation and processing of cancer antigens, and they have the ability to modulate both innate and adaptive responses.[104-106] It has been widely accepted that lymph nodes (LNs) are critical targets of cancer vaccines because antigen presentation and initiation of T-cell-mediated immune responses occur primarily at these locations. DNA vaccines are plasmids that deliver genes that encode linked tumour antigens to induce an adaptive immune response in cancer immunotherapy. Polymeric micelles can protect siRNA molecules and antigens while delivering them to the same target areas, ensuring that CTL responses are augmented synergistically.[107]

Table 2: Polymeric micelles for cancer vaccination [118]

Polymer	Mechanism of action	Adjuvant and Immunogen	Cancer Types	References
PEOz-PLA and carboxylate-Pluronic F127	LNs targeting	Ova and CL264	Lymphoma	108
PEG-PE and PSA	LNs targeting	Trp2 and CpG	Metastatic melanoma	109
Curcumin-PEG	Reduction of MDSCs and Tregs and increased CD8 T cells	Trp2	Melanoma	110
PLGA-PEG		Trp2	Melanoma	111
PSA	DC targeting	Trp2	Melanoma	112
PEG-b-PAGE-b-PLGA	-	Ova	-	113
PLGA-NPs	DC targeting	CD40, Fcg, avb3 and avb5 integrin receptors antibodies	-	114
P [Asp (DET)]/PEG-b-P[Asp (DET)	Elevated CTLs and NK	SART3	Colon cancer	115-116
PEG-PLL-PLLeu	DC activation	STAT3 siRNA and Ova	Melanoma	117-118

2. Polymeric Micelles for Treatment of COVID-19

The outbreak of the novel b-coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); family: Coronaviridae) responsible for Corona Virus Infectious Disease-2019 or COVID-19 is regarded as the worst since World War II. [119,120] Nanotherapies have emerged as an appealing approach to overcoming these limitations and delivering potential therapeutic candidates to the lung. [121] The polymeric micelle type of nanocarrier structure allows for greater drug loading while minimizing off-target drug release. [122] Polymeric micelles can be used as a targeted drug delivery vehicle by surface modification with specific ligands. Because of the hydrophilic outer layer of the micelle, the entire micelle remains stable and biocompatible with tissues and blood. [123] PluronicVR, a polymeric micelle of isoniazid and rifampicin made from ethylene oxide propylene oxide tri-block copolymers, was developed in a study. [124] To treat influenza virus infection, a multifunctional PLA-b-PEG modified copolymer methyl-b-neuraminic acid (mNA) was prepared as drug delivery micelles. Amantadine loaded in these micelles has been found to inhibit hemagglutination by binding to the hemagglutinin of influenza viruses and effectively alleviating viral infection.

One of the major drawbacks to successfully treating respiratory illness in COVID-19 infected patients is the limited intracellular intake of antiviral drugs due to limited aqueous solubility. As a result of the amphiphilic auto-assembly nature of polymeric micelles, these nanocarrier systems can be used to deliver insoluble hydrophobic antiviral and anti-inflammatory therapeutics for COVID19-related ARDS treatments. [125,126]

3. Polymeric Micelles for Oral Drug Delivery

The oral route is the most preferred route for drug administration because it has several advantages. [127] Despite the fact that it is widely used in the pharmaceutical industry, there is a problem with the drug's low bioavailability, which affects the formulation of the drug in oral delivery. The lower the polymeric micelles CMC values, the better the drug dilution and stability in the gastrointestinal environment. The presence of many hydrophobic regions in the micelle core usually results in a low CMC value. To achieve a lower CMC, the chain length at the polymer shell should be controlled while the chain length in the polymer core is increased. [128,129] Several researchers have demonstrated the importance of the hydrophobic chain in the micellar core in terms of CMC values. Kang et al demonstrated that increasing the hydrophobic chain of a triblock copolymer, polyvinylpyrrolidone-block-poly (D, L-lactide)-block-polyvinylpyrrolidone (PVP-b-PDLLA-b-PVP) the CMC values get reduced. To ensure micelle stability in the GI tract, not only is it necessary to manipulate the polymeric micelles CMC value, but another parameter that must be considered to achieve good polymeric micelle absorption is a change in the pH range. [128,130]

4. Polymeric Micelles for Enhancement of Bioavailability

Special Stability of PMs for Enhancement of Bioavailability: To ensure drug delivery to absorption sites, PMs must be able to withstand rapid dissociation upon dilution and maintain a stable core-shell structure prior to target sites. The entanglement of polymer chains in the inner core is known to provide PMs with two aspects of structural stability, thermodynamic and kinetic. [131-133] To be thermodynamically stable, a micelle's copolymer concentration should be greater than its CMC. The hydrophilic-lipophilic balance (HLB) of the block copolymer influences the CMC. When the copolymer concentration falls below the CMC, the second aspect, kinetic stability of PMs, enters the picture. For nonequilibrium drug delivery conditions, kinetic stability may be more important than thermodynamic stability. [134]

pH-Sensitive PMs for Enhancement of Bioavailability: It has been suggested that non-pH-sensitive micelles may improve drug solubilization but not necessarily drug absorption. One of the most important requirements for GI absorption is that a drug be in a free (readily absorbable) form. However, drug release from such PMs will occur only through diffusion when the polymer concentration is significantly higher than the CMC, preventing complete drug release. [135] Several PMs systems designed to increase the oral bioavailability of hydrophobic compounds have release times that far exceed the small intestine transit time. [136,137]

Introduction of pH-Sensitive PMs: The pH of blood and normal tissues is 7.23, as is well known.[138] The mildly acidic pH found in tumors (pH 6.8), as well as endosomes and lysosomes (pH 5.0–5.5), may act as a trigger to accelerate the degradation of pH-sensitive PMs and the release of encapsulated drugs. As a result, numerous pH-sensitive polymeric micellar systems for intravenous administration of anticancer drugs to tumors have been developed. [139-141] The pH of the gastrointestinal tract ranges from highly acidic in the stomach (pH 1.0–2.5) to neutral or slightly alkaline in the small intestine (pH 5.1–7.8). [142] The wide pH variation along the GI tract has been used to control drug release from carriers. Using the pH gradient to prevent GI degradation or promote absorption in the intestine appears to be a promising strategy. [143]

Mechanisms of pH-Sensitive PMs for Enhancement of Bioavailability: Among the various polymers that make up micelles, polyacids or polybases can be used as building blocks to give drug release pH sensitivity. [144,145] Amines, for example, are uncharged and thus hydrophobic at high pH, but become hydrophilic upon protonation at low pH. Acidic core units, on the other hand, such as carboxylic acids, are uncharged when protonated at low pH and become negatively charged when protonated at high pH. Many "protonation" approaches to triggering micelle destabilization have been reported, including the incorporation of L-histidine, pyridine, and tertiary amine groups in their hydrophobic segments. PMs are formed at pH levels higher than the protonatable group's pKa, where

the hydrophobic segment is essentially uncharged. As the pH falls below the pKa, the polymer ionization causes increased hydrophilicity and electrostatic repulsions, resulting in micelle destabilisation and controlled drug release. [146–148]

Mucoadhesive PMs for Enhancement of Bioavailability: Mucoadhesive PMs have at least three different fates in the GI tract: mucoadhesion, translocation through the mucosa or transit, and direct faecal elimination. Among the many variables, the surface charges of PMs appear to play a significant role in particle uptake. On the one hand, the negatively charged intestinal mucosa attracts more positively charged PMs due to the presence of glycocalyx. As a result, a large number of studies have been conducted to increase residence time in the GI tract using positively charged polymers such as chitosan. [149,150] On the other hand, particle mobility appears to be strongly dependent on surface charges, and transport rates were found to be inversely related to particle surface potentials. Negatively charged particles move at significantly faster rates than near neutral or positively charged particles, whose movement is likely limited by particle aggregation and electrostatic adhesive interactions with mucosa. Crater and Carrier demonstrated that anionic particles diffuse 20–30 times faster than cationic particles, proving the above-mentioned opinion. As a result, controlling the balance between mucoadhesion and mucus penetration is critical for efficient oral delivery. [151]

5. Polymeric Micelles as Cutaneous Drug Delivery System

Polymeric micelles have been studied as alternative delivery systems for parenteral, oral, ocular, pulmonary, and nasal administration. [152, 153] However, research into targeted cutaneous delivery using polymeric micelles is rare, and the mechanism of their action is not well understood. Polymeric nanoparticles, on the other hand, have been observed to penetrate the stratum corneum and accumulate in hair follicles. [154]

Lapetva et al. formulated ciclosporin A (CsA) loaded polymeric micelles using MPEG dihexPLA diblock copolymer and tested them on in vitro porcine ear skin in one of their studies. CLSM was then used to detect micelle and drug penetration pathways using fluorescein labelled CsA (Fluo CsA) and Nile Red (NR) labelled copolymer. These formulations increased CsA's aqueous solubility by 518 times. Even though CsA delivery from the micelle formulation was 18 times greater than the control formulation, CsA permeation across porcine skin was extremely low, with only very small amounts reaching the systemic circulation, which is an appropriate feature when the disease is limited to the skin. Finally, Fluo CsA skin penetration was observed to be deeper into skin layers by releasing drug from micelle in the intercluster region, which is likely one of the penetration pathways for cutaneous drug delivery. [155]

Mejkalová et al. created polymeric micelles from hyaluronan and loaded them with NR using a solvent evaporation method. Micelle diameters ranged from 21 to 230 nm. They proposed that the penetration route is transcellular using CLSM.[156]

6. Formulations of Antifungal Agents

The need for safe and effective chemotherapeutic agent delivery modalities to treat systemic fungal infections in immunocompromised AIDS, surgery, transplant, and cancer patients is critical. Low solubility and, in some cases, high toxicity of antifungal agents pose difficulties in their delivery. Amphotericin B, for example, has a low compatibility with the hydrophobic cores of polymer micelles formed by many conventional block copolymers. To improve amphotericin B solubilization, the core-forming blocks of methoxy-PEO-b-poly(L-aspartate) were derivatized with stearate side chains. [157-160] Micelles were formed because of the block copolymers. Amphotericin B interacted strongly with stearate side chains in the micelle core, resulting in efficient drug entrapment and subsequent sustained release in the external environment. Because amphotericin B was solubilized in the micelles, the onset of hemolytic activity against bovine erythrocytes was delayed compared to the free drug. [159] It was demonstrated that micelle-incorporated amphotericin B retained potent in vivo activity in a neutropenic murine model of disseminated candidas. The same group used pluronic block copolymers to encapsulate nystatin, another poorly soluble antifungal agent. [160] This is a commercially available drug that has demonstrated systemic administration potential but has never been approved for that purpose due to toxicity concerns. Overall, further scientific advancements using polymer micelle delivery systems for fungal infection treatment should be expected. [161–163]

7. Delivery of Polynucleotides

To improve the stability of polycation-based DNA delivery complexes in dispersion block and graft copolymers containing segments from polycations and nonionic water-soluble polymers such as PEO, new dispersion block and graft copolymers containing segments from polycations and nonionic water-soluble polymers such as PEO were developed. [164-166] When these copolymers bind to DNA, micelle-like block ionomer complexes ("polyion complex micelles") are formed, with hydrophobic sites formed by the polycation neutralized DNA and hydrophilic sites formed by the PEO chains. Because of the PEO chains, complexes remain stable in aqueous dispersion despite charge neutralization. [167] PEO modified polycation DNA complexes form stable dispersions and do not interact with serum proteins. [167-168] These systems were successfully used in rats to deliver an antisense oligonucleotide and suppress gene expression in the retina. [169] Furthermore, they exhibited prolonged plasma clearance kinetics. [170,171] Furthermore, such polyplexes may be targeted to specific receptors on the cell's surface, for example, by modifying the free ends of PEO chains with specific targeting ligands. [172, 173] Alternatively, polycations were modified with amphiphilic Pluronic molecules to improve complex binding to the cell membrane and transport of polynucleotides

within cells. [174,175] One recent study demonstrated the ability of Pluronic-polyethyleneimine-based micelles to deliver antisense oligonucleotides to tumours in vivo and demonstrated tumour sensitization to radiotherapy due to systemic administration of the oligonucleotide-loaded micelles. [176]

8. Drug Delivery to the Brain

By proscribing drug transport to the brain, the blood intelligence barrier (BBB) represents a formidable obstacle for therapy of Genius tumors and neurodegenerative diseases, such as HIV-associated dementia, stroke, Parkinson's and Alzheimer's diseases. Two strategies using polymer micelles have been evaluated to enhance transport of biologically energetic sellers to the brain. The first method is based on modification of polymer micelles with antibodies or ligand molecules succesful of transcytosis across Genius microvessel endothelial cells comprising the BBB. The 2nd method makes use of Pluronic block copolymers to inhibit drug efflux systems, particularly Pgp, and selectively make bigger the permeability of BBB to Pgp substrates. An early find out about used micelles of Pluronic block copolymers for transport of the CNS capsules to the brain.[177,178] The modified micelles have been used to solubilize fluorescent dye or neuroleptic drug, haloperidol, and these formulations have been administered intravenously in mice. Both the antibody and insulin amendment of the micelles resulted in stronger transport of the fluorescent dye to the brain and drastic will increase in neuroleptic impact of haloperidol in the animals. Subsequent studies the usage of in vitro BBB fashions demonstrated that the micelles vectorized through insulin undergo receptor-mediated transport across talent micro-vessel endothelial cells.[179] Overall this approach has a doable in developing novel modalities for delivery of a variety of drug to the brain, including chosen anti-cancer marketers to treat metastatic intelligence tumors as well as HIV protease inhibitors to eradicate HIV virus in the brain. [180,181]

9. Solubilization

The micellar core is a well-matched micro-environment and a hub for incorporating water-insoluble visitor molecules. The hydrophobic molecules can be covalently coupled to the block copolymers or bodily included into the hydrophobic core of micelles. The solubilization method leads to enhancement of their water solubility and thereby bioavailability.[182] It is frequently determined that the gastrointestinal (GI) uptake of particles is affected drastically by using particle size. A 15 to 250-fold higher uptake efficiency of particles about one hundred nm in diameter by way of the GI tract was stated forty nine than that of the micro-meter-sized particles. Thus, polymeric micelles (nanosized) bring up uptake and beautify bioavailability.[183] The extent of solubilization depends upon the micellization process, the compatibility between the drug and the core forming block, chain length of the hydrophobic block, attention of polymer, and temperature.[184] Above CMC, there is a sharp enlarge in the solubility of drug as it gets greater area to occupy in the aggregates of the hydrophobic phase of the micelle. The occupancy of the core vicinity by using drug leads to an expanded Rc of the micelle. It is worth bringing up that the core region has restrained ability for accommodation, for instance, Pluronic P85 has a core place which is 13% of the whole micelle weight.[185] The have an effect on solubilization potential of hydrophobic block length has been examined for griseofulvin in polyoxyethylene and polyoxybutylene copolymer micelles with various wide variety of hydrophobic block lengths and hydrophilic block lengths adequate for formation of spherical micelles. It was once located that the solubilization capability used to be dependent on the hydrophobic block length up to a sure extent (15 devices of hydrophobic block), after which the solubilization potential grew to become independent of the same.[186] Dong and co-workers also studied the impact of hydrophobic block length on solubilization of toluene in diblock and triblock polyurethane surfactants. It was once concluded that solubilization potential of polyurethane surfactants accelerated with an increase in the hydrophobic phase for the identical block chain structure.[187]

10. Tumor Targeting

Polymeric micelles are normally greater stable in physiological options than surfactant micelles because Polymeric micelles are shaped from amphiphilic block copolymers. The small dimension (<100 nm) of polymeric micelle offers a surface-smoothing effect and lets in longer retention time circulating in the blood and consequences from a higher accumulation of drug at the goal site. Passive and lively focused on has been used as delivery techniques to goal anti-cancer pills to fascinated physiological sites. Those strategies can enhance their therapeutic index and limit the harm to other non-target organs.[188]

Passive targeting: It is now a time-honored reality that under sure prerequisites such as inflammation or hypoxia, which is traditional for tumors, the endothelium of blood vessels will become more permeable in contrast to normal blood vessels. Those blood vessels in tumor websites will leakier than regular ones due to their incomplete tumor vasculature culture. Therefore, those cultures permit selectively more desirable permeation of macromolecules, but small molecule tablets will no longer be affected due to their brief circulation time. This phenomenon is called the EPR effect. Thus, polymeric micelles can be used to encapsulate these small-molecule drugs and beautify their extended systemic circulation to furnish tumor selectivity and reduce side effects. This concentrated on approach is called passive concentrated on due to the fact it depends on provider traits and tumor biology, however it does not incorporate any particular ligands to bind target tissue or organ.[189]

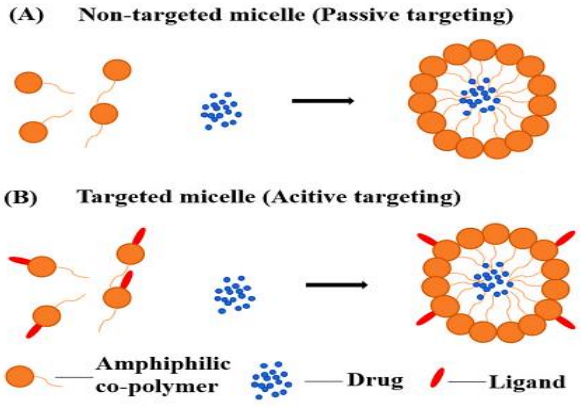

Figure 2: Assemble scheme for (A) non-targeted PM used for passive targeting and (B) focused PM used for energetic targeting.[189]

Active targeting: Active targeting can significantly make bigger the quantity of delivered tablets to the goal than passive targeting. Active targeting is accomplished via editing the surface of polymeric micelles with particular ligands that bind to receptors on the target tumor cells. Active concentrated on is specifically superb in treating most cancers due to the over expression of cancer cell receptors. The attachment of unique ligands to the hydrophilic floor of block polymers can be used to produce energetic focused on micelles. Such amendment will improve the affinity of the polymeric micelles for the goal tumor, decorate the drug effectivity and reduce aspect outcomes to regular tissues. Another method of energetic focused on is to manipulate polymeric micelles' response to particular stimuli special to sickness conditions. Drugs can be launched with the aid of inner stimuli such as pH, temperature, by means of exterior stimuli such as light, heat, or with the aid of a combination of both stimuli.[190]

11. Imaging Systems Based on Polymeric Micelles

Efficient transport of imaging agents to the website of disease in the body can enhance early diagnostics of most cancers and different diseases. The studies in this vicinity the usage of polymer micelles as carriers for imaging dealers have been initiated through the crew of Torchilin.[191] For example, micelles of amphiphilic PEO-lipid conjugates were loaded with[192] In and gadolinium diethylenetriamine penta-acetic acid phosphatidylethanolamine (Gd-DTPA-PE) and then used for visualization of neighborhood lymphatic chain after subcutaneous injection into the rabbit's paw.[193] The picture of local lymphatics have been acquired the use of a gamma camera and a magnetic resonance (MR) imager. The injected micelles stayed inside the lymph fluid, as a consequence serving as lymphangiographic dealers for indirect MR or gamma lymphography. Another polymer micelle gadget composed of amphiphilic methoxy PEO-b-poly[epsilon,N-(triiodobenzoyl)-L-lysine] block copolymers labeled with iodine was administered systemically in rabilts and visualized by using X-ray computed tomography.[194] The labeled micelles displayed splendid 24 hr half-life in the blood, which is probably due to the core-shell structure of the micelle carriers that protected the iodine-containing core. Notably, small polymer micelles (< 20 nm) may also be superb for bioimaging of tumors in contrast to PEG-modified long-circulating liposomes (ca. 100 nm). In particular, the micelles from PEO-distearoyl phosphatidyl ethanolamine conjugates containing In labeled mannequin protein have been more efficacious in delivery of the protein to Lewis lung carcinoma than larger long-circulating liposomes. Overall, polymer micelles loaded with quite a number agents for gamma, magnetic resonance, and computed tomography imaging represent promising modalities for non-invasive diagnostics of quite a number diseases.[195]

CONCLUSION

Polymeric micelles have best impact as pharmaceutical nanocarrier to various drug delivery because of the successful micelles are small in size, biodegradable and biocompatible, localized and retained in tumour tissues and demonstrate prolonged residence time in the body, as well as improve the overall pharmacokinetic profile of the incorporated hydrophobic drugs allowing them to reach tumour tissues via the enhanced permeability and retention (EPR) effect. The first class of PM aimed to be used as solubilizers of hydrophobic compounds. Polymeric micelles served as Intelligent Drug Delivery System's purpose. These carrier systems have more considerable attention in drug delivery and targeting field because of their high drug loading capacity for drug carrier. In the recent years, polymeric micelles have gained interest and have become one of the well-studied nanocarriers in the diagnosis and pharmacotherapy of cancer. Polymeric micelles bring the most efficient methodology in oral drug delivery, cutaneous and brain drug delivery. Thus, polymeric micelles, as drug carriers, have a promising future.

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