Polymeric Micelles: A Novel Approach towards Nano-Drug Delivery System

Rutuja Hemant Vinchurkar and Ashwin Bhanudas Kuchekar*

School of Pharmacy, Dr. Vishwanath Karad MIT World Peace University, Pune- 411 038, India.

Nano delivery systems, polymeric micelles represent one of the most promising delivery platforms for therapeutic compounds. It has shown that a poorly soluble molecule which has high potency and remarkable toxicity can be encapsulated with the polymeric micelle. There are various poorly soluble drugs used in micellar preparations, mostly for their anti-cancer activity. Drugs in the inner core protect the drug from degradation and allow drug accumulation in the tumour site in the case of cancer treatment. Block copolymers are chosen based on the physicochemical characteristics of medicinal drugs. The amphiphilic block copolymer structure has both lipophilic and hydrophilic blocks, which enclose tiny hydrophobic molecules. It is a targeted drug delivery method because of its high effectiveness for drug retention in tissue, prevention of enzymes from degradation, and improvement of the cellular absorption mechanism. In an experimental environment, variations in temperature and solvent polarity stimulate copolymer micelle self-assembly. This is a thermodynamically guided procedure in which self-assembly happens by converting polymeric micelles. These aggregates go from a non-equilibrium to a thermodynamically equilibrium state, and they stay stable for a long time. The balance of thermodynamic and kinetic forces is critical in micelles self-assembly because the kinetic process predicts assembly behaviour and hierarchical structure. The purpose of this special issue is to provide an updated overview of micelles, a number of polymers and drugs commonly used in micellar preparation and their application.

Keywords: Anti-Cancer Drugs; Block Polymers; Nano Delivery; Polymeric Micelles.

The assembly of polymeric micelles in an aqueous medium is caused by an amphiphilic block copolymer with a core-shell structure with a size range of 10 to 100nm. It has gained much attention for research and is one of the most studied systems[1, 2] A micelle's core can be used to encapsulated drugs that have a low water solubility, thus improving drug solubility, stability, and pharmacokinetic profile as well as stabilizing compounds that are degradable. Targeted drug delivery systems have great efficiency in retaining drugs in the tissues, conserving enzymes, and enhancing uptake mechanisms at the cellular level[3,4]. Additionally, the EPR effect is used to deliver targeted and localized treatments, which are also advantageous in terms of drug safety profiles[5]. A variety of morphologies of subunits like rods, vesicles, and hierarchical morphology result in variations in assembly of polymeric micelles at higher levels as well as kinetic trapping of

copolymer micelles in thermodynamic transitions. The purpose of this article is to provide a brief overview of preparation and introduction to micelle for self-assembly drug delivery systems.

Strategies of Drug Targeting[76]

Passive Targeting

Drug delivery approaches focused at systemic circulation are referred to as passive delivery systems. Because of the ability of certain colloid to be taken up by Reticulo Endothelial Systems (RES), notably in the liver and spleen, they can be used as a passive hepatic drug target (Fig. 1).

Inverse Targeting

The approach is known as inverse targeting because it seeks to circumvent passive uptake of colloidal carrier by RES. The normal function of the RES is suppressed by pre-injecting massive amounts of blank colloidal carriers or macromolecules like dextran sulphate to accomplish inverse targeting. This strategy results in RES saturation and the inhibition of defence mechanisms. This method of targeting drug(s) to non-RES organs is quite effective.

Active targeting

Instead of spontaneous RES absorption, a drug-carrying carrier system is supplied to a particular location by surface modification in this manner (Fig. 1). Surface modification techniques include coating the surface with a bioadhesive, non-ionic surfactant, specific cell or tissue antibodies (monoclonal antibodies), or albumin protein. Active targeting can be modified on multiple levels, as follows:

1. First order targeting (organ compartmentalization) - The drug carrier system is only distributed to the capillary bed of a pre-determined target site, organ, or tissue.

2. Second order targeting (cellular targeting) - The delivery of a medicine to a specific cell type, such as tumour cells, with pinpoint accuracy (& not to the normal cells).

3. Third order targeting (intercellular organelles targeting) - Drug delivery to the intracellular organelles of the target cells.

Block copolymers

Block copolymers are used to encapsulate therapeutic substances into micelles through several interactions which help to shield the medication from the outside surroundings while also assisting in the improvement of the pharmacokinetic profile [6]. For smaller molecules such as nucleic acids, proteins and molecular substances, block copolymers are mainly used[7]. Depending upon the physicochemical properties of therapeutic compounds, the desired block polymers are used. The lipophilic blocks and hydrophilic blocks are present in the amphiphilic block copolymer structure which encapsulates small hydrophobic molecules[8-10]. The core and corona of the polymeric micelles form in such a way that the therapeutic medication is lacking during spontaneous self-assembly of micelles during self-assembly of amphiphilic block copolymers. The small drugs are water-insoluble conjugates with core-forming blocks by the chemical interaction of block copolymers, which then self-assembles to form a polymeric micelle having the drug in the core part. Charged blocks are required for electrostatic interactions in biopolymers for encapsulation in polymeric micelles[11, 12]. Amphiphilic block copolymers have hydrophilic shells and a hydrophobic core that, when coming into contact with aqueous media, form micelles by self-assembly. This shell protects the drug in the core and avoids aggregation and precipitation of micelles. In the preparation of polymeric micelles, (P)-hydrophilic and (Q)-hydrophobic blocks are necessary, which are most commonly used to make (P-Q) diblock and (P-Q-P) triblock copolymers. The Q-block, having a hydrophobic character, has been used recently for encapsulation of drugs which have less water solubility as it shows great interaction with poorly soluble drugs[13.] Kozlov et al. demonstrated that block copolymers show complex interactions as they have both hydrophilic and hydrophobic blocks present in them, and they are interdependent as they contribute to the microenvironment in the formation of micelles containing less soluble drugs[14]. The Luxenhofer group showed that in the case of polymeric micelles with high drug loading capacity, hydrophilic blocks play a key role in polymer and therapeutic drug interactions[15]. Each copolymer block serves a critical function in micelle production. The total quantity of loaded drug into the polymeric micelles can influence the external appearance of the micelle, the size of the micelle, and stability in aqueous media. This complex interdependency and length of block structure give a unique capacity for

solubilization of therapeutic drugs. However, it is more challenging to understand the interactions and the design of block copolymers[13].

Methods of preparation

Micelles are prepared with different methods, which are mainly dependent upon the physicochemical properties of the block copolymer[57]. An appropriate method is selected as per the solubility of a block copolymer of the micelle in the aqueous solution. The following are the methods of preparation of polymeric micelles[71:]
• Direct Dissolution
• Precipitation/Evaporation
• Oil in Water Emulsion
• Thin Film Hydration
• Ultrasonication
• Dialysis
• Freeze Drying

Direct Dissolution

It is the most commonly used method for micelle formation. Block copolymers with high aqueous solubility are used. In an aqueous medium, the drug is dissolved along with the polymer. It requires stirring and heating for drug loading in the micelle. Dehydration of core-forming blocks initiates the micelle formation. This technique involves the preparation of micelles using a drug and a polymer, mostly poloxamer. Separately, they are dissolved in an aqueous solution. Micelles are formed when both solutions are combined together with an acceptable drug-polymer ratio.Water-soluble copolymers have the advantage of easy drug and copolymer dispersion in water or a buffer. Low encapsulation efficiency is a disadvantage.

Precipitation/evaporation

In this method, a suitable volatile solvent is selected to dissolve both the therapeutic substance and polymer. After dissolution, a slow aqueous phase is incorporated into the mixture. It is then stirred continuously in order to remove the organic media. Withdrawal of the organic phase initiates the formation of the micelles.Precipitation creates pure and homogeneous material, which is its main advantage.It has several disadvantages, including the need for separation of the product after precipitating, and producing a large volume of salt-containing solutions.In addition, if the precipitation is done discontinuously, it is difficult to maintain a consistent product quality.

Oil in water emulsion

Lipophilic drug is solubilized in chloroform, dichloromethane or ethyl acetate solvents which are water-immiscible. Distilled water is added to form an emulsion which is oil in water type. The organic solvent is slowly evaporated to obtained drug-loaded micelles (Fig. 3). An advantage of polymeric micelles is their ease of preparation and uniform size. The difficulty in removing free drugs and organic solvents is a significant drawback.

Thin Film Hydration

Lipophilic drug substances in an organic phase, the copolymer is dissolved. The solvent is evaporated using a rotary evaporator which results in the formation of dry film. Aqueous media is added to the film and it is stirred and sonicated as a result of which drug-loaded micelles are formed (Fig 4).The easiest technique for making liposomes is lipid film hydration, which does not need the use of any expensive or difficult equipment and does not need the use of high pressure or temperature. Drawback is the efficiency of encapsulation is poor for micellar preparation.

Ultrasonication

Hydrophilic drugs with amphiphilic polymers are solubilized in aqueous media whereas the organic phase in the hydrophobic rotating evaporator is used to extract the medication. The finished product solution is sonicated to get drug-loaded micelles (Fig 5).Studies such as those conducted by Nakabayashi et al. suggest that nanoemulsions formed by ultrasonication are stable and transparent without surfactant.However, disadvantage of this method is that it can only prepare small batches of nanoemulsions[70.]

Dialysis

This method is used when an amphiphilic copolymer has low water solubility. Lipophilic drugs with copolymers are added and mixed in the same organic solvent media as dimethyl sulfoxide (DMSO), N, N-Dimethylformamide (DMF), acetonitrile (ACN), tetrahydrofuran (THF), acetone or dimethylacetamide are used for solubilization purposes. Aqueous media is added to the mixture which stimulates the micelle formation, then it is dialyzed in opposition to water for some period to remove organic solvents (Fig 6).The dialysis method is suitable for hydrophobic drugs and

copolymers soluble in organic solvents. Major disadvantage is that it is difficult to remove organic solvents and free drugs from the block copolymer in organic solvents.

Freeze drying

Copolymer, along with therapeutic drugs, is dissolved in a mixture of aqueous solvents with organic solvents like water and Ter-butanol and subjected to lyophilization. The obtained freeze-dried mixture is reconstituted by adding an injectable vehicle that spontaneously forms drug-loaded micelles. Drugs and copolymers are dissolved in a mixture of water and organic solvent, which is advantageous. Risk of residual organic solvents is a disadvantage.

Self-assembly of copolymers

Self-assembly of copolymer micelles is activated by changes in temperature and polarity of solvent in an experimental condition. It is a thermodynamically steered process in which self-assembly occurs by converting from a condition of non-equilibrium polymeric micelles to a state of thermodynamic equilibrium, and these aggregates are steady for a prolonged period (Fig 7). The force that propels the copolymer micelles assembly may be divided into three categories. oleophobic interaction, electrostatic interaction and molecular forces.

Solvophobic Interactions

Most commonly, solvophobic interaction is used when non-ionic copolymers are used in micelle preparation. This interaction is increased by a change in solvent, adding a solvophobic agent or by changing the temperature[58]. This type of self-assembly can be categorised into two manners, i.e., theoretical simulation-driven assembly, core-core coupling assembly, corona-corona coupling assembly, and electrostatic interactions.

Core-core coupling assembly

It is most appropriate for polymeric micelles with rod coils as the core and corona forming chain are anisotropically distributed and also parallelly stacked and this influences both rod and coil chain distribution and these loosely located corona forming chains at binding sites can be specified regions.

Corona-corona coupling assembly

Micelles are linked together via corona binding. This attraction reduces the solubility of chains of corona forming units. Compartmentalized corona micelles as well as Janus micelles are the perfect candidates for this.
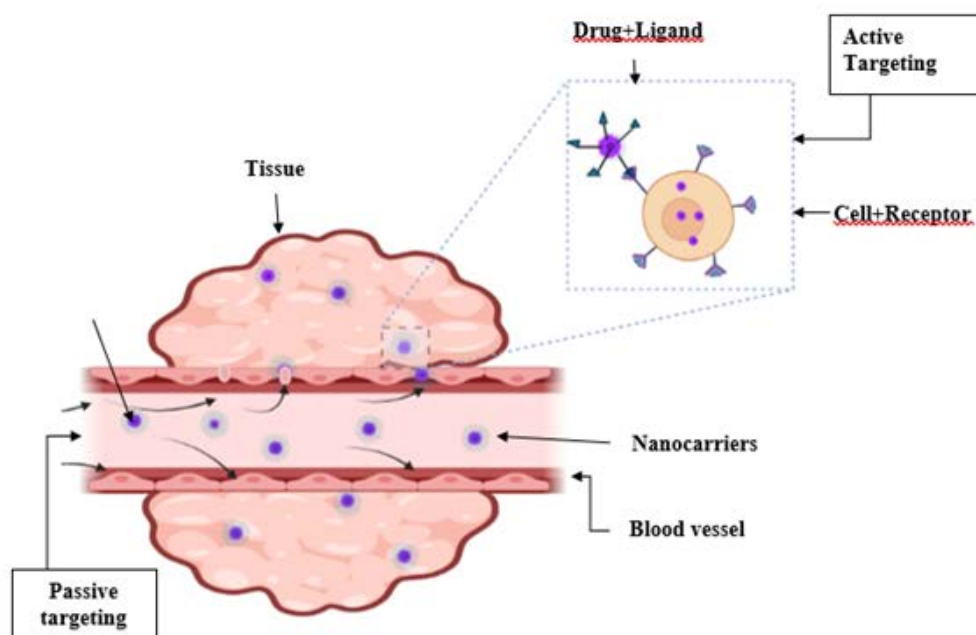

Fig. 1. Active targeting and Passive targeting

Theoretical simulation-driven assembly

It provides information about the micelle and its every effect, like attractive and repulsive interactions between the core and the corona. Simulation helps us to understand the polymer chain arrangement. Theoretical simulation gives an approximation of energy variation before and after the assembly of aggregates on a microscopic scale[59].

Electrostatic interactions

Electrostatic forces are one of the primary forces during the formation of polyelectrolyte-based micelles and are one of the most widely researched micelle formation techniques. Various mechanisms that have been observed are as follows:

pH-induced copolymeric assembly

It is the most simplistic, yet efficient method for the fabrication of desired nanomaterials. Zhou and colleagues described a pH-induced self-assembling co-polymer vesicle with a hydrophobic core of hyperbranched copolymer poly (3-ethyl-3-oxetanemethanol)-star-PEO (HBPO-star-PEO), an electroneutral layer of PEO, and a positively charged HBPO-star-poly (2-(dimethylamino) ethyl methacrylate (HBPO with an increasing pH from 1M NaOH to 3M NaOH, the copolymer changed its conformation from isotropic to anisotropic due to the formation of PDMAEMA patches that served as binding sites for vesicles to aggregate. The anisotropic micelles formed by pH-induced self-assembly can be further researched and can serve as a direction for future progress[60].

Counter ions triggered assembly

The addition of counter ions in polyelectrolyte-based copolymeric vesicles triggers self-assembly effectively. They can be used for preparing micelles with biological properties, e.g., Chen and his group prepared micelles using a negatively charged plasmid as a base. The negative charge on the plasmid was used as a core in which a saturated deionized CO_2 water to PEG-block-poly (4-vinylpyridine) (PEG-b-P4VP) methanol solution was added. The self-assembly progressed through two stages, the first being the one in which DNA wrapped itself around the polymer, leading to the formation of a monodispersed form of 'beads on a string'. In the second stage, multiple monomers
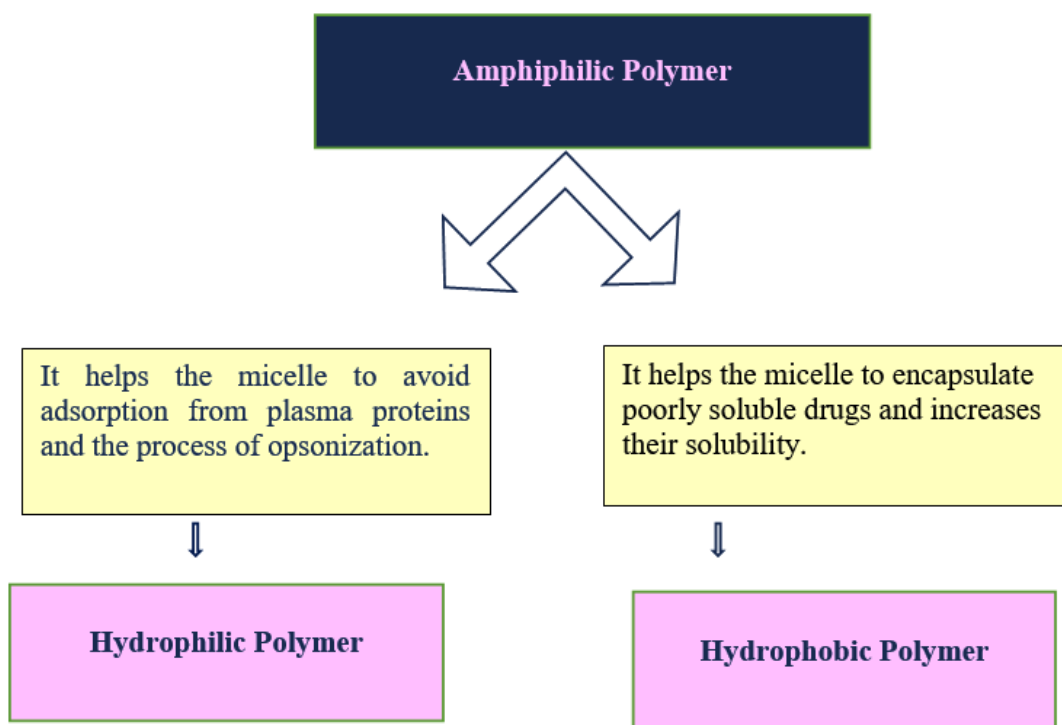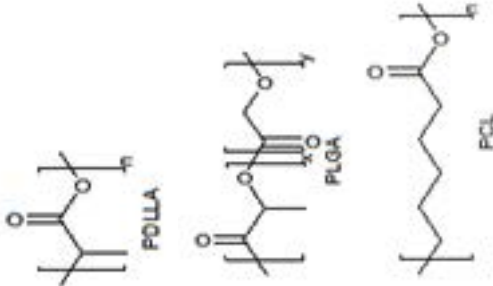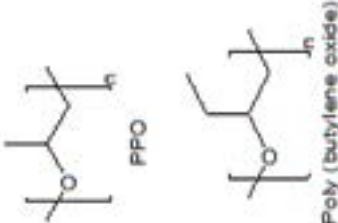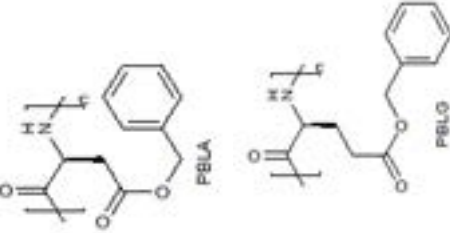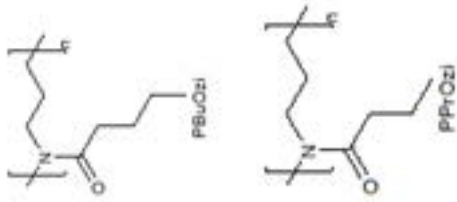

Fig. 2. Property of Amphiphilic Polymer

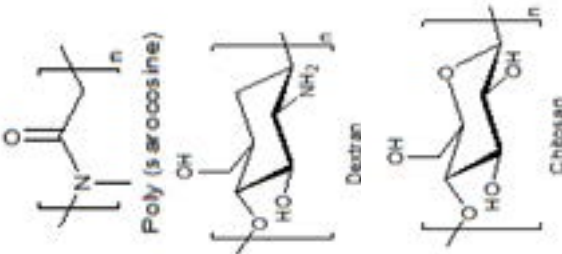**Table 1.** Hydrophobic polymers used for creating amphiphilic block copolymer

Name of polymer	Structure	Properties	Synthesis	Advantages	References
Polyesters		Clinically approved drugClinically biodegradable PLGA is used as a surgical suture.	Ring-opening polymerization (ROP) of cyclic monomers	Biodegradable, High loading capacity	[17-20]
Polyethers		PPO is a part of Triblock copolymer (poloxamers– PEO-PPO-PEO)	Anionic ROP of alkylene oxides	Block copolymers are commercially available e.g., poloxamers	[21-23]

|					
Poly (amino acid) s		Biodegradable. Hydrophobicity is increased because of the benzyl pendant group.	Polymerization of á-amino acid	High loading capacity, [poly(glutamic acid)] approved clinically, with cargo greater affinity	[24-26]
Poly(2-oxazine)s		Poorly soluble drugs can be highly loaded e.g, curcumin	LCRP (2-oxazine monomer)	The ultra-high capacity of drug loading.	[27-30]

Poly(2-oxazoline)s

The flexibility of the polymeric structure.

LCRP
(2-oxazoline monomers)

Ultra-high capacity for loading of poorly soluble drugs e.g., paclitaxel

[31-33]

PDLLA- poly(D,L-lactide), PLGA- poly(D,L-lactide-co-glycolide), PCL- poly(-caprolactone), PPO- poly(propylene oxide), PBLA- poly(â-benzyl-l-aspartate), PBLG- poly(â-benzyl-á-l-glutamate), PBuOzi- poly(2-n-butyl-2-oxazine), PPrOzi- poly(2-n-propyl-oxazine), PBuOx- poly(2-n-butyl-2-oxazoline), PiPrOx- poly(2-isopropyl-2-oxazoline), PPrO- poly(2-n-propyl-2-oxazoline)

Table 2. Hydrophilic polymers used for creating amphiphilic copolymers

Name of polymer	Structure	Properties	Synthesis	Advantages	References
PEG		It has stealth property, shell-forming block copolymer	Living anionic ROP of ethylene oxide	PEG has a hydrophilic shell which avoids the opsonization process. Used in Genexol® PM (clinically approved nanoformulation)	[34-35]
Poly(sarcosine)		Used as PEG replacement	á-aminoacid-N-carboxyanhydrides living polymerization	Biodegradability.	[36-38]
Polysaccharides		Component of block and graft copolymers. Molecular weights are varying in numbers.	Enzymatic synthesis	Biodegradable. FERAHEME® (Injectable) clinically approved product.	[39-42]

[43]
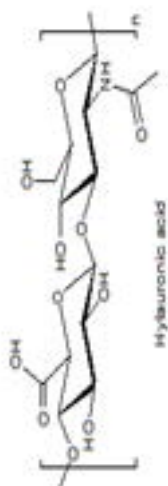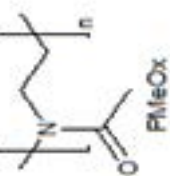
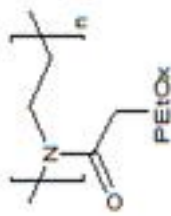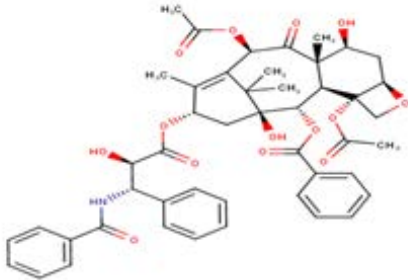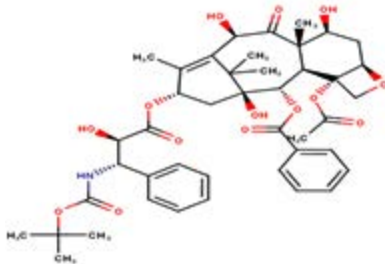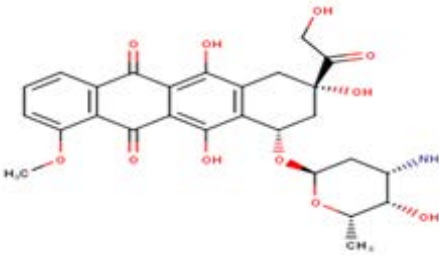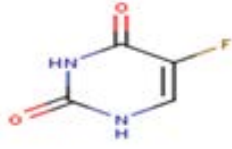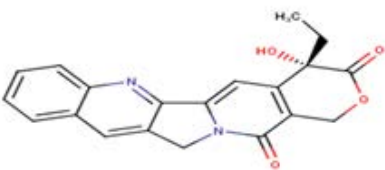|			
Hylauronic acid	Used as PEG replacement.		
Poly(2-oxazoline)s		Living cationic ROP (LCRP0 of 2- oxazoline monomers.	PMeO is more hydrophilic as compared to PEG.
PMeOx			
PEtOx			
Miscellaneous	PVP has potential immunogenicity, Nonbiodegradable	By fragmentation chain transfer in reversible addition radical polymerization of the atom.	PVP is used as an . excipient in formulation designs
PVP			
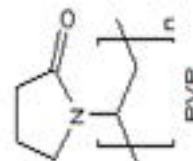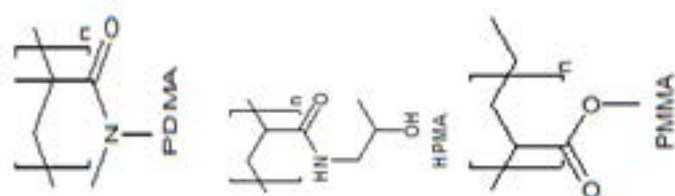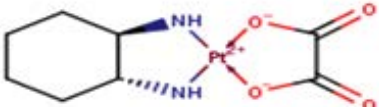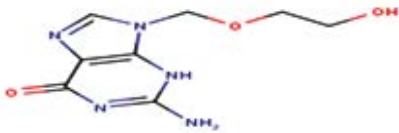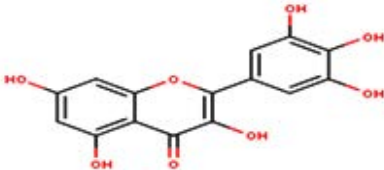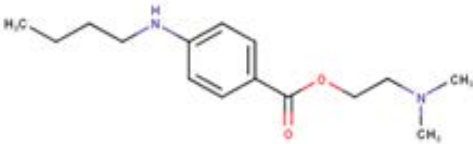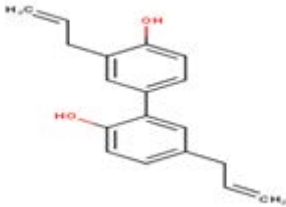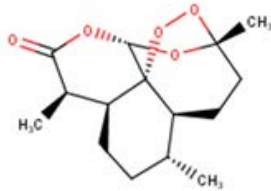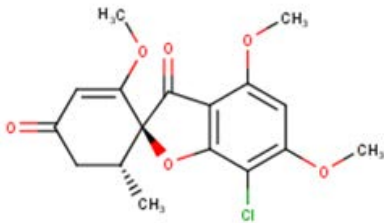
PEG- polyethyleneglycol, mPEG- methoxy-PEG, OH-PEG- hydroxyl-PEG, PMeOx- poly(2-methyl-2-oxazoline), PEtOx- poly(2-ethyl-2-oxazoline), PVP-
poly(vinylpyrrolidone), PDMA- poly(N,N-dimethylacrylamide), HPMA- poly[N-(2-hydroxypropyl)methacrylamide], PMMA- poly(methyl methacrylate)

Table 3. Poorly soluble drugs used in preparation of micelle formulation

Properties	Drug	Structure	References
Anti-cancer	Paclitaxel		[44]
	Docetaxel		[45]
	Doxorubicin		[46,47]
	5-Fluorouracil		[48]
	Camptothecin		[49]
	Cisplatin		[50]

	Oxaliplatin	[51]
Ophthalmic	Acyclovir	[52]
	Myricetin	[53]
Local Anesthetic	Tetracaine	[54]
Neuroprotective	Honokiol	[55]
Anti-Malarial	Artemisinin	[56]
Anti-fungal	Griseofulvin	[57]

led to the formation of complex polymeric nano-rings. They added spheres in later research containing carboxylate groups on their surface. In this solution, the rings could interact with spheres that resemble 'host-guest interactions on a nano-scale[61].

Co-assembly by opposite charges

Liu and colleagues reported the co-assembly of copolymer nanofibers bearing carboxyl groups (CNFs) from poly (2-cinnamoyloxyethylmethacrylate)-block-poly (tert-butyl acrylate) (PCEMA-b-PtBA) and nano-cylinders bearing amino groups (ANCs) from poly (tert-butyl acrylate)-block-poly (2- A solution of ANC was added to the CNF, and when the mass ratio of ANC: CNF reached 5:1, wrapping of ANC took place around the CNF. This process is induced by opposite charges of carboxyl and amino groups. It results in the formation of a multi-layered composite cylinder with a PCEMA core, inner-shell PDMAEMA, intermediate-shell PCEMA, and outer-shell PtBA. These cylinders can be utilised

as medication delivery devices or even as a contrast agent for imaging systems[62].

Molecular force-directed interactions

Molecular forces are called short-range forces, which include crystallinity, covalent bonds, and host-guest interactions. When the copolymer has a reactive functional group, the molecular forces between these groups and the crystallisation of the chain can lead to the aggregation of copolymer micelles. Crystallization driven self-assembly (CDSA) is the most broadly studied self-assembly in which the core termini possess crystalline faces which stand active for further growth and is composed of crystallised PFS chains. The initial fibre-like micelles are used to prepare micelle seeds, which the termini of get epitaxially crystallised by the unimers, which leads to the formation of uniformly structured fibre-like micelles[63].

Gene therapy

Purpose of Gene therapy has demonstrated to have a lot of promise in treating human diseases
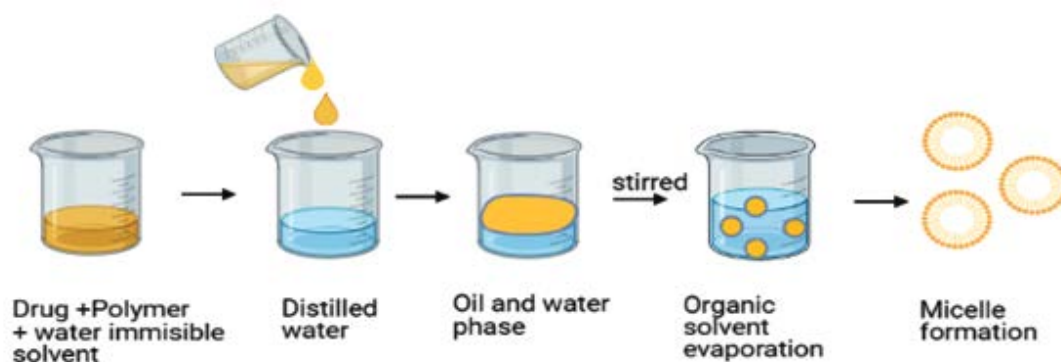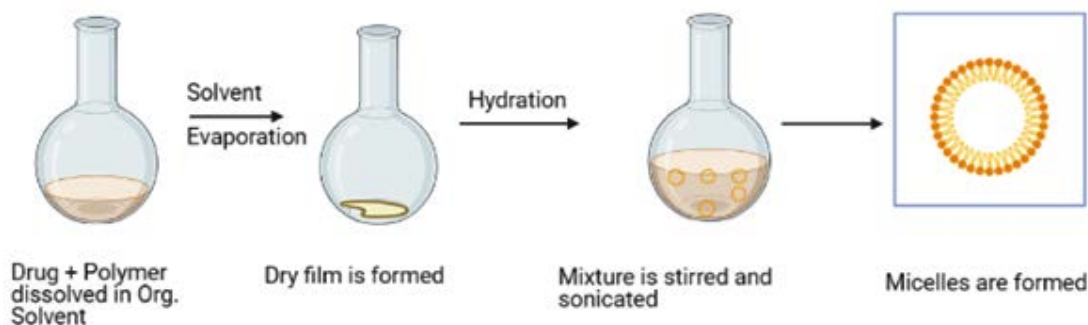

Fig. 3. Oil in water emulsion technique

Fig. 4. Thin film hydration technique

caused by gene mutations, such as cancer. When polymer microparticles are compared to polyplexes (complexes of polymer and DNA), polyplexes, in most cases, are more stable. The tiny size of these particles makes them ideal for delivering nucleic acids. Encapsulation, therefore, protects genes much better against serum breakdown than chemical modification. The absence of tumor-selective, safe, efficacious, and non-toxic gene transfer vectors is the fundamental impediment to the actual implementation of cancer gene therapy[74.] An ideal gene therapy vector should be inert and able to be used as a payload in the cell at the target spot, resulting in effective transfection. The vector should have a buffering capacity for improved transfection, a small enough size and stability to avoid aggregation in the blood, the ability to efficiently target cells and release the DNA intracellularly, and the ability to import the DNA into the nucleus. As non-viral gene carriers, cationic polymers provide the possibility to create carrier systems with unique properties that can be fitted to any system. Micelles can provide the capacity to load genes/gene-drugs into distinct micelle compartments based on the coreshell structure of polymeric micelle systems[75.]

Classification of polymeric micelles

Different kinds of polymeric micelles exist depending upon their amphiphilic character and the solvent parameters such as type of solvent, concentration of polymer, ionic strength, pH etc. Different micelles can be obtained (Fig 8.) When in the amphiphilic block copolymer, the length is longer for the hydrophilic block and the length is shorter for the hydrophobic block, which gives spherical micelles. In normal micelles, the hydrophobic tail is at the core part and the outer head part has a lipophobic character. The hydrophobic tail flocks to the inside for minimal interaction with aqueous fluids, while the hydrophilic head stays on the outside for maximum contact. It is the most commonly used polymeric micelles as it is easy to prepare as compared to other types of micelles. When the hydrophobic block of micelles is longer, it will try to form rods and lamellae morphologies. Typically, because of the hydrophobic interactions, the blocks form the inner core. When charged block copolymers are used, the electrostatic interaction takes place. Polyion complex micelles are formed as a result of this process. In reverse micelles, the core has a hydrophilic head and the outer part has a hydrophobic tail. These types of micelle formation occur mostly in oil-water mixtures where the amount of water is very small, so the hydrophilic head flocks to the interior, thus water resides inside the micelle. In the case of metal-ligand, hydrogen bonding is used to coordinate and create the complex. It can contribute to the process of micellization. Multi-compartment micelles can be formed by using triblock copolymers which give several well-differentiated compartments, and both the core and the corona can be compartmentalized, enabling concomitant drug loading and release. In triblock copolymer, if the hydrophobic end is small and it has a long hydrophilic chain, then it forms flower-like polymeric micelles[64].

Challenges and future development

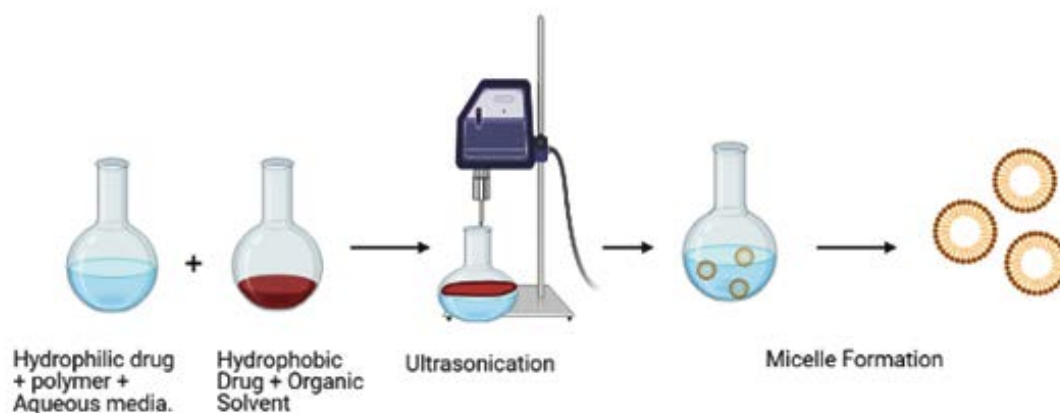The micelle subunits improve the

Fig. 5. Ultrasonication technique

flexibility of the self-assembly system despite the fact that the mechanism for it is still limited. This is because in self-assembly, many obstacles need to be notified and you still need to get deep inside knowledge. In micelles self-assembly, the balance of thermodynamic and kinetic is very important because the process of kinetics predicts the assembly behaviour and hierarchical structure. The ongoing studies have mostly concentrated on the variation in structures that are seen in aggregates, so the main hurdle is to have an effective path to study the morphological development through the self-assembly process. The goal of future research is to determine the most effective kinetic technique for micelle self-assembly.

Supramolecular polymerization has received significant heed, involving a one-dimensional theory of microscale self-assembly of copolymer micelles. A few research groups have studied the polymerization in supramolecular micelles with various micelles, and Winnik and Manner found that living polymerization reaction characteristics are similar to those of one-dimensional CDSA[65]. Lin's team obtained polypeptide-based polymerization of copolymeric micelles that follows the fundamental rule of the mechanism of step polymerization with characteristics of second-order reaction in polymeric micelles[66]. In supramolecular chemistry, the formation of advanced theory on supramolecular polymerization can become an advancing lead.

Theoretical simulations have come up as an effective method to look into micelle assembly as they give information about the microscopic and mesoscopic copolymer assembly of micelles. Zhou et al. found that via condensation–coalescence mechanisms, micelles can be arranged into high-ordered superstructures, but they are still limited and the only study has withdrawn help from the simulation. As a result, simulations are being considered more in the future to solve vexing problems[67]. A.B Kuchekar et al utilized statistical PB design for identify influencing variables such
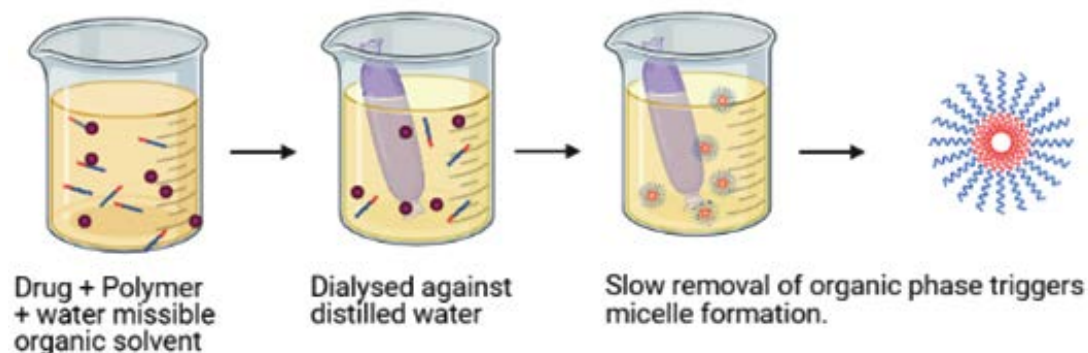

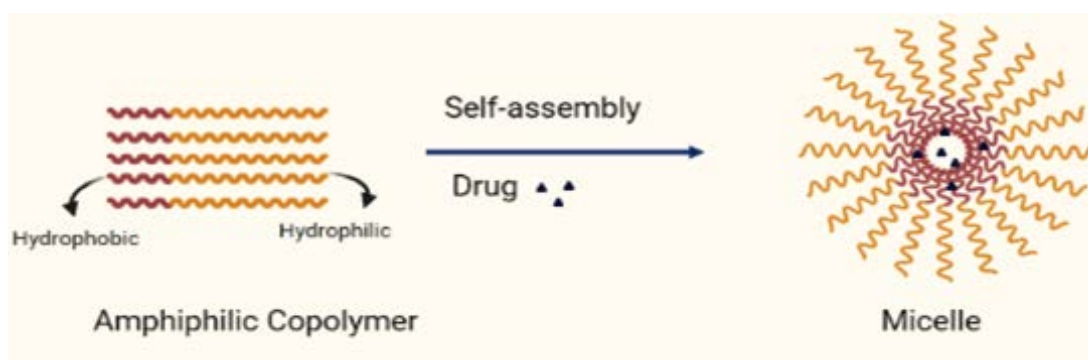**Fig. 6.** Dialysis technique

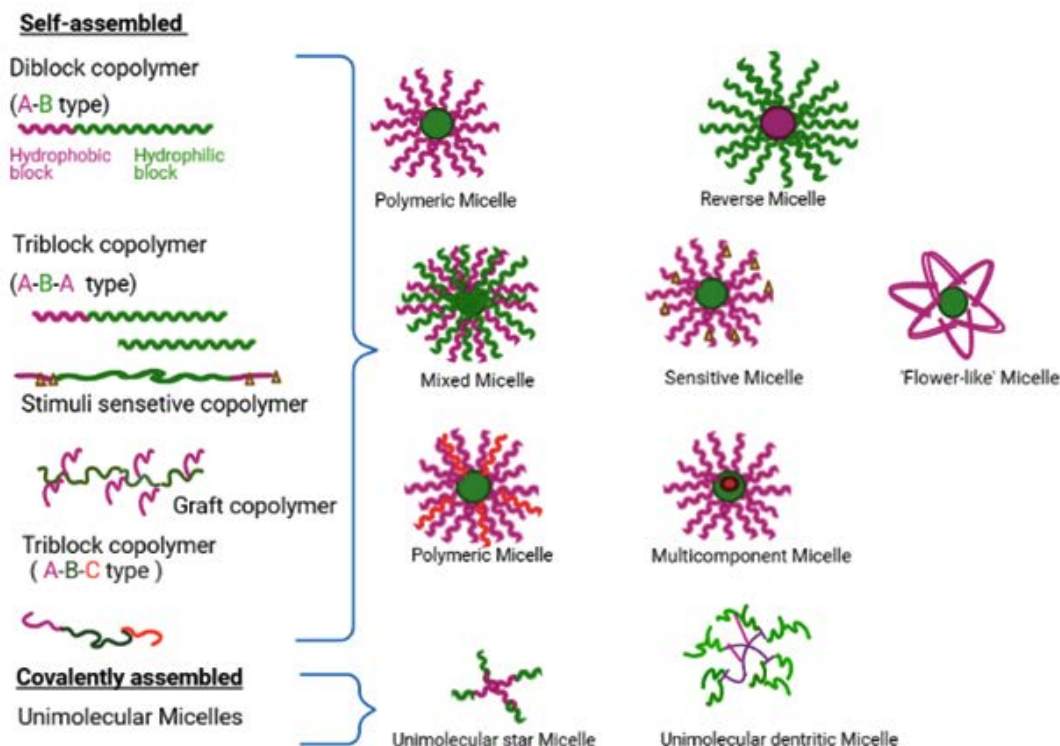**Fig. 7.** Diagrammatic representation of Self-Assembly of Copolymer

Fig. 8. Classification of different types of polymeric micelles

as HP â-CD and Eudragit S100 that can be used for investigation.[68] A.B Kuchekar et al found most significant factors influencing mean particle size and zeta potential of the polymeric micelle formulation.A.B Kuchekar et al conducted preliminary batches employed to screen the significant formulation and process variables of CTB loaded polymeric micelles by Quality-by-Design (QbD) approach[69]. To treat Influenza virus infection, a multifunctional PLA-b-PEG copolymer modified methyl-b-neuraminic acid (mNA) has been developed by Amisha et. al. as drug delivery micelles[72.]The backbone resonance assignment for NS4A was discovered in micelles. Full-length Dengue NS4A was created for structural investigation, according to Yan Li et al[73.]

CONCLUSION

The techniques of micelle formation, polymers utilised, alternative ways of self-assembly, and current advancements in copolymer micelles are included in this study. In general,

a micelle should possess an anisotropically distributed composition of polymer subunits. Electrostatic, solvophobic, and molecular force interactions can all be used to control micelle self-assembly. All of these rules can be used to provide instructions in this area and also provide stimulation for future studies. Due to a lack of in-depth understanding of assembly kinetics, there are many challenges ahead and limited information is available on theoretical simulation assembly of micelles. In order to develop and promote the advances in supramolecular chemistry, we believe this strategy of hierarchical assembly should continue.

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Conflict of interest

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