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Antoine Al-Achi

Jonathon Lawrence

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Micelles: Chemotherapeutic Drug Delivery

Antoine Al-Achi[1]* and Jonathan Lawrence BS[2]

[1]Department of Pharmaceutical Sciences, Campbell University College of Pharmacy & Health Sciences, USA
[2]Campbell University College of Pharmacy & Health Sciences, USA

Micelles have become one of the main players in nanoparticle research. Although micelles have been around for decades, it was not until recently that these particles were finally utilized in advanced drug delivery systems. Micelles formation is an efficient method for delivering poorly water-soluble drugs [1], and its usefulness is in particular applicable to chemotherapeutic agents [2]. Polymer-based micelles have been the main focus of researchers in the past several years. Cancer has unique characteristics that can be exploited for drug delivery. Tumor vasculature specifically has become a burgeoning area of research over the past few decades. The enhanced permeability and retention effect (EPR) in solid tumors is one of the main reasons that polymeric micelles are able to selectively distribute to tumor cells as opposed to normal tissues [3]. Bradykinin, nitric oxide, peroxynitrite, and VEGF are vascular permeability factors found to be elevated in the tumor environment which enhances angiogenesis [4]. Collagenases also help induce vascular permeability by causing disintegration of matrix tissue surrounding blood vessels [4]. Fenestrations in regular vessels are too small for penetration of nanoparticles, compared to those as large as 600-800 nm in tumor tissue [3]. Therefore, polymeric micelles are able to penetrate tumor tissue selectively, achieve higher concentrations, and have a longer duration of action than regular dosage forms, subsequently requiring less dosing. Regular body processes also play a role in drug permeability and retention. The reticuloendothelial system (RES), comprised of monocytes and macrophages, is responsible "for engulfing and clearing old cells, miscellaneous cellular debris, foreign substances, and pathogens from the bloodstream" [5]. Polymeric micelles are able to effectively avoid opsonization by the RES and achieve longer circulation times. Longer circulation times again allow enhanced permeability to tissues resulting in a greater therapeutic response.

Understanding micelle structure is a key to realizing their potential as novel drug delivery systems. Micelles are surfactant molecules, which aggregate in aqueous or oily liquids [4]; the micelles occupy the dispersed phase of a colloidal system [6]. Amphipathic monomers, each containing a hydrophilic and hydrophobic domain, make up a polymeric micelle. Micelle's ability to aggregate and carry drugs is conferred by a property known as the critical micelle concentration (CMC). These amphipathic monomers do not aggregate until the CMC is reached, at which time spontaneous aggregation occurs resulting in polymeric micelles. CMC values for nanoparticles are generally much lower than most commercially available products (on the order of 10^{-6} or 10^{-7}); if the micelles faced dilution, (i.e., injection into the body) then a drop in concentration below the CMC would cause loss of structural integrity. The CMC phenomenon is due to the dehydration of the hydrophobic tails, leading to a favorable state of entropy [4]. The hydrophobic domains comprise the micelle "core" while the hydrophilic domains make up the micelle exterior or "corona" [3]. Hydrophobic cores are ideal for encapsulating hydrophobic drugs, which is where most research has been focused and has found success. Formation of van der Waals bonds between the hydrophobic polymer core and drug help stabilize the micelle. The hydrophilic corona also helps stabilize the micelle structure due to the formation of hydrogen bonds with the surrounding aqueous solution [4]. Encapsulation of hydrophilic drugs has been attempted, but currently has been unsuccessful and needs to be studied further. The entire complex of micelle and drug can then vary in size from ten to hundreds of nanometers; although, nanoparticles under 100 nm seem to fair the best *in vivo*. So how would someone realistically create these compounds? There are several popular methods of nanoparticle synthesis which will be highlighted: emulsification-solvent evaporation, solvent displacement, and salting out.

Emulsification-solvent evaporation usually utilizes a simple emulsion (w/o) or double emulsion (w/o/w) technique. Simple emulsions are used mainly for hydrophobic drugs. Like most stabile emulsions, sufficient shear is needed to disperse the aqueous phase in the organic solvent. Dichloromethane, ethyl alcohol, and other volatile solvents immiscible with water are used commonly as organic solvents, while drugs mixed with the chosen polymer occupy the dispersed phase. The dispersed phase must also contain appropriate levels of surfactant (sodium cholate, poly-vinyl alcohol, etc) to form micelles with the drug molecules. In order to provide the necessary amount of shear, complex methods of mixing, such as homogenization or probe sonication are employed. Micelles are collected by centrifugation after mixing, the solvent is removed by evaporation, and the final product is distributed in water. A double emulsion is formed similarly; however, when the primary emulsion (w/o) is formed with the drug and organic solvent, this emulsion is then dispersed throughout another aqueous phase (w/o/w). Double emulsions are useful for encapsulating hydrophilic drugs [7].

Solvent Displacement, also known as nanoprecipitation or solvent diffusion, was first described by Fessi et al. (1989) [8]. In this method, solvents miscible with water are used (acetone, etc). The drug, polymer, and surfactants are dispersed throughout the organic phase. "A submicron o/w emulsion is spontaneously formed due to immediate reduction of the interfacial tension with rapid diffusion of acetone into the aqueous phase (the Marangoni effect)" [7]. The final steps are similar to the emulsification-solvent evaporation method; however, solvent displacement is not used to encapsulate water-soluble drugs. Advantageously, lesser shear is required in this method [7].

The salting out method can be used to encapsulate hydrophobic drugs only. A primary o/w emulsion is formed with the drug and polymer in the organic phase. "As salting out agents can be used electrolytes, such as magnesium chloride, sodium chloride, or

***Corresponding author:** Antoine Al-Achi, Associate Professor, Department of Pharmaceutical Sciences, Campbell University College of Pharmacy & Health Sciences, P.O. Box 1090, Buies Creek, NC 27506, USA, Tel: 910-893-170; E-mail: alachi@campbell.edu

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magnesium acetate and non-electrolytes, such as sucrose" [7]. The main purpose of the salting out agent is to make a usually water-soluble solvent such as acetone insoluble by supersaturating the solution. Acetone diffusion into the aqueous phase then causes the formation of nanoparticles [9].

Synthesis of the polymeric micelle is a tricky task itself. However, once formed, micelles must achieve the proper therapeutic effect, last for a desired amount of time, and be eliminated with ease without any complications. As knowledge of micelle structure and kinetics grows, drug delivery utilizing polymeric micelles will become smarter. The basis of any drug's structure is its inherent components and size. Polymer-based micelles, specifically A-B co-block polymers, have gained much attention recently. In this structure the A segment is hydrophilic and the B segment is hydrophobic. Polyethylene glycol is the most commonly used hydrophilic segment because it is a FDA approved nontoxic polymer [3]. Poly(lactide-co-glycolide)(PLGA) is the most commonly used hydrophobic segment in research. However, many other compounds or variations can and have been used. An increase in the internal/external phase ratio leads to a slight decrease of the nanoparticle's average size, whereas a nanoparticle size increase was observed when the polymer/surfactant ratio was higher [9].

The preparation of nanoparticles via emulsion based techniques requires the use of compounds to stabilize the formulation. Poly(vinyl alcohol)(PVA) and human serum albumin (HSA) have been used effectively as stabilizers in Doxorubicin-loaded PLGA nanoparticles. PVA seems to be more effective; however, Lecithin has been used to increase the activity of HAS and found to be better than PVA [10]. Nanoparticle size appears to decrease with increases in stabilizer concentration between 0.5 and 5% w/v [9]. In order to make sure adequate levels of drug are being delivered inside nanoparticles, one must study several parameters: Nanoparticle recovery (%) and encapsulation efficiency, which is broken down into drug content (drug loading, % w/w) and drug entrapment (%). Changing the aqueous phase pH from 5.8 to 9.3 increased procaine hydrochloride nanoparticle recovery from 65.1 to 93.4%, drug content from 0.3 to 1.3% (w/w), and drug entrapment from 11.0 to 58.2% [11]. Poly(styrene-co-maleic acid)(SMA)-tanespimycin micelles were reported with a loading efficiency of 93%, while an even higher loading efficiency with Paclitaxel nanoparticles of 96% was seen [12,13]. The loading efficiency of Paclitaxel nanoparticles was found to be decreased when the external aqueous phase volume was doubled (nanoprecipitation method). The method of preparation of the organic phase may also influence the loading efficiency [14]. Some strives have been made to simulate the compatibility of drugs with certain co-block polymers. In one example with PEO-*b*-PCL block copolymers, Flory-Huggins interaction parameters were found to be more consistent with experimental solubility data than the traditional group contribution method used in the pharmaceutical industry [15]. Regardless of the design, it is important to note that high nanoparticle recovery is required for reducing manufacturing costs. High entrapment efficiency will reduce the amount of carrier needed for the administration to the target site and help eliminate wastage during manufacturing.

Other studies have examined the possibility of multiple drug carriers. It is well known that chemotherapy regimens using multiple drugs will enhance tumor inhibition. For example, common acronyms such as TAC, CMF, or TCH denote combination therapies for breast cancer [16]. Beyond inhibiting tumor growth, combination nanoparticle drugs will allow better dosage optimization and convenience. Unimers of Doxorubicin and Camptothecin conjugated to poly-L-lactide (PLA) can be controlled ratiometrically with over 90% loading efficiency. This control is achieved simply by adjusting the DOX-PLA:CPT-PLA molar ratio. This dual drug combination was proven to exhibit more cellular cytotoxicity than single drug-loaded nanoparticles [17]. Nanoparticles co-loaded with Doxorubicin and Paclitaxel in a concentration ratio of 2:1 showed high anti-tumor activity against three different types of tumor cells [18]. Again, these co-loaded nanoparticles were found to be superior to single drug formulations. A 3-in-1 injection of Poly(ethylene glycol)-block-poly(D,L-lactic acid)(PEG-b-PLA) micelles carrying the three anti-cancer drugs Paclitaxel, 17-allyamino-17demethoxygeldanamycin, and rapamycin reduced tumor volume by 1.6 fold [19].

Once ready to be administered, micelles are injected and enter cells by endocytosis. Drug targeting to specific cells can be specialized through ligand-receptor interactions. Octreotide conjugated micelles carrying Docetaxel were found to be a viable option for delivery to tumor cells over expressing the somatostatin receptor. This receptor is found over-expressed in many types of tumors such as prostate and breast cancer and regulates inhibition of hormone and growth factor secretion [20]. A ligand for Melanocortin 1 receptor, a ligand over-expressed in melanomas, was found to bind effectively and selectively while conjugated to micelles. However, some loss of affinity was noted when small peptides were attached to larger micelles [21]. Integrin-αvβ3 receptor, over-expressed in angiogenic tumor blood vessels, can be targeted using Arg-Gly-Asp (RGD); Folic acid can also be used to target the folate receptor over-expressed in many breast, lung, kidney, and brain cancers. An increase in uptake of RGD and folic acid conjugated nanoparticles to HUVEC and KB cells respectively was seen. Uptake was modulated by increasing or decreasing the density of the ligands on the nanoparticle surface [22]. Micelles modified with anti-nucleosome monoclonal antibody 2C5 demonstrated higher cytotoxicity in tumor cells than free drug against the B16 (murine melanoma) and 4T1 (murine mammary carcinoma) cell lines [23]. AS1411 is a DNA aptamer that specifically binds nucleolin, which is highly expressed in cancer cells and endothelial cells lining angiogenic blood vessels. Nanoparticles conjugated with AS1411 and carrying Paclitaxel enhanced uptake and thus tumor inhibition in C6 glioma cells. Entry of micelles into the cell has been explored by these methods and others as well; however, once inside, triggers exist to potentially obtain even better drug targeting.

Multiple methods of activation have been studied for nanoparticle release including: pH, temperature, ultrasound, light, and chemical reactions. One interesting example utilizes polymers conjugated to histidine and phenylalanine. These poly(L-histidine-*co*-L-phenylalanine) polymers are blended with poly(L-lactic acid)-*b*-PEG-folate (PLLA-b-PEG-folate) polymers in order to create a micelle that targets early endosomal pH (roughly pH 6). The histidine moiety, with a pK_a of around 6.5, transitions from hydrophobic properties at high pH, (>7.0) to hydrophilic properties at low pH (<7.0) due to ionization of the imidazole group at lower pH. However, the histidine conjugated polymers must be conjugated with phenylalanine moieties and then blended with PLLA-*b*-PEG-folate polymers in order to: i) create a drug effective against multi-drug resistant (MDR) tumors and ii) allow the micelle structure to maintain shape at physiological pH (pH 7.4) and still release drug at the tumor site when engulfed by endosomes (pH 6) [24]. Micelles synthesized with poly(N-isopropylacrylamide) (PNIPAAm) have a thermosensitive property that allows them to maintain stability at 37° Celsius and deform at 39.5° Celsius to release Doxorubicin [25]. Doxorubicin loaded micelles also were shown to enter cells and be released effectively by ultrasound. Yield

of intraperitoneal ovarian carcinoma tumors decreased from 70% for Doxorubicin to 36% for the same concentration of Doxorubicin loaded micelles with a 30 second sonication. This effect was independent of temperature, because of its occurrence at low ultrasound energies, well below that used for hyperthermia tumor treatment. The effect is thought to be related to ultrasound's ability to cause cell membrane disruption, resulting in a transient increase in cell membrane permeability of the tumor interstitial environment [26]. Micelle polymers conjugated with photochromic spiropyran (SP) units undergo reversible isomerization between colorless SP and colored merocyanine (ME). Irradiation with UV light (365 nm) completely disrupted the micelles, while irradiation with visible light (620 nm) effectively reversed the dissociation. This delivery system was used to carry the hydrophobic dye coumarin 102 [27]. Novel mechanisms will enable increased drug specificity for tumor tissue.

Once micelles are triggered, then how would we characterize their release profile? It has been well-documented that most polymeric micelles exhibit a biphasic release profile. Micelles containing procaine hydrochloride exhibited immediate release of about 65% over 15 minutes followed by release of the remaining drug over 4-6 hours [11]. Micelles containing Paclitaxel were found to release roughly 30% of the drug after 12 hours, followed by sustained release of roughly 65% of the drug over 72 hours [14]. Tanespimycin release from micelles occurred at 51% and 95% over 2 and 8 hours, respectively [12]. Sustained release was noted with release of Tamoxifen citrate from micelles conjugated with guar gum. Here it was noted that the predominant mechanism behind drug release was time dependent release and diffusion [28]. However, this is consistent with theories given by other researchers reporting biphasic release profiles, since it is believed that the initial rapid release is caused by drug adsorbed or close to the surface of the nanoparticles and large surface to volume ratio, while the sustained release may be due to diffusion of the drug from the core [11]. Biphasic release would be desirable since a drug's effect would then be immediate and long-lasting. Overall, it appears that the biphasic release characteristics of micelle systems vary with its composition. This would lead one to believe that desirable release characteristics could be achieved simply by changing these molecules. Contributions in this field could lead to a need for less dosing or reduced toxicity.

So what are some practical, *in vivo* applications of micelle systems? There are several FDA approved compounds that are currently in use for certain types of cancer. However, given the amount of research on micelles, FDA approved compounds remain relatively few: Genexol-PM, Oncaspar, and Abraxane. Published data associated with micelle toxicity is slim, probably due to the fact that there is a penchant to publish positive results. In addition, due to the increased specificity for target tissues, nanoparticles are less likely to cause systemic side effects. Toxic substances used in conventional drug delivery may become unnecessary if micelles dosage form is used instead. For example, an excipient in the formulation of Paclitaxel, Cremophor EL, has been associated with severe hypersensitivity reactions. Preparation of nanoparticles without Cremophor EL has been shown to reduce these undesirable reactions.

Micelles appear to have some role in delivering chemotherapeutic agents in an efficient and targeted way. However, complexity of preparation and stability remain issues of concern regarding this dosage form.

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