

## Polymeric Micelles: A Novel Approach for Solubility Enhancement in Drug Formulations

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### Abstract

The low aqueous solubility is a significant barrier in the development of pharmaceutical formulations and it can frequently confound the clinical efficacy and bioavailability of numerous promising drug candidates. To overcome this problem, the special nanocarrier systems like polymeric micelles (PMs) have come up as a new and efficient method to improve the solubility. Polymeric micelles are aqueous nanosized (10-100 nm) self-assembled core-shell structures, which are produced by amphiphilic block copolymers above a critical micelle concentration (CMC). Hydrophobic core entraps drugs with low solubility, and the hydrophilic shell stabilizes the system, enhances aqueous solubility and extends the systemic circulation. PMs have numerous benefits over other traditional solubilization methods, including solids dispersions and surfactant micelles, due to their high loading capacity, high stability, and release characteristics that can be tuned. They can be passively targeted by means of their nanoscale size, which allows the Enhanced Permeability and Retention (EPR) effect to be utilized, and the active target can be achieved through surface modification by ligands, in order to deliver drugs to the target site. Also, pH- or temperature- or redox-responsive PMs allow controlled and sustained delivery of drugs to diseased locations, reducing systemic toxicity. Depending on the physicochemical characteristics of the drug, flexible formulation design can be achieved by various preparation processes, such as solvent evaporation, dialysis, thin-film hydration, and co-solvent evaporation. All in all, polymeric micelles are a potential enduring nanotechnological development that is efficient in improving the solubility, stability, and bioavailability of hydrophobic drugs. Their structural flexibility, biocompatibility and ability to be targeted and controlled make them an influential platform of

next-generation pharmaceutical formulations, as well as personalized therapy.

**Keywords:** polymeric micelles, low aqueous solubility, bioavailability enhancement, nanocarrier drug delivery, controlled release

### I. Introduction

Biocompatible polymers have found wide application in pharmaceutical sciences in either of their uses; as excipients in traditional dosage forms or as a component in nanomedicine systems designed to optimize the pharmacologic effect of potent molecules of recalcitrant drugs [1, 2]. The issue of poor water solubility has become one of the greatest slowly moving challenges in drug development over the last few decades as it has curtailed the clinical performance of numerous promising drug candidates. A significant number of pharmacologically active molecules do not make it to clinical studies mainly due to poor aqueous solubility, which then results in a low rate of dissolution, lack of absorption, and bioavailability. Research has shown that about 35 percent of drugs sold and almost 90 percent of the new chemical entities currently being developed show low solubility leading to poor formulation design, inefficient pharmacokinetics and unpredictable pharmacologic reactions [3]. Ineffective solubility of drugs is normally linked to large doses in order to reach the preferred therapeutic plasma concentration, leading to systemic toxicity and lack of patient compliance. The biological activity, pharmacokinetics behaviour and therapeutic potential of drugs are directly dependent on water solubility and thereby, water solubility has been regarded as a paramount factor in determining the success of any dosage form [4]. The process of developing water-insoluble Active Pharmaceutical Ingredients (APIs) especially the ones that belong to

the Biopharmaceutical Classification System (BCS) classification II and IV is one of the crucial problems in contemporary pharmaceuticals [5]. BCS class II drugs are highly permeable but poorly soluble and the rate of dissolution acts as the rate limiting step in absorption and class IV drugs are difficult to absorb and have a very low solubility rate, thus making them very poor candidates as oral formulations.

In coming up with solutions to these drawbacks, several standard solubility enhancement techniques have been invented throughout the years. One of the most successful methods that have been embraced among these is solid dispersions. This method consists in dispersing a poorly soluble drug in a hydrophilic polymeric carrier like polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC) that increases the wettability of the drug, decreases the size of the particle and in many cases converts the crystal structure of the drug into an amorphous structure, making it more easily soluble, increasing its rate of dissolution [13,14].

Surfactants, cyclodextrins, and a very list of other old-time tricks are long the play book of hydrophobic recalcitrant drugs. For example, Tween 80, SLS, and Poloxamers, the drugs are packed into a micelle, which is a small water-soluble jacket that conceals the drug in its oily core. The inclusion complexes of cyclodextrins which are ring crystalized sugars squeeze the hydrophobic molecules into their cavity increases the water solubility (think nifedipine or ketoconazole). Nanoparticles, liposomes and solid lipid NPs as well as nanosuspensions assist in solubilizing, imparting speedy secure absorption, and specific delivery. However, these techniques may encounter low-long term stability, uncontrolled release, rapid clearance and low loading capacity.

Nano systems already exist, and polymeric micelles (PMs) are a more flexible and modern technology that avoids a lot of those pitfalls. PMs refer to 10-100nm self-assembled particles which develop as a result of dissolving amphiphilic block copolymers (imagine a water-loving tail attached to an oil-loving head of a block copolymer) in water. And beyond a critical micelle concentration (CMC), the hydrophobic components become clumped together to create a core upon which hydrophobic drugs can be properly encased, whereas the hydrophilic shell prevents aggregation (or recognition) by the immune system. The entire action comes about by a decrease in free energy: the

system would like to separate oily components and water.

One possible way to do things is to cleverly conjugate a drug to the hydrophobic block by means of covalent attachment, thereby forming a drug polymer conjugate which self-assembles into a micelle. This increases the retention of drugs and enables a release at a predictable level. Charged polymer segments can also be attracted to ionic drugs with the help of electrostatic forces and can expand the list of the drugs that PMs can deliver.

Concisely, polymeric micelles combine the superiority of surfactants, cyclodextrins, and nano-carriers with a platform, which is stable, versatile and enhances solubility, drug protection, and tighter control of how and when the drug is delivered.

Various methods can be used in the manufacture of polymeric micelles (PMs) such as dialysis, oil-in-water emulsion solvent evaporation, solid dispersion, simple solvent evaporation, direct dissolution, and chemical conjugation each with its own benefits in drug-loading capability, particle size and stability. The selection of block copolymer is also very important. Popular systems include di-, tri-, or graft-block copolymers prepared by using biocompatible building blocks which include poly (ethylene glycol) (PEG), poly (lactic acid) (PLA), poly (caprolactone) (PCL), and poly (aspartic acid) (PAA). PEGylated copolymers in particular are especially popular since steric hindrance conveys the longevity of systemic circulation due to steric-hindrance brought about by the hydrophilicity of the shell. With the tuning of block lengths, molecular weight, the hydrophilic to hydrophobic ratio, researchers are able to effectively regulate drug loading, release kinetics and biodistribution.

PMs have a number of strengths as compared to traditional solubilization methods. They are actively targeted to tumor cells because of their nanoscale dimensions and the passive tumor targeting through the enhanced permeability and retention (EPR) effect, i.e. allowing them to accumulate in leaky tumor tissues or in inflamed tissues. Active targeting is now enhanced by conjugation of targeting ligands, such as antibodies, peptides, or folic acid; this increases its effectiveness and limits off-target toxicity. Enclosing hydrophobic drugs with core enhances apparent solubility, and protects the core against premature degradation or enzymatic activity degradation of the payload. The hydrophilic shell

does not only enhance biocompatibility but also maintains the formulation in circulation making PMs a promising platform in both intravenous and oral delivery. Besides, they are able to be designed to release therapeutic drugs in a controlled and sustained manner by either diffusion or the degradation of the polymer so that levels of the drug are maintained with minimal dosage periods.

Regardless of these advantages, the development of powerful PMs requires the consideration of extensive attention to the composition of polymers, the stability of micellar systems, and the compatibility of drugs with polymers. Critical micelle concentration (CMC), molecular weight of a polymer and pH of the environment are what affect self-assembly profiles and release. A significant problem is the preservation of the micelles integrity during storage and dissociation after being diluted in vivo; when the CMC is less than the level, efficacy could be affected. In turn, the emphasis of the research is shifting towards stimuli-responsive or cross-linked micelles that are stable during dilution in the physiological system but release their cargos in response to pH, temperature or redox conditions. Such inventions provide PMs with expanded capabilities in the therapeutic approaches to beyond improving solubility with targeted cancer therapy, delivery of gene and combination therapy.

Polymeric micelles in conclusion, polymeric nanocarriers can be viewed as an efficient nanocarrier platform that can be used to leverage the advances in nanotechnology and polymer science in order to overcome the longstanding problem of low drug solubility and bioavailability. The potential to alter their structure, their ability to release therapeutics and their association with a variety of therapeutics make them one of the best approaches to come up with safe, effective, and patient-friendly drug formulations that can revolutionize contemporary pharmaceutical practice.

## CONCEPT OF POLYMERIC MICELLE

Polymeric micelles are small colloidal carriers nanosized which have attracted much attention in the contemporary pharmaceutical research because of the capability of improving the solubility and bioavailability of drugs that have low water solubility. They are normally created through self-assembly of amphiphilic block copolymers in water. These are copolymers that have two different

segments, a hydrophobic group of these copolymers that do not interact with water and a hydrophilic group of such copolymers that readily interacts with the water molecules. At a point beyond a specific concentration of the polymer, which is referred to as the critical micelle concentration (CMC), the molecules automatically assemble themselves into a core-shell known as a polymeric micelle [28].

In this type of structure, hydrophobic core is used as a storing place of poorly soluble drugs and hydrophilic shell is used to stabilize the micelle in aqueous media and prevent aggregation and recognition by body immune system [29]. This special design grants polymeric micelles enormous potential in targeted and controlled drug delivery, especially in cancer radiotherapy, where such micelles can accumulate selectively in tumour tissues by an enhanced form of permeability and retention (EPR) effect [30]. Polymeric micelles have a number of strengths with respect to conventional surfactant micelles including improved Thermodynamic stability, reduced CMC values, extended circulation in the blood, and controlled drug release behaviour. Besides, their surface could be readily altered with the ligands or anti-bodies to obtain active targeting of particular tissues or receptors [31]. All in all, polymeric micelles present an excellent prospective system of nanocarrier such that it can deliver hydrophobic drugs, peptides and even genetic materials with a better pharmacokinetic profile with fewer side effects.

Amphiphilic block-copolymers form one of the most useful families of nanocarriers. When the concentration of the molecules is very high between the critical micelle concentration (CMC) and the required core micelle forming concentration; the self-assembly of the molecules results to the formation of core-shell micelles; a hydrophobic core consisting of the insoluble blocks that are able to sequester poorly water-soluble drugs and a hydrophilic corona composed of the soluble segments that provide the particles with colloidal stability, aqueous solubility and reduced rapid clearance (MDPI 1). The resulting assemblies are of the order of 10-100nm diameter which is the gold mean between effective cellular uptake and poor renal clearance (MDPI In addition to their simplicity (in structure) these polymeric micelles can take a variety of morphologies and can be assembled by a broad range of techniques - solvent-exchange, dialysis, or microfluidic mixing - and thus they are adaptable to a large variety of biomedical applications, including oral and intravenous drugs

delivery, imaging contrasts, or theragnostic systems [32].

Both polymeric and surfactant micelles improve solubility of insoluble drugs in water though it varies in stability and efficacy. Low-molecular-weight surfactants form surfactant micelles which are readily disrupted during dilution leading to premature release of the drug [41, 42]. Conversely, PMs consist of high-molar-weight block copolymers of amphiphilic including very low critical micelle concentration (CMC), which guarantees high stability and long-term drug release [43, 44]. They can also provide greater drug-loading capacity, excellent biocompatibility as well as targeted delivery that can be achieved via surface modification [45]. Therefore, particular nanocarriers such as polymeric micelles prove to be better and more precise than the traditional surfactant micelles in regulated and site-specific delivery of drugs [47,48].

a hydrophobic interaction poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) [57].

Types of Polymeric Micelles Simple Micelles When in an aqueous environment, freely floating micelles are a self-assembling structure of copolymer amphipathy. They are prepared in an aqueous solution, or the aqueous environment, with an exterior of the Aquaphilic region and an inner zone of the Aquaphobic region. Some of them are PEG-poly(lactic acid), PEG-PLGA, and poloxamers. Such structures are the self-assembled amphiphilic copolymer structures in a non-aqueous medium. They possess the interior Aquaphilic zone and exterior Aquaphobic region, and they are produced in organic medium. An example of this is PCL-P2VP micelles in oleic acid and Chloroform Phosphorene micelles [49]. Inverted Micelles These are the amphipathic co polymer structures, which were self-assembled in an aqueous solution. They possess an internal Aquaphilic zone and external Aquaphobic zone and are made in organic medium. Single Molecular Micelles with These polymers allow an individual molecule to assemble into a micelle since they have both plenty of Aquaphilic and Aquaphobic areas within a single molecule. They are formed by amphipathic molecules in an aqueous media, which includes Core (Laur) PEG micelles. They are special single molecule forms that enable them to exist in extreme variations of temperatures, pH, ionic power, and other environmental variables. Such changes include extreme dilution [50].

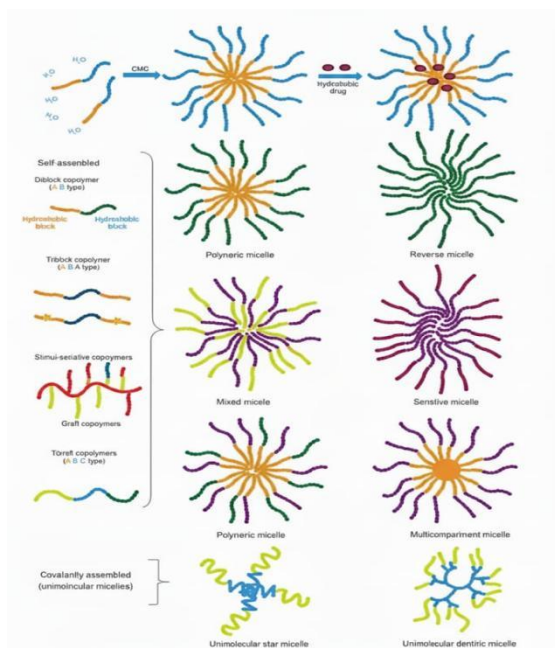


Fig. 1.1 Concept of Polymeric Micelle

## TYPES OF POLYMERIC MICELLE

### Conventional

In the aqueous solution, the core and the shell interact hydrophobically resulting into micelles. An example of amphiphilic block co-polymer which is

### pH Sensitivity PMs For Enhanced Bioavailability

It is stated that non-pH-sensitive micelles can result in a greater solubility of drugs, but most likely not necessarily the process of drug absorption. One of the most critical requirements to be absorbed in the GI tract is free (readily absorbable) form of a drug. Nevertheless, release of drugs by such PMs will be solely through diffusion where the concentration of the polymer is far much better than CMC thus avoiding full release of the drug [51]. In addition, Camilleri also measured the stomach emptying time (ca. 177 min) and the raw bowel transit time (ca. 168 min) in healthy human subjects by tracing the movement of a radio-labelled marker that had been added in their foodstuff [52]. Therefore, too, there is a chance that the PMs may be excreted before full drug release or simply drug may not be released even near its absorption window in the GI tract. A number of PM systems that were intended to enhance the oral bioavailability of

hydrophobic compounds have release times that were significantly higher than the transit time in small intestine [53,54]. The same applies to surfactant micelles that have been discovered at certain instances to hinder absorption of hydrophobic drugs by high-retention in the micellar phase which is considered to be excessively retentive [55]. Therefore, the rate of release must be appropriately regulated in the development of the oral formulations of drugs that are not highly soluble in water to prevent either precipitation of the drug with dilution or entrapment in micellar phase that could cause incomplete absorption of the drug.

## METHOD OF PREPARATIONS

### Dialysis technique

In this procedure polymer and drug solution is melted in a natural solvent such as dimethyl formamide in the development of small amount of water. Subsequently, do dialysis with the excess of water in few hours besides make use of dialysis pack in the removal of natural solvent, Medication stacking requires 36hr of dialysis [ 56].

### Direct dissolution method

It consists of the incorporation of block copolymer and drug in an aqueous solution. It generally employed the hydrophobic copolymer like poloxamers. The temperature is raised to 5 whereby micelles are formed by dehydrating core forming segments. [58, 59, 60]

### Solvent Evaporation Method

In this case, the polymer and the drug are dissolved in a volatile organic solvent (e.g. chloroform, dichloromethane) and emulsified in water. When the organic phase is evaporated, the amphiphilic copolymer will form a micelle. This technique is the best way to use hydrophobic drugs and high drug loading efficiency is achieved [61].

### Thin Film Hydration Method

In this method, solvent evaporation is used to create a thin polymer-drug film which is afterwards hydrated with water and mildly agitated. On hydration, micelles are formed spontaneously. It is a straightforward and reproducible approach that is commonly employed to prepare large-scale [62].

### Solvent Casting Co-Solvent Evaporation Method

The polymer and drug are dissolved in a co-solvent mixture of water-soluble solvents and water immiscible solvents. The organic fraction is removed slowly to produce micellization in the aqueous phase decreasing stress of the fragile drugs [63].

### Microphase Separation Method

In this technique, an organic solvent is removed out of a homogenous polymer-drug solution under controlled conditions, which causes the formation of microphases and formation of micelles. It can in particular be used with temperature- or pH-sensitive copolymers [64].

### Co solvent / emulsification Method

Polymer + drug are dissolved in an organic solvent that is soluble in water (good: acetone, acetonitrile, THF). The rapid introduction of that solution into water (non-solvents) leads to the quick diffusion of solvent into the water and the formation of amphiphilic block copolymer into micelles where the hydrophobic block is located in the core [65].

### Parameters that have an influence on Polymeric Micelle Formulation

The stability and formation of polymeric micelles are determined by a number of physicochemical parameters that control self-assembly, drug loading and release.

#### Critical Micelle Concentration (CMC)

Targeting, Imaging and Triggered Release Polymeric Micelles in Anticancer Therapy. Pharmaceutical Research. 2010. The paper presents the fact that the concentration that amphiphilic copolymers form micelles at (the CMC) is an important parameter in the stability and design of the micelles [66].

#### Temperature

Direct and Reverse Pluronic Micelles: Design and Characterization of promising drug delivery Nano systems. This paper discusses the influence of the temperature on micellization, size of a micelle, and CMC of Pluronic-type block copolymers [67].

### Polymer Ratio (Hydrophilic/Hydrophobic Balance)

An overview of Polymeric Micelles and their applications. Polymers. 2022. The review explains the influence of ratio of hydrophilic/hydrophobic block (polymer composition) on the micelle morphology, stability as well as CMC [68].

### Solvent selection

Information on the influence of the selection of organic solvent (e.g., DMF, THF, acetone) on the formation of the micelles, their size and drug loading presents the same paper "Formulation conditions on the drug loading properties of polymeric micelles" (Pak J Pharm Sci) [69].

### Characterization And Evaluation

Characterization Character Analysis. It is necessary to characterize the polymeric micelles in order to learn about the physicochemical characteristics of the micelles, their stability, and the process of drug delivery. The therapeutic efficacy of the formulation depends on parameters like particle size, zeta potential, drug loading and release behaviour [75].

### Particle size and Zeta Potential (DLS, TEM, AFM)

Determined that AFM clearly measured particle sizes and provided reliable information on the zeta potential of particles. The size of the particle affects its stability, biodistribution and cell entry where optimal nanocarriers tend to be 10-100 nm. Dynamic Light Scattering (DLS) is commonly used to measure both size and polydispersity index (PDI) whereas Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) can be used to see the surface morphology and uniformity of the structure [76].

### Drug Loading and Entrapment Efficiency

Drug Loading and Entrapment Efficiency. Drug loading (DL) and entrapment efficiency (EE) are used to provide information on the ability of the drug to be absorbed into the micellar core. They are typically identified by isolating free drug through ultrafiltration or centrifugation then measuring encapsulated drug by using HPLC or spectrophotometry of UV-Vi [77].

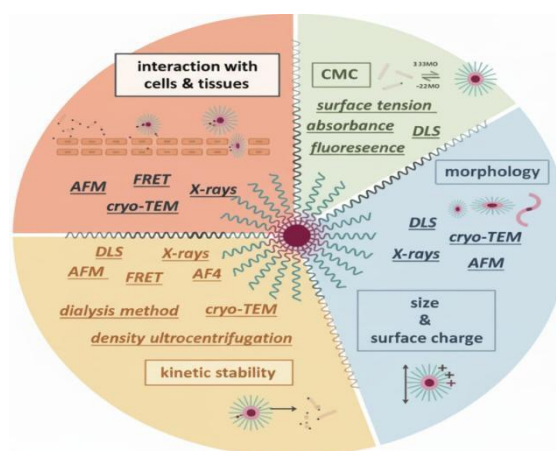


Fig. 1.2 Characterization and Evaluation of PM

### Critical Micelle Concentration (CMC) Determination

The CMC is the lowest polymer concentration to form micelles. Reduced CMC means that it is more thermodynamically stable and more resistant to dilution in the body fluids. Most widely used of them is the pyrene fluorescence probe method in which alteration of I3/I1 ratio reflects the formation of micelles [78].

### In Vitro Drug Release Studies

Drug release profiles display sustained or burst release behaviour of the formulation. They are normally conducted by way of the dialysis bag diffusion method in phosphate-buffered saline at physiological temperature (37 degC). The data are subsequently adjusted to some zero-order based or Higuchi kinetic models to project in vivo performance [79].

### Stability Testing and Compatibility Testing

The stability studies are performed to make sure polymeric micelles do not change size, charge, and drug content upon storage. FTIR and DSC are just some of the compatibility tests used to determine the drug-polymer interactions to ensure that there is no chemical incompatibility [80].

### Surface Morphology and Structure Surface Morphology and Structure (SEM/TEM)

Micellar architecture is referred to through Scanning Electron Microscopy (SEM) and TEM where the morphology of the miRNA is observed to be spherical with no aggregation. These methods

confirm consistency and integrity of structure that are specific in delivering drugs in a regular manner [81].

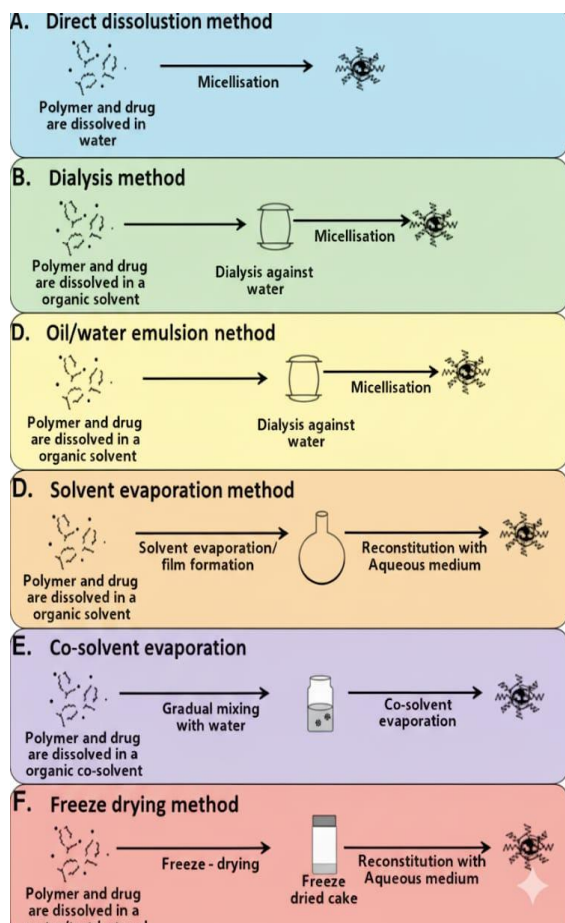


Fig. 1.3 Method of Preparation of Polymeric Micelles

## MECHANISM OF DRUG SOLUBILIZATION AND RELEASE.

Drug solubilization mechanism in polymeric micelles.

### Self-assembly

Amphiphilic block copolymer (hydrophilic block + hydrophobic block) in aqueous conditions assemble past a specific critical micelle concentration (CMC) in which the hydrophobic blocks constitute the micelle core and in the hydrophilic block the shell.

The Hydrophobic (poorly water-soluble) drug molecules are partitioned to the hydrophobic core of the micelles through hydrophobic interaction,

occasionally with the help of hydrogen bonding (or van der Waals interaction between the drug and polymer block forming the core). Solvability is dependent on compatibility of drug with core block, core block length/hydrophobicity, polymer concentration, temperature etc.

### Chemical conjugation or ionic complexation

In other cases, the drug molecules can be chemically conjugated to the polymer core in which case the drug is located in the core or in the inner shell containing the core and stabilises the particle.

### Stabilisation:

Micelle and drug loaded by a hydrophilic shell (e.g., PEG) is protected against the aqueous environment and reduces drug precipitation and enhances apparent solubility and stability [85, 86].

### Mechanism of Drug Release From Polymeric Micelles

Drug release mechanism of polymeric micelles. The release of the drug with polymeric micelles is mediated by a number of different mechanisms (either individually or a combination of them) based on arrangement, polymer-drug interactions, environment, etc. Here are the main pathways

**Dissociation / destabilisation of the micelles,** At lower polymer concentration than CMC (vitro as concentration decreases when the polymer is diluted in blood) polymerization can cause the micelle to separate (unimers disperse) and release the drug encapsulated by the core. Owing to environmental influences (pH, temperature, ionic strength), disruptions in the interaction components (serum proteins) may cause micelle disassembly and resulting drug release. **The diffusion of the drug out of the core of the micelle,** In the case when the micelle is still intact, the drug molecules may diffuse out of the hydrophobic core, over the core-shell interface, and into the external medium. It is based on core hydrophobicity / rigidity, drug-polymer interaction (high binding retards release), micelle size, and shell barrier. **Drug/polymer bond (conjugated) cleavage by chemical,** When the drug is conjugated to the polymer or is contained in an interior core of a cross-linked network, the bond must be broken (e.g., by hydrolysis) before diffusion can take place. Triggers stimuli-responsive linkages can be utilized, like sensitive, redox-sensitive.

**Exchange and transfer to biological components,** In vivo, drugs may exchange proteins/membranes, etc: Switching the equilibrium causes the core of the micelle to be released. **Composite/combined mechanisms,** one or more of the above are followed by release: e.g. micelle slowly dissociates + diffusion + protein mediated transfer. Other authors model kinetics of release using empirical equations (e.g. Korsmeyer-Peppas) or Fickian / non-Fickian transport based on conditions [87].

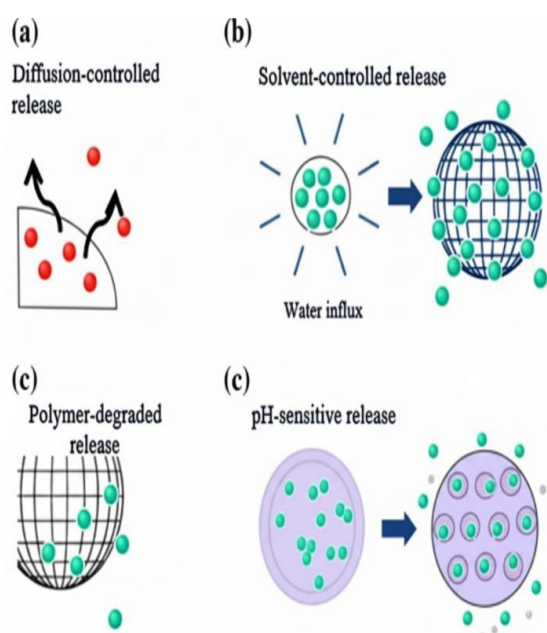


Fig. 1.4 Mechanism of Release

## ADVANTAGES OF POLYMERIC MICELLES

Polymeric micelles are new drug carriers that serve with a great number of benefits, including the minimized side effects of drugs, targeted delivery, retail stability, and dilatability stability [ 88, 92]. Moreover, polymeric micelles have nanoscale size and a small distribution [93, 94]. The micelles are capable of protecting drugs against oxidation in both in vitro and in vivo because of their core-shell structure [95]. More importantly, the polymeric micelles may be produced using suitable drug molecules [96]. The higher bioavailability and solubility of aqueous solutions. Polymeric micelles enhance the solubility of drugs that have poor aqueous solubility by entrapping their hydrophobic core, which increases the rate of absorption and overall bioavailability [ 97]. Less toxicity and degradation of drugs. Distinctive enzymatic

degradation and premature metabolism of encapsulated drugs can be avoided because the micellar core shields them, which reduces the adverse effects and toxicity of normal tissues [ 98]. Sustained and controlled drug delivery. They have a constant core-shell structure that allows them to be released under control and at extended durations to ensure the therapeutic levels of the drugs last longer [ 99]. Tumour targeting by enhanced permeability and retention (EPR) effect. Polycrystalline micelles are efficiently and passively tumour-targeted because of their size of nanoscale, which is dependent on the EPR effect in the tumour tissues [ 100]. Very stable, as opposed to surfactant micelles. Polymeric micelles have a low critical micelle concentration (CMC), which leads to a high thermodynamic stability and dilution resistance [ 101].

**Other advantages** are Inverse micelles are applicable in the food technologies industry e.g. in the extraction of protein and enzymes [102]. Bis-(2-ethylhexyl) sulfosuccinate sodium was used to reverse micelles that separated  $\alpha$ -glucosidase and mouse intestine extract using counter current chromatography. This micelle is suggested to be used in the separation of proteins [103]. The reverse micelles were prepared using the CTAB which was then applied in extracting proteins off grape seeds. Grape seed proteins extraction was determined to be 82.3% [104]. The complexation of DNA was done using a cylindrical micelle via a click type of reaction [105]. PEG was also used as a block in preparing a diblock copolymer in bulk, with the other block being poly (D, L-lactide) (PDLA), copolymers of poly (D, L-lactide-co-caprolactone) (PDLACL), or poly(glycoside-co-caprolactone) (PGACL) that is prepared using bulk ring-opening polymerization. The result of PDLACL-PEG was an optimal polymer to be used to solubilize paclitaxel in contrast to PDLA-PEG polymer. Micelles made with the PDLA-PEG had a dissociation of loaded paclitaxel of 95% in rat blood in 15 h [106]. Ring-opening polymerization was used to produce an amphiphilic brush copolymer namely poly(L-lysine)-g-(oligo(g-benzoyl-L-glutamate)-b-PEG (PPL-g-(PBLG-b-PEG) or PLL-g-(oligo (e-benzyloxy carbonyl-L-lysine)-b-PEG). PLL was used as a backbone whereas PBDL-b-PEG or PZLL-b-PEG was used as a side chain. This amphiphilic brush polymer was the one to form unimolecular micelles in which was loaded a hydrophobic probe in loading pyrene and oil red [107].

## LIMITATIONS AND CHALLENGES

Although polymeric micelles have a great potential in solubility improvement and targeted drug delivery, they also have various shortcomings that limit their bio-clinical application. Low Drug-Loading Capacity Lots of polymeric micelles have a poor drug-loading capacity especially in cases where the drugs are hydrophilic or large in size. Hydrophobic core can only accept a very little drug that may decrease therapeutic efficacy [70]. Several methods like core modification or mixed copolymer usage are being investigated in order to solve this limitation [71]. During storage, physical instability may occur. The aggregation, dissociation, drug leakage may occur during long term storage of micelles as in diluted biological systems. Change in temperature and pH may alter the hydrophobic-hydrophilic equilibrium of the small molecule, causing premature drug release [72]. Cross-linking or lyophilization (stabilization) methods are also being evaluated as a method to achieve shelf life. Scale-Out and Replicability Problems. The question is complicated in translation of the laboratory-scale formulations of the micelles into industrial production. This is in the form of batch-to-batch variation, solvent removal problem, and inability to control the size distribution of the micelle, which present manufacturing challenges [73]. It has been suggested to use continuous manufacturing and microfluidic techniques to enhance scalability and reproducibility [74]. Regulatory issue and potential Polymer Toxicity. A few polymers in micelles such as PEG, PLGA, and PCL can lead to mild toxicity or immune response even after prolonged use. The formation of anti-PEG antibody can be caused with repeated exposure, conditioning the drug effect to diminish [82]. Some end products of polymer degradation can also be irritating of tissues [83]. The regulatory acceptance is not an easy task because the polymeric micelles have no specific universal guidelines. Individual formulations have to demonstrate that they are safe, stable, and reproducible before clinical application [84].

## RECENT ADVANCES AND APPLICATIONS OF POLYMERIC MICELLES

**Targeted Drug Delivery** Polymeric micelles may be functionalized with ligands, peptides or monoclonal antibodies which identify receptors that are specifically over expressed on cancer or diseased cells. This enables the direct delivery of drugs to the target site and hence least toxicity on normal tissues.

Hydrophilic corona of the micelles is also useful in evading immune elimination and prolonging the circulation period. As an illustration, the tumour-selective accumulation of folate-/transferrin-conjugated micelles and enhanced treatment correlations have been demonstrated to be outstanding [108]. **Stimuli-Responsive Micelles** Smart or stimuli-responsive polymeric micelles are modelled to react to a certain environmental cue, including pH, temperature, redox potential or external light. The acidic pH and elevated glutathione concentrations in tumour tissues may induce the disassembly of the micelles which results in regulated and localized drug delivery. Micelles containing drugs that respond to temperature are released under heat, whereas light-sensitive micelles can be distributed to the target site using light therapy. Such intelligent systems enhance therapeutic accuracy and reduce instead of premature leakage of drugs [109]. **Co-Delivery Systems** Polymeric micelles are multi-purpose carriers that can be loaded with hydrophobic and hydrophilic agents at the same time. The co-delivery systems have been developed to carry mixtures of drugs and genes, or drugs and imaging agents, within the same carrier. This is combined delivery, which increases the efficiency of therapy and additional monitoring of drug release and tumour response by imaging. As an example, micelles transporting both doxorubicin and siRNA have been reported to efficiently silence genes and cause tumour regression in induced models in vertebrates [110].

## ANTI CANCER DRUGS (PACLITAXEL, DOXORUBICIN) IN POLYMERIC MICELLES

Polymeric micelles containing anticancer drugs (Paclitaxel, Doxorubicin). Polymeric micelles (PMs) are self-assembled nano-carriers typically of amphiphilic block copolymers (hydrophobic core + hydrophilic shell, e.g., PEG), which are able to entrap poorly-soluble drugs, extend staying time, improve tumour accumulation (EPR effect) and minimise the off-target toxicity [111]

**Paclitaxel (PTX):** Paclitaxel formulation has low aqueous solubility and is accompanied by severe side effects of the solubilising excipients. In preclinical models, one shade of the micellar product, NK105 (PEG-block-poly(aspartate) functionalized with hydrophilic moieties + paclitaxel physically loaded) demonstrated AUC (tumour) nearly 25-fold higher than free PTX,

enhanced antitumour activity, and then was used in clinical trials. Exploring Polymeric Micelles by Improving Delivery of Anticancer Agents" reported that PEG5K-CA8 micelles had the capability of solubilising paclitaxel at high load, and better antitumour effect than Taxol at mice [112].

**Doxorubicin (DOX):** On the same note, Doxorubicin micelle systems have been created. As an example, PEG2K-CA4 micelles loaded with DOX provided better accumulation and survival of the tumours in the lymphoma bearing mice. Sample: doxorubicin-conjugated PLA-PEG-Folate based polymeric micelle" (DARU 2014) - HSA hydrazone bond of DOX to copolymer, size: 4.65 ug/ml, IC50 in SKOV3 ovarian cancer cell: 4.65 ug/ml vs 13.51 ug/ml non-targeting. Drug-Polymer conjugated and paclitaxel- Physical encapsulation - Combination therapy - A synergistic combination therapy with paclitaxel and doxorubicin loaded micellar nanoparticles has been published [113].

## ANTI - INFLAMMATORY AND ANTI – FUNGAL DRUGS VIA POLYMERIC MICELLES

### Anti-inflammatory application

Example: Researchers have come up with pH-sensitive polymeric micelles to deliver Prednisolone (PD) to treat rheumatoid arthritis. The conjugate (PEG-hydrophobic drug) was amphiphilic and formed into micelles (~drug loading 19.3%). The PD micelles demonstrated high AUC in inflamed joints and in collagen induced arthritic mice, and superior anti-inflammatory/ disease-modifying efficacy in comparison with free PD. Another: RGD-polymeric-micelles-loaded with low-dose of methotrexate + Nimes Lide (anti-inflammatory) targeted rheumatoid arthritis; the R-M/N-PMs showed better distribution and efficacy in vivo [114].

### Antifungal applications

Nano-delivery - polymeric micelles are a promising platform: e.g. loading of Amphotericin B into a micellar system enhanced its solubility, solubility of Amphotericin B was enhanced at least 4-fold (0.001 to ~5mg/mL); retained bioactivity in murine candidiasis models. One particular study: Polymeric micelle gel with luliconazole: in vivo efficacy against cutaneous candidiasis in Wistar rats (2024) the micelles of luliconazole had a long release of the

substance, and they had better anti-fungal efficacy compared with the commercial formulations.

### Another application

Sometimes, polymer micelles made of P(PEGMA-b-DEAEMA) demonstrated anti- biofilm effects (Candida albicans and Candida tropicalis) and improved efficacy in cases of co-loading with fluconazole/amphotericin B [115].

## CNS Delivery (Crossing the BBB)

One of the hardest of the modern drug delivery problems is the delivery of therapeutic agents to the central nervous system (CNS) due to the presence of the blood brain barrier (BBB), a highly selective interface that helps in keeping the brain free of toxins, but also limits the passage of most drugs. BBB consists of closed endothelial pores, efflux transporter (e.g., P-glycoprotein, BCRP), and metabolic enzymes which combine to restrict diffusion of drugs. These biological environments exclude almost 98 percent of small molecules and virtually all large biomolecules to get into the brain in effective concentrations [116]. To eliminate these challenges, polymeric micelles have become potentially useful nanocarriers in CNS delivery. Their nanoscale dimension (less than 100 nm) permits them to take long periods in circulation and be passively adsorbed as transcytosis by the receptors on endothelial cells when the surface is modified with targeting ligand like transferrin, lactoferrin, or apolipoprotein E peptides. As an example, doxorubicin and curcumin when encrypted to transferrin-decorated micelles have been demonstrated to be efficient in the delivery of these drugs to brain tumours in preclinical models [117, 118, 119]. PEG-PLA angiopep-2 functionalized micelles were also demonstrated to exhibit superior transport across the BBB to treat glioma in another study [120]. Regardless of these developments, there are still a number of things that are not solved. The safety, biodegradability, and clearance of polymeric micelles in the brain tissue in the long-term requires research. In addition, a high degree of control in the release of the drug in the specific areas of the brain and the elimination of non-specific deposition are also significant objectives. Further investigation in the direction of multi-stimuli-responsive micelles and biodegradable polymers would render CNS-targeted micellar therapy clinically useful [121].

## RECENT PATENTS AND MARKETED FORMULATIONS

The PMs were investigated with respect to transdermal delivery using Hyaluronic acid and were found to be effective in transdermal delivery. Actually, hyaluronan per se may serve as a permeation enhancer [122]. An experiment that was done using Nile red, coenzyme Q10 and a fluorescence resonance energy transfer probe was effective in clarifying the mechanism of drug delivery across skin. Internalization by the transcellular method was observed in the micelles and their accumulation was on the epidermis (less) and dermis (more). With longer incubation period, there was more accumulation. The fluorescence experiments were an indication of a co-transport effect. Meanwhile, the destruction of polymer micelles was observed in the fluorescence resonance energy transfer studies as it penetrated deeper into the skin layer. The PMs succeeded in improving the in vitro and in vivo activity of the coenzyme Q10. In addition, the cream formulation made using it was identified to be stable [123]. The process of uptake of hyaluronan-based PMs was investigated and defined in another study conducted by the same group. Curcumin was the drug molecule they used in their study. They investigated oleyl-hyaluronan and hexyl-hyaluronan micelles. The fluorescence tracer was Nile blue. Their research proposed active and passive processes of the transport of drug carriers. Specifically, oleyl-hyaluronan was discovered to raise the viscosity of cell membrane and augment passive transport [124]. Formulation and delivery of mycophenolic acid in polymer micelles could increase the anti-psoriasis effect of mycophenolic acid. An evaluated conjugate of poloxamer-mycophenolic acid is effective against psoriasis in an in vitro model of tumour necrosis factor- $\alpha$ -induced HaCaT cell. Conjugate The conjugate forms micelles much more effectively (12 times lower critical micelle concentration) than poloxamer. Juxtaposition of conjugate micelles increases water solubility and therapeutic activity. It has also been pointed out that micelles exhibit an enzyme-dependent sustained-drug-release effect [125].

## ANTI CANCER DRUGS (PACLITAXEL, DOXORUBICIN) IN POLYMERIC MICELLES

Polymeric micelles containing anticancer drugs (Paclitaxel, Doxorubicin). Polymeric micelles (PMs) are self-assembled nano-carriers typically of amphiphilic block copolymers (hydrophobic core + hydrophilic shell, e.g., PEG), which are able to entrap poorly-soluble drugs, extend staying time, improve tumour accumulation (EPR effect) and minimise the off-target toxicity [111]

**Paclitaxel (PTX):** Paclitaxel formulation has low aqueous solubility and is accompanied by severe side effects of the solubilising excipients. In preclinical models, one shade of the micellar product, NK105 (PEG-block-poly(aspartate) functionalized with hydrophilic moieties + paclitaxel physically loaded) demonstrated AUC (tumour) nearly 25-fold higher than free PTX, enhanced antitumor activity, and then was used in clinical trials. Exploring Polymeric Micelles by Improving Delivery of Anticancer Agents" reported that PEG5K-CA8 micelles had the capability of solubilising paclitaxel at high load, and better antitumor effect than Taxol at mice [112].

**Doxorubicin (DOX):** On the same note, Doxorubicin micelle systems have been created. As an example, PEG2K-CA4 micelles loaded with DOX provided better accumulation and survival of the tumours in the lymphoma bearing mice. Sample: doxorubicin-conjugated PLA-PEG-Folate based polymeric micelle" (DARU 2014) - HSA hydrazone bond of DOX to copolymer, size: 4.65 ug/ml, IC50 in SKOV3 ovarian cancer cell: 4.65 ug/ml vs 13.51 ug/ml non-targeting. Drug-Polymer conjugated and paclitaxel- Physical encapsulation - Combination therapy - A synergistic combination therapy with paclitaxel and doxorubicin loaded micellar nanoparticles has been published [113].

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## FUTURE PERSPECTIVE

### Personalized Nanomedicine using Polymeric Micelles

Polymeric micelles can be tailored to the needs of each patient in the future. It implies that a doctor will be able to design a particular drug carrier depending on genetic makeup and disease type and the way the body reacts to the drug. This personal treatment contributes to enhancing the efficacy of drugs and minimizing the side effects [126].

### Hybrid Micelle Systems

The hybrid micelles are state-of-the-art systems that consist of a combination of polymers and lipids (fats) or inorganic substances, including metals or silica. These hybrid systems are able to enhance the strength of the micelles, the capacity that they can contain, and aid their capacity to arrive at the correct destination within the body [127].

### AI-based Formulation Design and 3D Printing

The new approaches that can assist scientists in developing improved micelle-based drug systems are 3D printing and artificial intelligence (AI). AI is capable of estimating the most effective materials and combinations of drugs, and a 3D printer can give control over the shape and size, and thus drug delivery is more accurate [128].

### Regulatory Developments of Nanocarrier Based Formulations

Polymeric micelles should be strictly tested and regulated by the government when they are to be used in humans. New regulatory developments will assist in ensuring that these nanocarriers are of quality, safe and effective enough before they are introduced into the market [129].

## CONCLUSION

Polymeric micelles have now been viewed as one of the most promising nanocarrier systems, which assist in enhancing solubility, stability and therapeutic activity of low water solubility drugs. They have special core-shell architecture, which is self-assembling of amphiphilic block copolymer with the help of which the hydrophobic drugs can be incorporated in the core of the micelles and the high stability and biocompatibility of the micelles is provided with the presence of a hydrophilic outer shell. This form increases solubility in aqueous solution and bioavailability besides stable and gradual introduction of the drug. In addition, they are small in nanoscale, which is a plus since it enables passive antigen-targeting by taking advantage of the Enhanced Permeability and Retention (EPR) effect and active antigen-targeting by site-specific delivery to minimize systemic cytotoxicity and increase treatment efficacy. The fact that they can recognize the triggers by the aid of stimuli responsive polymeric micelles in response to the environmental factors (pH, temperature, redox, etc.) enabling them to release their decoding to the environment only makes them even more precise in medicine and targeted therapy. Irrespective of such advantages, several issues exist, including low drug loading capacity, instability during dilution below the critical concentration mix (CMC), and large-scale production issues. To overcome these shortcomings, a complex system will be required that consists of advances in polymer chemistry and nanotechnology, formulation of pharmaceuticals and clinical pharmacology. Polymeric micelles, therefore, have potential to become a promising system to enhance the solubility and targeted therapy and further interdisciplinary studies would be needed to maximize the construct and scalability of such micelles and to realize successful clinical translations, which will result in even more effective and patient-friendly treatment systems.

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