

MIXED MICELLE FORMATION METHODS AND IMPORTANCE

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ABSTRACT

One of the most widely studied subjects in nanoscience technology is related to the creation of supramolecular architectures with well-defined structures and functionalities. These supramolecular structures are generated as a result of self-assembly of amphiphilic block polymers. Self-assembly of block polymers via hydrophobic and hydrophilic effects, electrostatic interactions, hydrogen bonding, and metal complexation has shown tremendous

potential for creating such supramolecular structures with a wide array of applications. micelles have gathered considerable attention in the field of drug and gene delivery due to their excellent biocompatibility, low toxicity, enhanced blood circulation time, and ability to solubilize a large number of drugs in their micellar core. In this article we have reviewed several aspects of micelles concerning their general properties, preparation and characterization techniques, and their applications in the areas of drug and gene delivery. micelles can be used as drug carriers' for targeting certain areas of the body by making them stimuli-sensitive or by attachment of a specific ligand molecule onto their surface..

Key word: Granulation, Moisture activated dry granulation, Reasons of MADG , Process of MADG.

INTRODUCTION

A micelle is formed when a variety of molecules including soaps and detergents are added to water. The molecule may be a fatty acid, a salt of a fatty acid (soap), phospholipids, or other similar molecules. The molecule must have a strongly polar "head" and a non-polar hydrocarbon chain "tail". When this type of molecule is added to water, the non-polar tails of the molecules clump into the center of a ball like structure, called a micelle, because they are hydrophobic or "water hating". The polar head of the molecule presents itself for interaction with the water molecules on the outside of the micelle. Micelles are amphiphilic colloidal structures, with particle diameters from 5 to 100 nm range [1]. Micelles consist of molecules containing two completely different regions that have opposite affinities against water. These amphiphilic molecules, which form the micelles, associate at certain temperatures and in appropriate concentrations. The core of the micelle is formed by the hydrophobic fragments of amphiphilic molecules, whereas micelle's shell consists of hydrophilic fragments of micellar molecules. Micellar amphiphilic molecules at low concentrations exist separately in aqueous medium. The aggregation of micellar molecules takes place if their concentration is increased. But aggregation of micellar molecules happens only within a limited concentration interval. The critical micelle concentration is the concentration of a monomeric micellar amphiphile at which aggregation begins and micelles appear. The critical micellization temperature is the temperature at which aggregates appear and below which micellar molecules exist as monomers. The aggregation of amphiphilic molecules and formation of micelles happens after the removal of hydrophobic fragments of the micellar molecules from the aqueous environment and reconstitution of hydrogen bonds in water, leading to a decrease of free energy in the system. Micelles used as carriers for therapeutics in aqueous media can carry lipophilic drugs within its core while micelle's surface binds polar molecules. Improved aqueous solubility and thus better intestinal permeability of micelles is achieved by formation of polymeric micelles. Polymeric micelles are formed of amphiphilic block copolymers and compared to conventional micelles show greater stability in vivo. Viruses use lectin receptors on host cells for their entry into the cells; the infected cells also express these lectins. In order to target viral reservoirs micelles consisted of PEG-poly lactide copolymer surface modified with galactose are constructed, since galactose residues can interact with lectins[2]

Types of Micelle:

Polymeric Micelle

Polymeric micelles are nanosized molecules of core-shell structure that are formed by the self-association of amphiphilic block copolymers when they are added to an aqueous solvent. Polymeric micelles are used in drug delivery because of their interesting characteristics, like biocompatibility, low toxicity, core-shell arrangement, micellar association, morphology, nano size, and relatively high stability. They are used in the treatment of many diseases, such as cancer, in estrogen therapy, and as an anti-influenza antiviral. The functionality of polymeric micelles depends on their core-shell structure, whereby the hydrophobic core carries and protects the drug, while the hydrophilic shell supports and stabilizes the hydrophobic core in the aqueous medium and enhances the water solubility of the polymers; and this also benefits administration of the drug. A lot of interesting clinical applications are offered by polymeric micelles, such as protecting the encapsulated drug and the solubilization of poorly soluble drugs. Most of the time these carriers are prepared by one of three techniques, direct dissolution, solvent casting, or dialysis. There are three different types of polymers used in the preparation of polymeric micelles. They are diblock copolymers, like polystyrene and poly(ethylene glycol) (PEG); triblock copolymers, like poly(ethylene oxide); and graft copolymers, like stearic acid and G-chitosan. Polymeric micelles are divided into two groups according to how they handle the drug, either by physical encapsulation of the drug or by chemical covalent attachment to the drug [3]. The chemical type is more stable than the physical type, due to the drug-binding linkers that are found in the chemical type, which control the release of the drug. However, the drug molecule can be entrapped in the polymer in three different regions according to its polarity: in the core if the drug is nonpolar, in the shell if the drug is polar, or in between the core and the shell if the drug has intermediate polarity. And from another point of view, polymeric micelles are divided into three types based on intermolecular forces: the conventional type, which is prepared from hydrophilic interactions, an example of which is poly(ethylene oxide); the polyion complex micelle type, which is prepared from electrostatic interactions that occur between oppositely charged polymers, for example, PEG; and finally the noncovalently connected polymeric micelles that are obtained by self-assembly of polymers; poly(4-vinyl pyridine) is an example of this type [4].

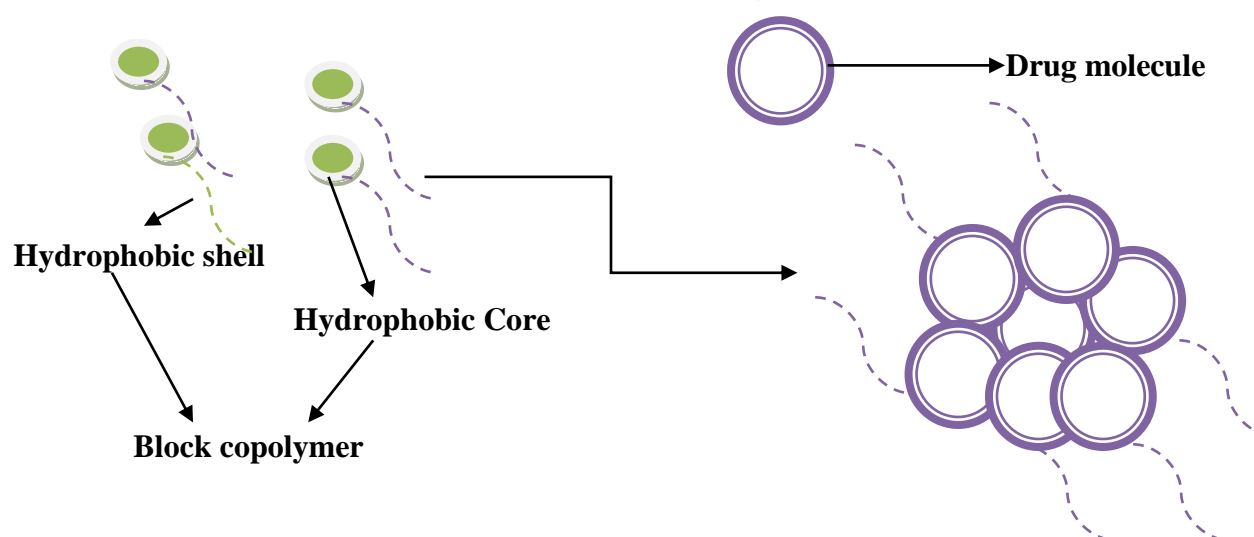


Figure: Formation of Polymeric Micelle

Polymeric micelle characteristically has a core-shell type of architecture, where the inner core is hydrophobic and the outer shell is hydrophilic by nature. These micelles are submicroscopic in size when suspended in liquid forming a colloidal system. The formation of these micelles is governed by the balance between the attractive and repulsive interactions. The attractive forces include hydrophobic interactions, electrostatic interactions, and complexation which direct the segregation of the core segment from the aqueous phase. On the other hand, steric interactions, electrostatic repulsion, and hydration contribute to the repulsive forces [5,6]. These forces prevent the unlimited growth of micelles. Similar to low-molecular-weight surfactants, amphiphilic copolymers also possess a critical micelle concentration (CMC) in the process of micelle formation. At concentrations below the CMC, the copolymers only exist as individual molecules in solution. When the concentration is above the CMC, the amphiphilic copolymer chains can associate and form micelles in a way that the hydrophobic part of the copolymer would avoid direct contact with the aqueous media. Polymeric micelles are generally composed of several hundred molecules; where the corresponding diameter typically ranges from 10 to 100 nm.

Polymers used in Polymeric micelle

Polymers
N-phthaloylcarboxymethylchitosan
Poly(2-ethylhexyl acrylate)-b-poly(acrylic acid)
Poly(tert-butyl acrylate)-b-poly(2-vinylpyridine)
Poly(ϵ -caprolactone)-b-poly(methacrylic acid)
Poly(ethylene glycol)-block-poly(aspartate-hydrazide)
Stearic acid-grafted chitosan oligosaccharide

Table: polymers used in polymeric micelles

Micelle-forming amphiphilic copolymers can be either block copolymers (di, tri, or tetra) or graft copolymers. A graft copolymer is one which comprises a polymer chain as a backbone and another polymer chain as side "grafted" parts. These copolymers usually demonstrate properties of both, i.e., polymeric backbones as well as of the graft. 'Click' reactions have emerged as a means to incorporate polymer chains onto polymeric backbones to result in well-defined [7].

Preparation method of polymeric micelle

Diafiltration Method

The micelles were prepared by a diafiltration method. Briefly, 10 mg of drug were dissolved in 2 mL of DMSO. Subsequently, 0.5 mL deionized water was added dropwise into the solution. The resulting solution was stirred for 0.5 h and then transferred into a pre-swollen dialysis membrane (MWCO: 3.5 kDa) and dialyzed against deionized water at 4°C. The outer phase was replaced with fresh deionized water at 1, 2, 4, 6, and 12 h. After 24 h, the dry P1 micelles were obtained by lyophilization and stored at 4°C [8].

Film Hydration Method

Polymeric micelles were prepared by film hydration. Lipophilic phase consisted of 1.5 g cholesterol, 1 g lecithin and 1.5 mL oleic acid were blended and dissolved in 10 mL chloroform and kept in a rotary evaporator at 120 rpm and 60 °C for 15 min to form a uniform lipid film. To remove residual amount of solvents, the films were placed in a vacuum oven at 40 °C, overnight. Then, dried lipid films were hydrated with aqueous solution containing DFO (5 mg/mL), surfactant, polymer and co-surfactant at 50 °C and 120 rpm and then sonicated in a bath sonicator at 500 W at 25 °C for 5 min [9].

Oil and Water Emulsion Method

The oil in water (O/W) emulsion method was used to prepare the polymeric micelle solutions. Firstly, 50 mg of a block copolymer was dissolved in 5 mL of acetone. Secondly, the solution was dripped into 50 mL water which was then stirred for 24 h followed by lyophilization[10].

Dialysis Method

A block copolymer (5.0 mg) and drug (0.5 mg) was dissolved in 1.0 ml of dimethyl sulfoxide (DMSO). This solution was dialyzed against distilled water using a dialysis membrane (Spectrapor 4, molecular weight cutoff: 12,000–14,000). After overnight dialysis, the solution in the dialysis membrane was collected and filtrated through a No. 1, 2 or 5A filter . And then polymeric micelle is obtained [11].

Evaporation Method

A block copolymer and Drug was dissolved in chloroform in a glass tube. This solution was stirred by a magnetic stirrer in a N₂ gas flow. Chloroform was completely evaporated at room temperature. Distilled water was added in this glass tube, followed by sonication for 2 min using a probe type sonicator. equipped with a standard 6 mm probe in a cycle of sonication for 0.5 s and standby for 0.5 s at 48C. The obtained solution was treated by the following two ways. 1. The solution was filtrated using a 5A filter paper. 2. The solution was centrifuged at 3900 rpm for 10 min. The supernatant was collected and filtrated through a nylon membrane filter with 1mm pore [12].

Mixed micelle

The incorporation of solubilizates into a surfactant micelle results in the formation of a mixed micelle. Solubilization is thus closely related to mixed micelle formation. As ususally used, however, the mixed micelle means a micelle composed of surfactants capable themselves of forming micelles. By this usage, mixed micellization is a special case of solubilization. Many papers have appeared on mixed micelle formation but almost all of them are based on the phase-separation rather than the mass-action model of micelles. This is also true for solubilization. As has been emphasized repeatedly in the foregoing chapters, micelles are not a separate phase but a chemical species [13]. Therefore, mixed micelles also should be treated as a chemical species. Unfortunately, the interpretations of mixed micellization based on the mass-action model have not agreed well with experimental CMC values, 1 probably because the physicochemical properties of mixed micelles are quite different from those of pure

micelles of the individual components. In addition, the micellar aggregation number and the association of counterions with micelles change dramatically with composition in mixed micelles, even though mixed micelles of homologous surfactants differing only in hydrophobic chain length are expected to have surface properties similar to those of pure micelles of each surfactant [14]. In fact, theoretical mixed CMC values of homologous surfactants agree well with experimental values over the whole composition range.

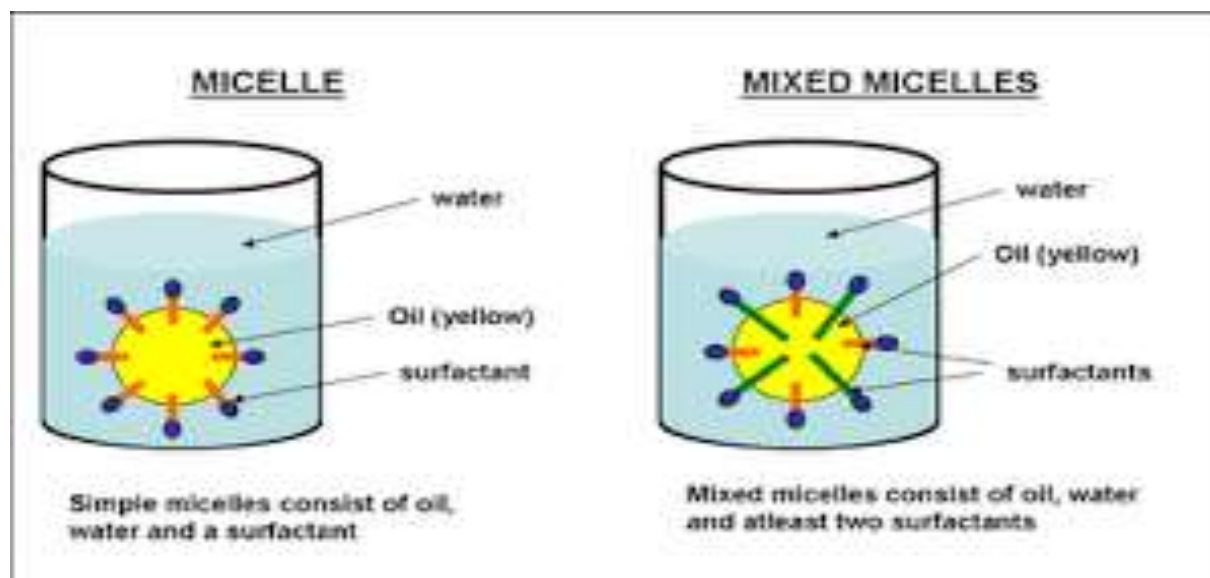


Figure 1: Formation of mixed Micelle

Methods of Mixed Micelle Formation

Film Dispersion Method

Mixed micelles containing drug were prepared by an ameliorated film dispersion method [19]. Accordingly, drug and Soluplus were mixed into methanol. The mixed solution was evaporated under reduced pressure by a rotary evaporator at 35°C, and then, a thin film with drug was achieved. The thin film was hydrated with deionized water containing TPGS, followed by moderate stirring for 2 h. The drug-mixed Soluplus with TPGS-mixed micelles was obtained by filtration of the micelle through a 0.22 μm polycarbonate membrane to separate nonencapsulated drug. In addition, drug Soluplus micelles were prepared using the same protocol of drug-mixed Soluplus micelles except that TPGS were not used in the procedure, and used as the control [15].

Rotary Evaporation Method

The drug-free mixed micelles were prepared by rotary evaporation method. In brief, a methanol solution of mPEG-PLA and Solutol HS15 with different molar ratios was evaporated under vacuum at 60°C to form a homogeneous film. The resulting film was dispersed in 10 mL of water at 60°C and then vortexed for 3 min. Then the mixture was filtered through a 0.45- μm filter (Millex-GV, Millipore, USA) to obtain a clear and homogeneous micelle solution. The drug-loaded mixed micelles were prepared by mixing drug and the prepared drug-free micelle solution under magnetic agitation at room temperature. Then the resultant mixture was incubated at 4°C for 30 min and filtered. The filtrate was filled into ampoules and sealed under nitrogen [16].

Self-Assembly Method

Drug-loaded phospholipid–Tween 80 mixed micelles were prepared by self-assembly method with slight modifications as per composition. A specific amount of phospholipid was dissolved in 0.5 ml of dehydrated ethanol followed by mixing with a suitable quantity of Tween 80 under stirring at room temperature. Final volume was made up to 1 ml with dehydrated ethanol, to which 10 mg of drug was added and the resultant mixture vortexed for 10 min to obtain a homogenous phase. Sufficient distilled water was added under magnetic stirring at 2000 rpm for 30 min followed by sonication for 10 min to obtain 10 ml of the mixed micellar suspension. PBG-loaded mixed micelles were separated from the free crystalline drug by filtration through a 0.45 μm membrane filter. Blank mixed micelles (devoid of Drug) were prepared in a similar manner [17].

Solvent evaporation method

Mixed micelle were prepared by a solvent evaporation technique. Briefly, drug and TPGS (at 1:1 and 1:2 mol ratios) were dissolved in 1 ml of ethanol. The prepared solution was then added dropwise into a beaker containing double distilled water (10 mL) under stirring at 500 rpm. The stirring was continued until complete evaporation of ethanol. The resultant solution was centrifuged at 5000 rpm to obtain a clear supernatant micellar solution. The Drug-loaded MMs (at 1:1:1 and 1:2:2 mol ratios) were also prepared similarly [18].

Polymers Used in Mixed Micelle

Polymers
Pluronic F-127
Pluronic F-123
Soluplus
Tween- 80
TPGS(tocopheryl polyethylene glycol succinate)
Polyethylene Glycol

Table: polymers used in mixed micelles

Mixed micelles self-assembled from two or more dissimilar block copolymers provide a direct and convenient approach to improve physical stability and enhance drug loading capacities of conventional polymeric micelles for drug delivery. The versatility of this approach also allows for the concomitant integration of multiple functionalities into a single system a feat that is synthetically challenging to accomplish with micelles formed from a single copolymer. Through the careful selection and blending of structurally and/or functionally diverse block copolymers, a population of novel and multi-functional micelles bearing desirable attributes of each constituent copolymer can be easily fabricated without the need for elaborate synthetic schemes. As such, this review is focused on the various strategies used to form and stabilize mixed micelles for drug delivery and the methodologies employed to ascertain the establishment of mixed micelle formation [19].

Reverse Micelle

Reverse micelle formed In a non-polar solvent, it is the exposure of the hydrophilic head groups to the surrounding solvent that is energetically unfavourable, giving rise to a water-in-oil system. In this case, the hydrophilic groups are sequestered in the micelle core and the hydrophobic groups extend away from the center. These inverse micelles are proportionally less likely to form on increasing headgroup charge, since hydrophilic sequestration would create highly unfavorable electrostatic interactions. Synthesis of nanomaterials with desired shape and size is very important for their potential applications. The properties of the nanoparticles synthesis not only vary with size but also changes with shape and morphology which in turn depends on the synthesis methods. There are many synthesis methods but among them reverse micellar method is one of the interesting chemical method and is very useful technique for the synthesis of nanoparticles with desired shape and size. In this method reverse micelles are formed by least three components; two of them are non-miscible and the third one is called surfactant which is characterized by amphiphilic properties. Reverse Micelles are water droplets that are obtained from the action of sulphates when dispersed in water. They are nanometer-sized. Surfactant atoms compose with the polar part to the internal side ready to solubilize water and the apolar part in contact with the natural dissolvable. Proteins can be solubilized in the water pool of switch micelles. Studies on the structure-work connections of proteins in switch micelles are imperative since the microenvironment in which the protein is solubilized has physical-synthetic properties distinctive from a large volume of aqueous solution. For biocatalysis, the readiness of mass, naturally dissolvable permit manufactured responses to be performed by means of the control of water substance and the solubilization of hydrophobic substrates. This is proficient with a higher interfacial region (around $100 \text{ m}^2/\text{mL}$) than the traditional biphasic frameworks, limiting mass exchange issues [20].

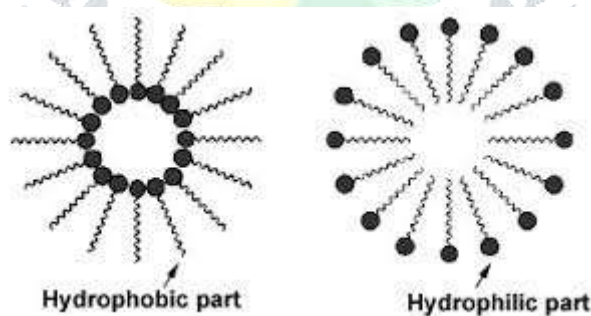


Figure: A. Normal Micelle B. Reverse Micelle

Methods of Formation of reverse micelle

Microemulsion method

Nanoparticles were prepared by a reverse micelle microemulsion method. Aqueous solutions of Copper chloride, chromium chloride and dodecylbenzenesulfonate (Aldrich, 98%) were mixed and stirred for ~ 1 h. A large volume of toluene was added to the mixture and stirred overnight to form the reverse micelles. Methylamine was added to the micelle solution, stirred for ~ 2 h, and then refluxed for ~ 4 h. Following removal of $\sim 3/4$ volume of toluene by distillation, the resulting brown product was washed with ethanol and water to remove excess surfactant. The nanoparticles were collected using centrifugation. The sample was annealed in air at a ramping rate of $1 \text{ }^\circ\text{C}/\text{min}$ and

held at 600 °C for 20 h and became a fine black powder. To vary the composition, appropriate molar ratios of the metal cation solutions were used. Variable sized nanoparticles were prepared by adjusting the water-to-toluene ratio for samples with composition [21].

Polymers used in Reverse micelle

Reverse micelles (RMs) due to their polar internal cavity and hydrophobic exterior. Apart from accounts on the micellization of amphiphilic linear poly(styrene) copolymers, RMs have primarily been obtained from branched macromolecules, and a variety of water-soluble dendritic, hyperbranched or star-shaped polymers have been used to that end. Notwithstanding architectural differences, these branched polymers share similar characteristics such as a compact structure, low viscosity in solution in addition to a high density of end-group functionality (i.e. hydroxyl or amine) which can be modified to generate amphiphilic derivatives. The core-shell structures obtained from hydrophobically-modified branched polymers are often claimed to be unimolecular, although in many cases aggregation cannot be completely avoided and plurimolecular micelles may also be present in solution. [22]

Polymers
Poly(Amidoamine)
Poly(Propyleneamine)

Table: polymers used in reverse micelles

Supermicelles

Supermicelle is a hierarchical micelle structure (supramolecular assembly) where individual components are also micelles. Supermicelles are formed via bottom-up chemical approaches, such as self-assembly of long cylindrical micelles into radial cross-, star- or dandelion-like patterns in a specially selected solvent; solid nanoparticles may be added to the solution to act as nucleation centers and form the central core of the supermicelle. The stems of the primary cylindrical micelles are composed of various block copolymers connected by strong covalent bonds; within the supermicelle structure they are loosely held together by hydrogen bonds, electrostatic or solvophobic interactions [23].

Application of micelle

Formulations of Antifungal Agents

The need for safe and effective modalities for delivery of chemotherapeutic agents to treat systemic fungal infections in immunocompromised AIDS, surgery, transplant and cancer patients is very high. The challenges to delivery of antifungal agents include low solubility and sometimes high toxicity of these agents. These agents, such as amphotericin B, have low compatibility with hydrophobic cores of polymer micelles formed by many conventional block copolymers. Thus to increase solubilization of amphotericin B the core-forming blocks of methoxy-PEO-b-poly(L-aspartate) were derivatized with stearate side chains. The resulting block copolymers formed micelles.

Amphotericin B interacted strongly with stearate side chains in the core of the micelles resulting in efficient entrapment of the drug in the micelles and subsequent sustained release in the external environment. As a result of solubilization of amphotericin B in the micelles the onset of hemolytic activity of this drug toward bovine erythrocytes was delayed relative to that of the free drug. Using a neutropenic murine model of disseminated candidiasis, it was shown that micelle-incorporated amphotericin B retained potent *in vivo* activity. Pluronic block copolymers were used by the same group for encapsulation of another poorly soluble antifungal agent, nystatin. This is a commercially available drug that has shown potential for systemic administration, but has never been approved for that purpose due to toxicity issues. The possibility to use Pluronic block copolymers to overcome resistance to certain antifungal agents has been also demonstrated. Overall one should expect further scientific developments using polymer micelle delivery systems for treatment of fungal infection [24,25].

Delivery of Imaging Agents

Efficient delivery of imaging agents to the site of disease in the body can improve early diagnostics of cancer and other diseases. The studies in this area using polymer micelles as carriers for imaging agents were initiated by the group of Torchilin. For example, micelles of amphiphilic PEO-lipid conjugates were loaded with In and gadolinium diethylenetriamine pentaacetic acid phosphatidylethanolamine (Gd-DTPA-PE) and then used for visualization of local lymphatic chain after subcutaneous injection into the rabbit's paw. The images of local lymphatics were acquired using a gamma camera and a magnetic resonance (MR) imager. The injected micelles stayed within the lymph fluid, thus serving as lymphangiographic agents for indirect MR or gamma lymphography. Another polymer micelle system composed of amphiphilic methoxyPEO-b-poly[epsilon-N-(triiodobenzoyl)-L-lysine] block copolymers labeled with iodine was administered systemically in rabbits and visualized by X-ray computed tomography. The labeled micelles displayed exceptional 24 hr half-life in the blood, which is likely due to the core-shell architecture of the micelle carriers that protected the iodine-containing core. Notably, small polymer micelles (< 20 nm) may be advantageous for bioimaging of tumors compared to PEG-modified long-circulating liposomes (ca. 100 nm). In particular, the micelles from PEO-distearoyl phosphatidyl ethanolamine conjugates containing In-labeled model protein were more efficacious in delivery of the protein to Lewis lung carcinoma than larger long-circulating liposomes. Overall, polymer micelles loaded with various agents for gamma, magnetic resonance, and computed tomography imaging represent promising modalities for non-invasive diagnostics of various diseases [28].

Delivery of Polynucleotides

To improve the stability of polycation-based DNA delivery complexes in dispersion block and graft copolymers containing segments from polycations and nonionic water-soluble polymers, such as PEO, were developed. [90,181,182] Binding of these copolymers with DNA results in the formation of micelle-like block ionomer complexes ("polyion complex micelles") containing hydrophobic sites formed by the polycation-neutralized DNA and hydrophilic sites formed by the PEO chains. [28, 29] Despite neutralization of charge, complexes remain stable in aqueous dispersion due to the effect of the PEO chains. Overall the PEO modified polycation-DNA complexes form stable dispersions and do not interact with serum proteins. These systems were used successfully for intravitreal delivery of an antisense oligonucleotide and suppression of gene expression in retina in rats. Furthermore, they

displayed extended plasma clearance kinetics and were shown to transfect liver and tumor cells after systemic administration in the body. In addition there is a possibility of targeting of such polyplexes to specific receptors at the surface of the cell, for example, by modifying the free ends of PEO chains with specific targeting ligands. Alternatively, to increase binding of the complexes with the cell membrane and the transport of the polynucleotides inside cells the polycations were modified with amphiphilic Pluronic molecules. One recent study has shown a potential of Pluronic-polyethyleneimine-based micelles for in vivo delivery of antisense oligonucleotides to tumors and demonstrated sensitization of the tumors to radiotherapy as a result of systemic administration of the oligonucleotide-loaded micelles[30].

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