Nanomicelle:Promising Nanostructured System for improved Pharmaceutical Performance

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Definitions

- Micelles are amphiphilic colloidal structures having a particle diameter ranging from 5 to 100 nm. Micelles constitute molecules having two regions of different affinities for water. The amphiphilic molecules forming micelles associate at certain temperatures and certain concentrations.
- The critical micelle concentration is the concentration at which aggregation begins and the micelles are formed.
- The critical micellar temperature is the temperature at which the micellar molecules aggregate and below which no micelles are formed and exist as monomers.

Types of Nanomicelles

- Due to the possession of both hydrophilic (polar) and hydrophobic (nonpolar) groups. The assembly of these molecules occurs due to the orientation of the groups to a suitable environment such as a solvent
- Normal nanomicelles: if the solvent is polar, the hydrophilic portion of molecules orients toward the outer surface to maximize contact with a polar solvent, while the hydrophobic parts are clustered in the core to minimize contact with a polar solvent.
- Reverse nanomicelles : the supramolecular assembly formed in the nonpolar solvent in which the hydrophobic portion orients to the surface to maximize the contact with the solvent and the hydrophilic portion orients to the core to escape the contact with a solvent.
- Non soluble drugs can be loaded into normal nanomicelles while soluble drugs can be loaded in reverse nanomicelles.

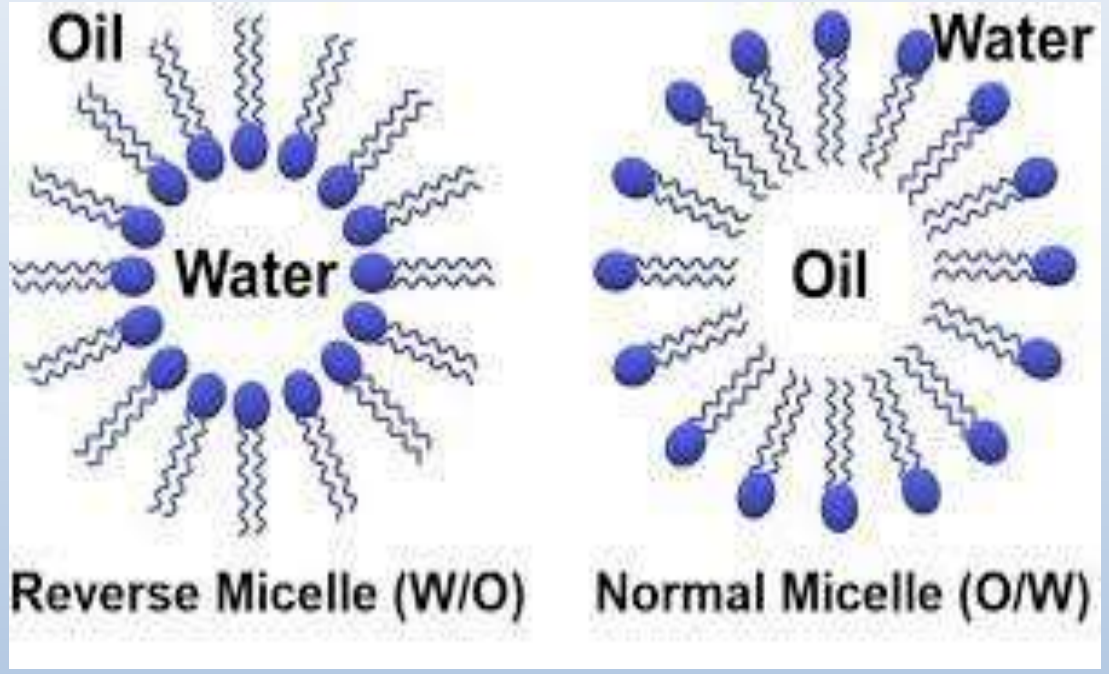


Figure 1.Stucture of reverse and normal micelle

Surfactant and Polymeric Nanomicelles

- **Surfactant micelle**
- Amphiphilic molecules have hydrophilic heads and hydrophobic tails. Surfactant tends to form a supramolecular assembly known also as a colloidal dispersion, which has a small diameter in the range from 5 to 100 nm.
- Head groups are classified into different groups such as charged (anionic or cationic), dipolar (zwitterionic), and noncharged (nonionic).

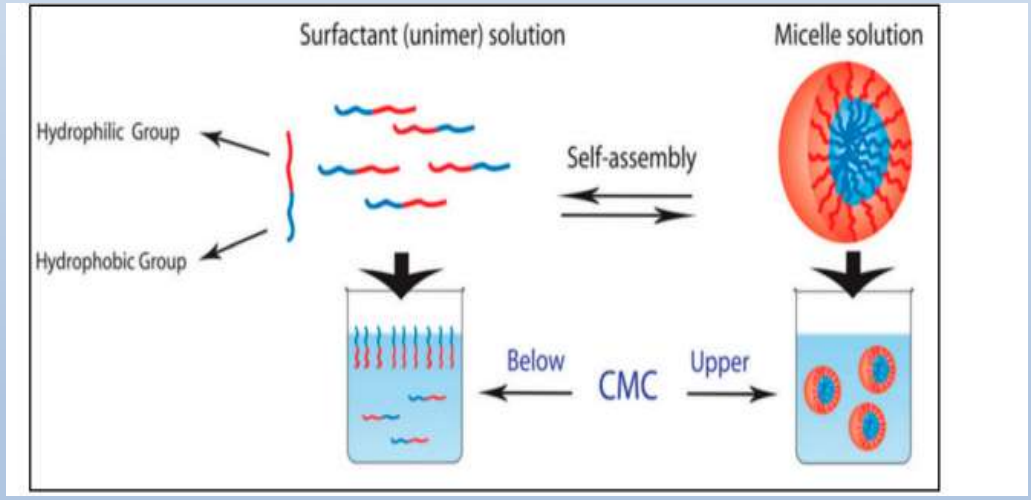


Figure 2. Schematic representation of unimer-micelle equilibrium in water.

Surfactant and Polymeric Nanomicelles

- Anionic surfactants include sodium dodecyl and cationic surfactants include dodecyl trimethyl ammonium bromide . Non-ionic surfactants are neutral such as n-dodecyl tetra (ethylene oxide) whereas zwitterionic surfactants carry both negative and positive charges such as dioctanoyl phosphatidyl choline.
- Low molecular weight surfactants have considerably higher CMC, which is 10−3 to 10−4 M.

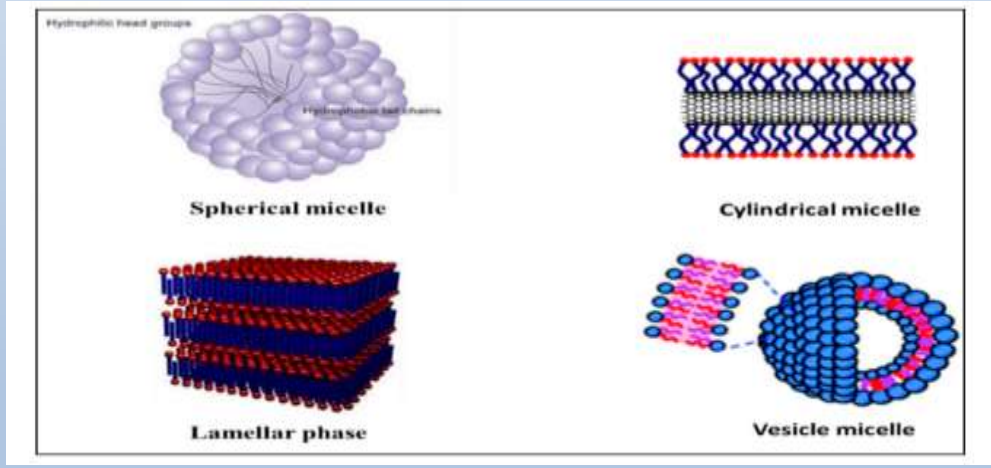


Figure 3. Illustration of some different self-assembled micelles structures.

Surfactant and Polymeric Nanomicelles

- **Polymeric nanomicelles**
- prepared from amphiphilic polymers; they have a size that ranges from 1 to 200 nm.
- This type of nanoparticle contains two functional portions, an “inner core” and an “outer shell”. The outer shell is responsible for controlling the pharmacokinetic properties in vivo, thus, it consists of a hydrophilic block of polyethylene glycol (PEG).
- modification of the outer shell can improve the properties of nanomicelles, for example, enhance the targeting.
- The inner hydrophobic core is responsible for drug entrapment, the stability of nanomicelles, and drug-release characteristics.

Surfactant and Polymeric Nanomicelles

- polymeric amphiphilic nanomicelle, has a CMC located in the range of 10−6 to 10−7 M.
- Micelles with lower CMC are preferable in DDSs because of
- their relatively higher stability
- insensitivity to the dilution, which enables their longer circulations in the bloodstream

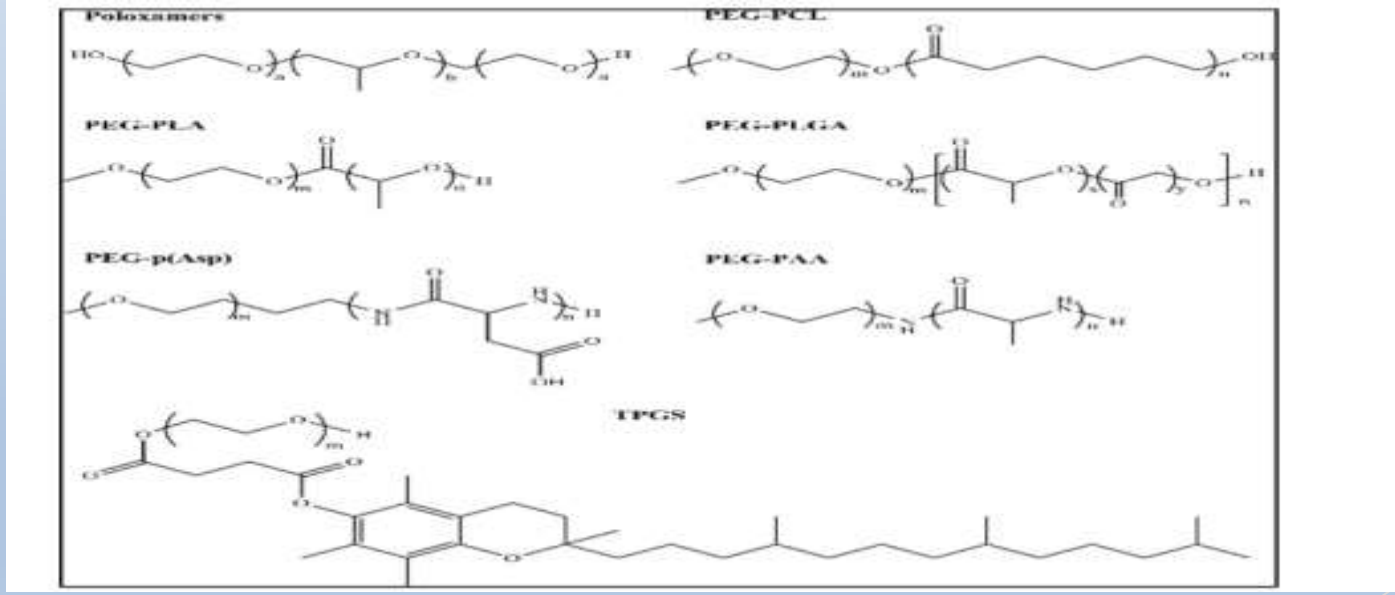


Figure 4. Structures of some commonly used polymers as micellar carrier

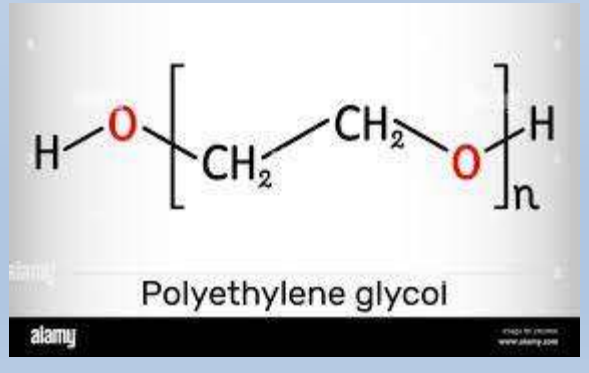
Polymeric nanomicelle

- **Hydrophilic Polymers in Block Copolymers**
- Polymeric micelles can be arranged as linear diblock (A-B), triblock (A-B-A), pentablock (A-A-B-A-A), and branched types.
- The modification of hydrophilic shells and physicochemical characteristics of hydrophilic micelles such as surface density and molecular weight have been closely linked to
- stability,
- circulation time,
- good biodistribution of micelles in vivo.

A block copolymer is defined as a polymer comprising molecules in which there is a linear arrangement of blocks, a block being defined as a portion of a polymer molecule in which the monomeric units have at least one constitutional or configurational feature absent from the adjacent portions.

Hydrophilic Polymers in Block Copolymers

- **Poly(ethylene glycol)**
- Low molecular weight PEG (20 kDa) has low toxicity. PEG has been the gold standard for nanomedicine polymers.
- Both the molecular weights and surface density of PEG are important factors when creating the shell. It was reported that PEG conformation significantly influences the circulation



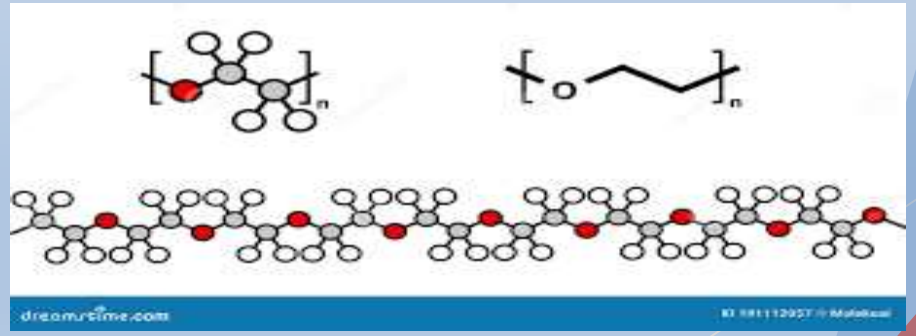


Figure 5. PEG structure

Hydrophobic Polymers in Block Copolymers

- The hydrophobic core consists of polyesters, polyethers, and polyamino acids.
- The major benefit of polyester over other polymers is that a wide range of polyesters was approved for biomedical usages
- poly(lactic acid) (PLA),
- poly(ε-caprolactone) (PCL),
- poly(propylene oxide) (PPO),
- poly(trimethylene carbonate) (PTMC),
- poly(lactic co-glycolic acid) (PLGA).
- These biodegradable hydrophobic polyester blocks are responsible for the formation of the hydrophobic core and they are usually conjugated with the hydrophilic block (mainly PEG), which forms an outer shell of micelles.

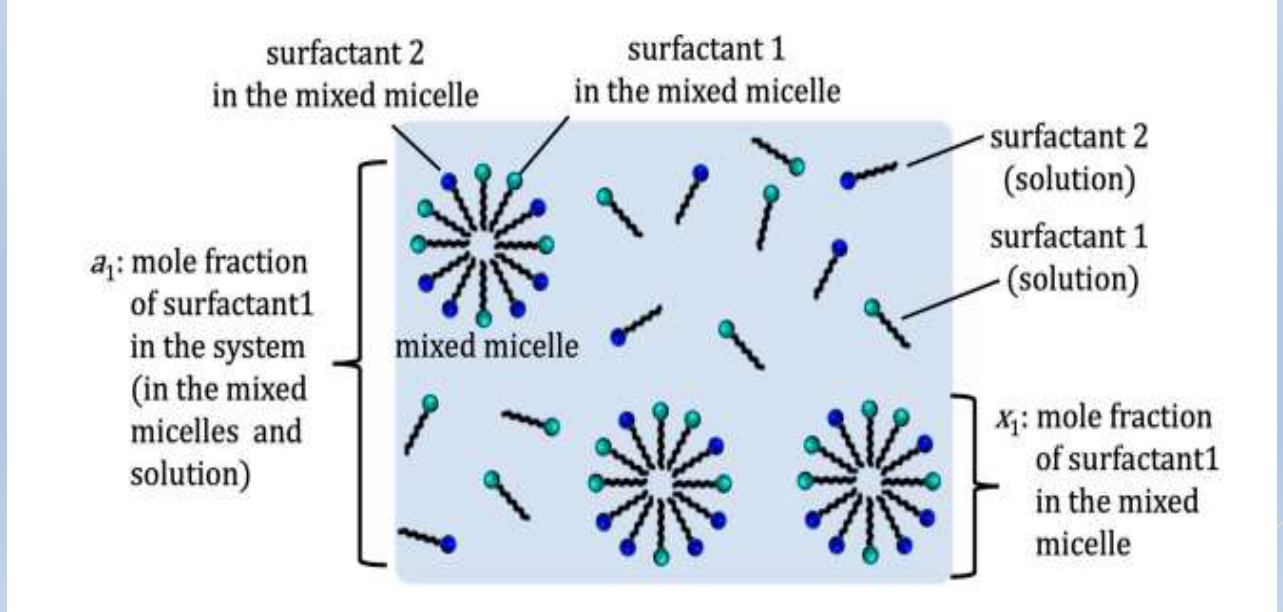
Effect of length of polymer chain

- When the core-forming segments are kept constant, increasing the length of the hydrophilic chains of the corona will lead to an increase in the value of the CMC.
- For example, when the PEG content exceeded 70 mol%, PEG-b-PLA micelles exhibited poor stability, given that the attractive forces between the relatively short PLA chains could not balance out the repulsive forces existing between the large PEG chains in the outer shell of the micelles.
- when the PEG content was below this threshold, the micelles showed proper stability with CMC values ranging from 0.07 to 0.09 mg/mL.

Mixed micelle

Mixed micelles are mixtures of amphiphile systems (including surfactants, polymers, and copolymers) that form micellar aggregates. They exhibit characteristics properties different from the individual amphiphile.

The combination of two or more block co-polymers in mixed micellar nanocarriers improves the qualities of single micelles in terms of carrier stability, precise size control, and easy surface modification with diverse components. This also enhances the effectiveness of drug encapsulation



Mixed Micelle

- When two or more surfactants are mixed, the critical micelle concentration (CMC) and solubilization capability are changed, and a careful selection of the combination promotes the micelle formation and enhances the solubilizing capability.
- $$\frac{1}{CMC\ theorotical} = \frac{X\ 1}{CMC\ 1} + \frac{X\ 2}{CMC\ 2} \quad \dots\dots\dots\dots\dots eq\ (1)$$
- where CMC_1 and CMC_2 represent the CMC values of polymer 1 and 2, respectively, and X_1 and X_2 denote the molar fractions of polymer 1 and 2, respectively. The molar fractions of polymer 1 and 2 were determined by dividing the number of moles of the constituent by the sum of the moles of the mixture's components

Preparation of Polymeric Micelles

- The preparation of nanomicelles can vary based on the properties of the polymer chain length. Two protocols can be used for nanomicelles preparation included
- (1) direct dissolution and
- (2) solvent casting.
- moderately Block copolymer usually is self-assembled in nanomicelles through direct dissolution also known as a simple equilibrium method. In this method, the simultaneous dissolution of drug and copolymer with the appropriate ratio occurs in the aqueous solution which is then heated to initiate the formation of nanomicelles. During heating, the core of the structure undergoes dehydration that leads to the formation of nanomicelles.

Solvent casting category

- (1) dialysis,
- (2) oil in water (o/w) emulsion
- (3) solution casting.
- (1) Drug and copolymer are dissolved in proper organic solvents miscible with water with a high boiling point. A solution of copolymer and drug is put into a dialysis bag and dialyzed against water for more than 12 hours. During the dialysis, the organic solvent is slowly evaporated which initiates the formation of nanomicelles loaded with the drug.
- it has limitations such as drug loss due to low encapsulation efficiency.

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Preparation of Nanomicelle

- (2) o/w emulsion which includes physical entrapment of components. The encapsulation procedure is based on the dissolution of a drug and polymer in a non-miscible organic solvent with a small volume of water. The removal of the solvent via evaporation induces the physical entrapment of the drug in the core of the formed nanomicelles .
- (3) solution casting, which includes organic and aqueous solvents. Drug and polymers are dissolved in an organic solvent to obtain a transparent solution. Drug-loaded nanomicelles in the form of a thin film can be obtained after the removal of organic solvents under a high vacuum then hydration of the thin film by the addition of water .

Biodistribution

- The concept behind utilizing a micellar carrier is to enhance the solubility and prolong the blood circulation time of a drug for great targetability and therapeutic benefits.
- Long circulation time depends upon biodistribution and metabolism. The in vivo biodistribution would influence the physicochemical properties of the micelles:
- size and shape,
- core properties,
- surface modifications,
- surface charge
- targeting ligand functionalization.
- Small particle size display broad distributions as they can simply cross tight endothelial junctions to enter into extravascular extracellular space (EES).

Improvement of drug solubility

- Class II therapeutic agents are characterized by poor aqueous solubility and high permeability.
- For these compounds to be absorbed through the GI mucosa and reach the blood circulation at concentrations above the therapeutic threshold, they must first be fully dissolved.
- Nanomicelles being an amphiphilic molecule, the hydrophobic drugs bind to the hydrophobic core of the nanomicelle and thus, this result into production of clear aqueous solution, increasing the solubility of the lipophilic drug by several folds.

Figure 7. Visual appearance of the nanomicelles. (**A**) Empty polymeric nanomicelles (PNM); (**B**) Empty mixed nanomicelles (MNM); (**C**) Silymarin (SLM)-loaded PNM; (**D**) SLM-loaded MNM; (**E**) SLM aqueous suspension.

Nanomicelles Delivering Anticancer Drugs

- Polymeric micelles represent a nanoscale medication distribution method and have been advanced as a crucial tool for cancer treatment.
- Biodegradable polymeric micelles are moreover ideal for targeted and controlled drug delivery of hydrophobic anti-cancer drugs which include paclitaxel (PTX) and doxorubicin (DOX). These nanocarriers
- (i) enhance water solubility of the anti-cancer drugs;
- (ii) can prolong drug circulation time;

Nanomicelles Delivering Anticancer Drugs

(iii) can passively target tumor tissues via the EPR effect.

(iv) improve bioavailability; and

(v) possess great biocompatibility and are also degradable into non-toxic products in vivo which can be absorbed and excreted further from the human body.

Targeting **Nanomicelles**

- **Target moieties can be paired to generate dynamic targeting nanomicelles, for maximizing distribution and minimizing side effects.**
- **These active nanomicelles can target cells** based on
- (1) relationships with particular targets
- (2) conjugation with locally functioning signal protein
- target agents such as antibody, peptides , and aptamers.

Targeting Nanomicelles

- Immuno-micelles, which can be prepared by coupling monoclonal antibody molecules to p-nitrophenyl carbonyl groups on the water-exposed termini of the micelle corona- forming blocks, demonstrate high binding specificity and target ability.
- Recently, Sarkar et al. developed stearic g-polyethyleneimine acid amphiphilic nanomicelles functionalized with folic acid-based carbon dots (CDs) for targeted anticancer drug (DOX) delivery and concurrent bioimaging for triple negative breast cancer (TNBC). The fluorescence property offered by folic acid derived CD allowed CD to act as a promising bioimaging tool for TNBC.

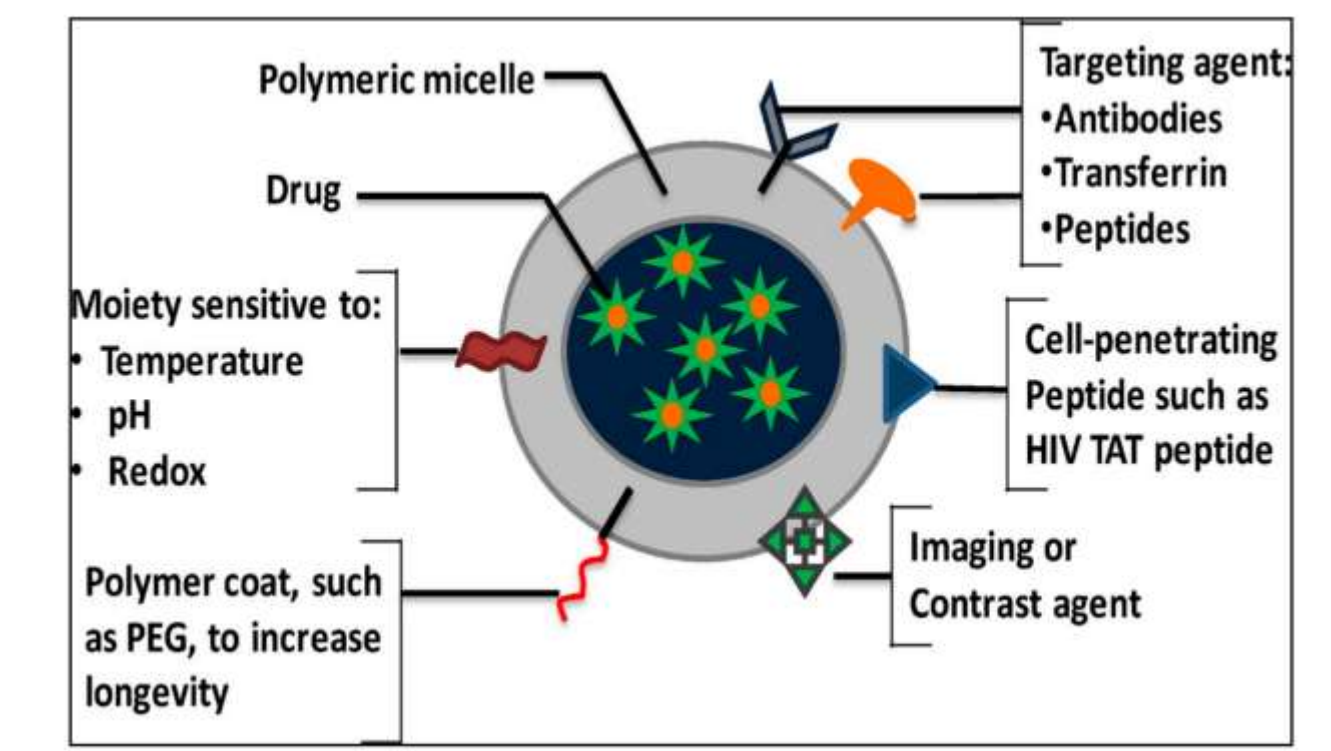

Figure 5. Schematic illustration of the polymeric nanomicelles targeting drug delivery

Stimuli-Responsive Nanomicelles

- **pH-Sensitive**
- Targeted and stimuli-responsive nanomicelles for drug delivery have been employing changing pH values of the human body.
- First through nanomicelles comprising ionizable groups, which experience solubility changes with environmental pH alterations.
- Second by the utilization of nanomicelles with acid-sensitive bonds, whose hydrolysis leads to the discharge of the drug from the nanomicelles core.

Temperature Sensitive

- Bioactive distribution to the human organism is effectively carried out by temperature-modulated polymeric systems.
- This is accomplished with the help of nonlinear, sharp, and irregular modification of the characteristics of delivery system constituents as a reaction to temperature rise and can frequently be observed in liposomes, polymer micelles, and nanoparticles because of low critical solution temperature. CMC may be significantly influenced by temperature fluctuations.
- N-isopropyl acrylamide, known as the most frequently utilized polymer, can transform into a hydrophobic polymer from a hydrophilic polymer at approximately 32 ◦C.
- A dual-responsive biocompatible nanocarrier with appropriate paclitaxel drug loading and controlled release efficiency.
- The size of the prepared nanocarrier and the encapsulation efficiency are ~100–230 nm and 98%, respectively.
- It was found that nanocarrier formed aggregates under slightly acidic pH (pH 6.9).
- Rapid release of PTX at high temperature (37 ◦C) and low pH (4, 6.8, 7.2) was compared to a lower temperature (20 ◦C) and pH (4). These findings indicated that nanocarriers would accumulate and release the drug selectively in cancer cell tissues to achieve targeted delivery of anticancer drugs

Ultrasound Responsive

- The ability of ultrasound to produce a frequency of about 20 kHz is proposed to use for drug uptake.
- Increasing drug delivery under ultrasound because of improved tissue penetration, correlation the features of cell membrane perturbation, and drug release .
- For example, DOX release and its intracellular uptake from such popular ultrasound-responsive nanomicelles as pluronic micelles were studied by Marin et al. The study showed increased DOX release under high-frequency ultrasound.

Conclusions and Future Perspective Developments

- In this regard, designing various nanoscale carrier systems allows avoiding static and dynamic barriers in the human body.
- Among them, the application of nanomicelles for drug delivery purposes is trending upward in recent years because of their prominent and advantageous intrinsic properties.
- Nano micelles have high drug loading capacity and sustainable drug release, excellent water solubility and unique colloidal stability along with prominent low toxicity.
- Such properties allow us to use them to deliver therapeutics to anterior segment.
- They could also enable the application of nanomicelles in the prevention of drug resistance and reducing the toxicity of anticancer therapeutics.
- The possibility to vary the size of such nanocarriers by choosing surfactant or polymer with suitable length increases their EPR effect, which is crucially important in anticancer therapy.

Thank you for listening