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REVIEW ARTICLE

NANOTECHNOLOGY

A REVIEW ON POLYMERIC MICELLAR NANOCARRIERS

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ABSTRACT

Micelles, self-assembling nanosized (5–100 nm) colloidal particles with a hydrophobic core and hydrophilic shell are currently successfully used as pharmaceutical carriers for water-insoluble drugs and demonstrate a series of attractive properties as drug carriers. These polymeric miscellar nanocarriers have applications in drug delivery primarily such as anticancer therapy, to the brain to treat neurodegenerative diseases, antifungal agents, stimuli-responsive nanocarriers for drug and gene delivery, Ocular drug delivery. Targeted drugs will hopefully reduce adverse reactions by limiting their action to cancer tissue only.

KEY WORDS

polymeric nanoparticles, Pluronic block copolymers,

1. INTRODUCTION

Fast developing nanotechnology, among other areas, is expected to have a dramatic impact on medicine. The application of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems has recently been determined. Among the approaches for exploiting nanotechnology developments in medicine, various nanoparticulates offer some unique advantages as pharmaceutical delivery systems and image enhancement agents**.(15,18)** Several varieties of nanoparticles are available, different polymeric and metal nanoparticles, liposomes, micelles, quantum dots, dendrimers, microcapsules, cells, cell ghosts, lipoproteins, and many different nano assemblies a major role in diagnosis and therapy. . Among particulate drug carriers, liposomes, micelles and polymeric nanoparticles are the most extensively studied and possess the most suitable characteristics for encapsulation of many drugs and diagnostic (imaging) agents. Among many possible applications of nanotechnology in medicine, the use of various nanomaterials as pharmaceutical delivery systems for drugs, DNA, and imaging agents has gained increasing attention. Many varieties of nanoparticles are available **(18)** such as different polymeric and metal nanoparticles, liposomes, niosomes, solid lipid particles, micelles, quantum dots, dendrimers, microcapsules, cells, cell ghosts, lipoproteins, and different nano assemblies. High through out drug screening initiatives are water-insoluble, but there are some unresolved issues. The therapeutic application of hydrophobic, poorly water-soluble agents is associated with some serious problems, since low water solubility results in poor absorption and low bioavailability **(16).** In addition, drug aggregation upon intravenous administration of poorly soluble drugs might lead to such complications as embolism **(17)** and local toxicity **(12).**

A very promising approach to overcome systemic toxicity is the application of drug-loaded nanosized drug carriers, such as liposome's, polymeric nanoparticles, dendrimers and micelles.

The incorporation of chemotherapeutic agents into nanosized drug carriers has several advantages compared to systemic chemotherapy. (**12-13)**

- Improves the solubility of poorly water soluble drugs.
- Prolongs the half-life of drug systemic circulation by reducing immunogenicity.
- Release drug at a sustained rate or in an environmentally responsive manner and thus decreases the frequency of administration.
- Delivers drug in a target manner to minimize systemic side-effects.
- it can deliver two- or more drug simultaneously for combination therapy to generate synergistic effect and suppress drug resistance

Targeted drugs will hopefully reduce adverse reactions by limiting their action to cancer tissue only. Nanoparticles can easily be functionalized to target specific types and may be promising delivery and imaging in the treatment of cancer Polymer-based drugs and drug delivery systems emerged from the laboratory bench in the 1990s as a promising therapeutic strategy for the treatment of certain devastating human diseases. A number of

polymer therapeutics are presently on the market or undergoing clinical evaluation to treat cancer and other diseases. Most of them are low molecular weight drug molecules or therapeutic proteins that are chemically linked to water-soluble polymers to increase drug solubility, drug stability, or enable targeting to tumors.

2. Micelles

Micelles are colloidal particles with a size usually within a range of 5–100 nm. Micelles consist of amphiphiles or surface-active agents (surfactants), which exist of two distinct regions: mostly a hydrophilic head-group and a hydrophobic tail.

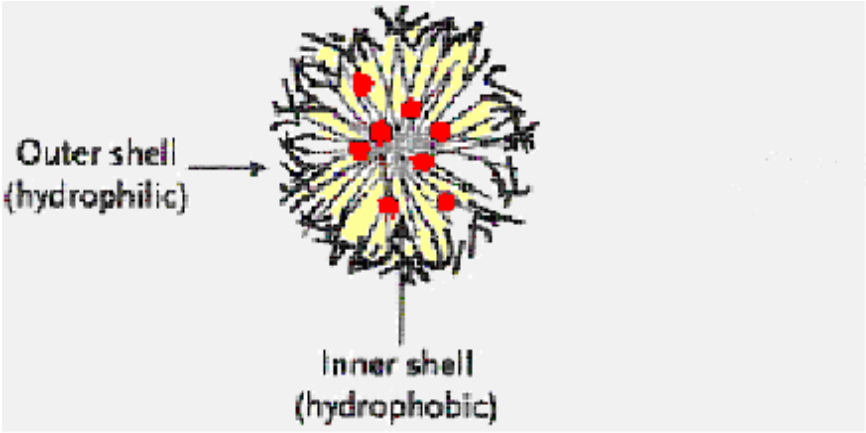

Fig 1

Cross Section of polymeric miscelles

At low concentrations in an aqueous medium, such amphiphilic molecules exist separately, however, as their concentration is increased, aggregation takes place within a rather narrow concentration interval. The concentration of a monomeric amphiphile at which micelles appear is called the critical micelle concentration (CMC), while the temperature, below which amphiphilic molecules exist as unimers and above as aggregates, is called the critical micellization temperature (CMT). The formation of micelles is driven by the decrease of free energy in the system because of the removal of hydrophobic fragments from the aqueous environment and the re-establishing of hydrogen bond network in water. Additional energy gain results from formation of Van der Waals bonds between hydrophobic blocks in the core of the formed micelles **(24, 28)** The use of certain special amphiphilic molecules as micelle building blocks can also extend the blood half-life upon intravenous administration. Because of their small size (5-100 nm), micelles demonstrate spontaneous penetration into the interstitium in the body compartments with leaky vasculature (tumors and infarcts) by the EPR effect a form of selective.

3. Polymeric micellar nanocarriers in drug delivery

The studies on the application of polymer micelles in drug delivery have mostly focused on the following areas that are considered below:

(1) Delivery of anticancer agents to treat tumors;
(2) Drug delivery to the brain to treat neurodegenerative diseases;
(3) Delivery of antifungal agents
(4) Stimuli-responsive nanocarriers for drug and gene delivery.
(5) Ocular drug delivery

3.1 Delivery of anticancer agents to treat tumors;

Chemotherapy is an essential component in the multidisciplinary management of most cancers. Cancer is a leading cause of death world-wide and is responsible for approximately 13% of all deaths, according to the World Health Organization. A very promising approach to overcome systemic toxicity is the application of drug-loaded nanosized drug carriers, such as liposome's, polymeric nanoparticles, dendrimers and micelles. Currently, many drug-loaded polymeric micelles for anticancer therapy are under investigation in preclinical Studies to improve drug efficacy. Five micellar formulations have been tested in clinical trials. They are as

Table.1 Ref (1, 2-5)

Polymeric micelle	Block Copolymer	Drug	Indication	Micelle Size (diameter)
Genexol PM	PEG-P(D,L-lactide)	Paclitaxel	Breast cancer,Pancreatic cancer,Small cell	20-50 nm
SP1049C	Pluronic L61and F127	Doxorubicin	lung cancer,	22-27 nm
		Cisplatin	Adenocarcinoma of oesophagus	30 nm
NC-6004	PEG-PGL(Cisplatin)	Paclitaxel	Solid tumors	85 nm
NK105	PEG-(aspartate)	SN-38	Advanced stomach cancer	20 nm
NK012	PEG-PGL(SN-38)		Breast cancer	

3.2 Drug delivery to the brain to treat neurodegenerative diseases;

By restricting drug transport to the brain, the blood brain barrier (BBB) represents a formidable impediment for the treatment of brain tumors and neurodegenerative diseases such as HIV-associated dementia, stroke, Parkinson's and Alzheimer's diseases. Two strategies using polymer micelles have been evaluated to enhance delivery of biologically active agents to the brain. The first strategy is based on the modification of polymer micelles with antibodies or ligand molecules capable of transcytosis across brain microvessel endothelial cells, comprising the BBB. The second strategy uses Pluronic block copolymers to inhibit drug efflux systems, particularly, Pgp, and selectively increase the permeability of BBB to Pgp substrates An earlier study used micelles of Pluronic block copolymers for the delivery of the CNS drugs to the brain. **(29, 30).** These micelles were surface-modified by attaching to the free PEO ends, either polyclonal antibodies against brain-specific antigen, a2-glycoprotein, or insulin to target the receptor at the lumenal side of BBB. The modified micelles were used to solubilize fluorescent dye or neuroleptic drug, haloperidol, and these formulations were administered intravenously in mice. Both the antibody and insulin modification of the micelles resulted in enhanced delivery of the fluorescent dye to the brain and drastic increases in neuroleptic effect of haloperidol in the animals. Subsequent studies using *in vitro* BBB models demonstrated that the micelles, vectorized by insulin, undergo receptor-mediated transport across brain microvessel

endothelial cells**. (27)** Based on one of these observations, one should expect development of novel polymer micelles that target specific receptors at the surface of the BBB to enhance transport of the incorporated drugs to the brain.

3.3 Delivery of antifungal agents

The need for safe and effective modalities for the delivery of chemotherapeutic agents to treat systemic fungal infections in immuno compromised AIDS, surgery, transplant and cancer patients is very high . The challenges to the 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-PEOb- poly(L-aspartate) were derivatized with stearate side chains.(**20-23)** The resulting block copolymers formed micelles. Amphotericin B interacted strongly with the stearate side chains in the core of the micelles, resulting in an efficient entrapment of the drug in the micelles, as well as 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.(**23)** Using a neutropenic murine model of disseminated Candidas, 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.(**30)** 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 also been demonstrated. **(20,30)** Overall, one should expect further scientific developments using polymer micelle delivery systems for the treatment of fungal infection.

3.4 Stimuli-responsive nanocarriers for drug and gene delivery

With parallel recent breakthroughs in molecular understanding of diseases and controlled manipulations of material at the nanometric length scale, nanotechnology offers tremendous promise in disease prevention, diagnosis, and therapy **(11).** Among the various approaches for exploiting developments in nanotechnology for biomedical applications, nanoparticulate carriers offer some unique advantages as delivery, sensing and image enhancement agents **(9).** Many bioactive used for pharmacotherapy, while have a beneficial action, can also exhibit side-effects that may limit their clinical application. There has long been the desire to achieve selective delivery of bioactives to target areas in the body in order to maximize therapeutic potential and minimize side-effects. For example, cytotoxic compounds used in cancer therapy can kill target cells, but also normal cells in the body resulting in undesired side-effects. For achieving better therapeutic application, nanocarriers are considered for target-specific delivery of drugs and gene to various sites in the body in order to improve the therapeutic efficacy, while minimizing undesirable side effects. Improvements in target-to-non-target concentration ratios, increased drug residence at the target site, and improved cellular uptake and intracellular stability are some of the major reasons for greater emphasis on the use of nanoparticulate delivery systems. With nucleic acid-based therapeutic modalities, there is substantial need for the therapeutic molecules to be delivered to desired sub-cellular compartments in an efficient and reproducible manner **(9).**he use of stimuli-responsive nanocarriers offers an interesting opportunity for drug and gene delivery where the delivery system becomes an active participant, rather than passive vehicle, in the optimization of therapy. Several families of molecular assemblies are employed as stimuli-responsive

nanocarriers for either passive or active targeting.

3.5 Ocular drug delivery

Various efforts in ocular drug delivery have been made to improve the bioavailability and to prolong the residence time of drugs applied topically onto the eye. eye is characterized by its complex structure and high resistance to foreign substances including drugs. The anterior and posterior segments of the eye, although in juxtaposition to each other, and very different in their anatomical and physiological aspects, function both independently and in tandem upon application of an ocular preparation. While it has been known since long that conventional topical formulations are amenable to application to the anterior portion, most of the applied dose is lost due to the defensive mechanism of the eye. Consequently, much concerted effort has been directed towards increased retention of the applied dose on the eye surface, with the premise that such increased retention will result in better therapeutic effect and lowered local and/or systemic effects. Since most drugs poorly penetrate the cornea, fulminating diseases of the posterior segment viz. vitreous, retina and choroid are required to be treated with either systemic administration or through intravitreal injections and vitreal implants. While therapy with systemic administration requires large doses due to strong blood-ocular tissue barrier, the other two routes are very invasive requiring skilled administration, ,and are associated with a high degree of risk, such as development of retinal detachment and endophthalmitis. Clearly there is a strong case in favor of formulating ocular delivery systems by focusing on improved ocular bioavailability and extended drug effect in targeted tissues. Prolonging pre-corneal residence time through viscosity enhancers and gels has only a limited value, because such liquid formulations are eliminated by the usual routes in the ocular domain. The highly sensitive corneal/conjuctival tissues towards penetration enhancers to maximize drug transport requires great caution in the selection of the enhancer. An alternative approach is to develop a drug delivery system that would circumvent the problems associated with the conventional systems, and provide the advantages of targeted delivery of drugs for extended periods of time and be patient-friendly. The latter requisite becomes more crucial in cases where the patient has to use the drug preparation throughout his life, e.g. in glaucoma. These advantages have been reported in the literature through the use of nanoparticles **(4).** Micro and nanoparticles for topical ophthalmic application are presently being researched based grossly on nanotechnology in which drugs can be administered as an eye drop. Also poorly water soluble or insoluble drugs can be successfully fabricated as effective systems to provide easy administration to ocular tissues and convenience to the patient as well as ophthalmologist to adjustment of dose and dosing frequency according to disease therapy. It has been found that biodegradable polymers can be combined with drugs in such a way that the drug is released into the eye in a very precise and controlled manner. The formulation of biodegradable polymers as colloidal systems holds significant promise for ophthalmic drug delivery, since it is suitable for poorly water-soluble drugs and would allow drop- By interaction with the glycoproteins of the cornea and conjunctiva they can form a precorneal depot resulting in a prolonged release of the bound drug. Nanoparticle formulations provide protection for agents susceptible to degradation or denaturation in region of harsh pH, and also prolong the duration of exposure of a new drug by increasing retention of the formulation through bioadhesion. In this context, more clinical studies are necessary to provide further information and insight into this new ophthalmic drug delivery system **(3).**

CONCLUSION

Applications of nanotechnology play a major role in diagnosis and therapy. Polymeric

micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. This was repeatedly demonstrated for a broad variety of drugs, mostly poorly soluble anti-cancer drugs, with micelles of different composition. In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature. Micelle specific targeting to required areas can be also achieved by attaching specific targeting ligand molecules (such as target-specific antibodies, transferrin or folate) to the micelle surface.

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