



Recent developments in nano micelles as drug delivery system

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ABSTRACT

Targeting of the drug directly to the cells, tissues, or organs with no impact on healthy cells is a challenge. In the current era, it's been made possible by therapeutic interventions. The novel drug delivery systems such as nano particulates, liposomes, aquasomes, phytosomes, dendrimers, nano sponges, nano micelles are developed. Nano micelles are developed for efficient targeting and are currently in trend as therapeutic carriers of water-insoluble drugs. Micelles are self-assembling Nano-sized colloidal particles with a hydrophobic core and hydrophilic shell. Among the micelle-forming compounds, amphiphilic copolymers, i.e., polymers consisting of hydrophobic block and hydrophilic block, are gaining increasing attention. Polymeric micelles possess high stability both *in vitro* and *in vivo* with good biocompatibility. Nano micelles are used widely because of the smaller size range of 10 to 100nm, with greater drug loading capacity. Advantages over other dosage forms include solubilization of poorly soluble drugs, sustained release, protection of drugs from degradation and metabolism. The property discussed includes CMC, size, and aggregation number, and stability. CMC is the minimum polymer concentration required for micelle formation. Aggregation number (N_{agg}) is the number of polymeric chains required to form micelles, and it ranges between tens to hundreds. Thermodynamic stability is based on size, the optical clarity of solution, viscosity, and surface tension. Kinetic stability accounts for micellar integrity. This review will discuss some recent trends in using micelles as pharmaceutical carriers such as to deliver drugs in conditions such as TB, cancer, ocular complications, etc.

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such as liposomes, microparticles, nano-associates, nanoparticle, and drug polymer-consolidates and polymeric micelles have been flourished. Nano micelles were developed for the first time in 1984 (Bader *et al.*, 1984). The polymers utilized to construct nano-micelles must be biodegradable. Extensively employed polymers counts poly (lactide), poly (propylene oxide) (PPO), poly (glycolide), poly (lactide-co-glycolide), and poly (ϵ -caprolactone) (PCL) among which ubiquitously utilized hydrophilic polymer being Polyethylene glycol (PEG).

INTRODUCTION

In order to ameliorate the discrete delivery of drugs with low therapeutic index, assorted drug carriers

Research on nano-micelles is propelling and is a provocative field of drug delivery for solubilization, stabilization, and delivery of definite drugs. Polymeric micelles possess attributes such as small size,

distinctive nanoscopic architecture, stability, compatibility with the drugs. The attributes of micelles scrutinized include critical micellization concentration (CMC), micellar aggregation number, structure, dimensions, and thermodynamic and kinetic stability. Polymeric micelles affiliate to the set of amphiphilic copolymers, which on clustering form nano-scale (1–200 nm) assemblage. The outer shell modulates in-vivo pharmacokinetic attributes, whilst inner core rehouses the drug, conserves stability, and drug delivery profile. The distinctiveness of the polymeric micelles is that they can encapsulate hydrophobic drugs in the core while the exterior can be refined correspondingly (Kwon and Okano, 1996; Cabral and Kataoka, 2014). They offer advantages such as facile composition, biocompatible, and considerable efficacy (Gong et al., 2012), porter for the abjectly-water soluble medication in their hydrophobic core (Zhang et al., 2014) and target specificity (Mohamed et al., 2014). Nano micelles are expensive and provide rise to toxicity issues (Amirmahani et al., 2017).

Requisites for the formulation of Nano micell

Polymers

(Vaishya et al., 2014) Table 1 depicts the polymers used in the formulation of nano micelles.

Approaches for the development of nano micelles

By contemplating the physical and chemical attributes of the polymer chain length and monomer features, nano micelles are composed in two ways,

1. Direct dissolution approach

Employed for hydrophobic block copolymers like block copolymers of poly (butyl acrylate) and poloxamers (Garnier and Laschewsky, 2006). Figure 1 describes the direct dissolution technique employed in the preparation of nano micelles.

2. Solvent casting approach

Methodologies include dialysis, o/w emulsion method, solution casting, and freeze-drying.

Dialysis

Principle: Application of high boiling point and the use of water-soluble organic solvents. Dimethylsulfoxide (DMSO) is a solvent of choice. Figure 2 shows the dialysis technique wherein the mixture is charged into a chemical analysis membrane bag for dialysis averse to water for a minimum period of 12hr with successive water substitution at a definite period of time. Evaporation of organic solvent entails the evolution of drug enriched micelles.

Constraints include drug mislaying and weak potency of encapsulation.

Oil in water emulsion methodology

Drug and copolymer are solubilized in oil miscible liquids along with water for entrapment. Vaporization of organic solvent on stirring incites evolution of hydrophobic drug entrapped nano micelle (La et al., 1996). Figure 3 shows o/w emulsion method involved in preparing nano micelles (Jones and Leroux, 1999).

Solution casting approach

(Cholkar et al., 2016, 2015a,b, 2014). Figure 4 illustrates the solution casting approach where redispersion of thin-film yields nano micelles (Cagel et al., 2017).

Freeze-drying / Lyophilisation approach

Single pace operation of yielding micelles where the therapeutic entity and copolymers are solubilised in tertiary-butanol together with lyophilized to obtain fine ice crystals. Sublimation of these crystals, as shown in Figure 5, generates freeze-thawed cake, which upon rehydration yields drug-stacked nanomicelles (Leroux, 2003).

Recent Developments

Ocular Drug Delivery

Nano micelles can be used to deliver drug intraocularly to improve corneal permeability and improve the ocular bioavailability. Table 2 indicates the advancements in the treatment of ocular disorders along with the polymers used.

Cancer

Gene therapy

Gene therapy comprises of nucleic acid – pluronic polyplex complex that exhibits improved stability by encapsulation of gene rather than adaptation chemically, thus defending against serum degradation (Tiwari et al., 2012; Felber et al., 2012). Mode of action is by clathrin-mediated endocytosis.

Glioma

Glioma is the recurrent and fatal tumour of the brain, and the rate of prognosis is poor (Hervey-Jumper et al., 2015). Quercetin nanomicelles were used in the treatment of glioma. Mechanism of action is by hindering the expression of the mutant p53 gene (Xavier et al., 2011) and elevating the rate of apoptosis in glioma affected cells (Siegelin et al., 2009). Quercetin loaded nanomicelles were composed by the solvent- evaporation technique and analyzed by HPLC (Wang et al., 2016).

Melanoma

Clotrimazole (CLT) loaded nanomicelles are used in the treatment of melanoma and acts on calcium, potassium channel, and apoptosis (Kaur et al.,

Table 1: Polymers used in the formulation of nano micelles

Polymers	Curative agent	Size
Peo-ppo-peo	Lacz gene contained in plasmid dna	155 ± 44 nm
PEG 40 stearate	Cyclosporine A	200 nm
Sympatene AS	Cyclosporine A	9.7 ± 0.05 nm
Sympatene AS and Sympatene ACS	Cyclosporine A	9 – 12 nm
Pluronic F127 with chitosan	Dexamethasone	25.4 – 28.7 nm
Quaternary ammonium palmito-glycol chitosan	Prednisolone	10 – 100 nm

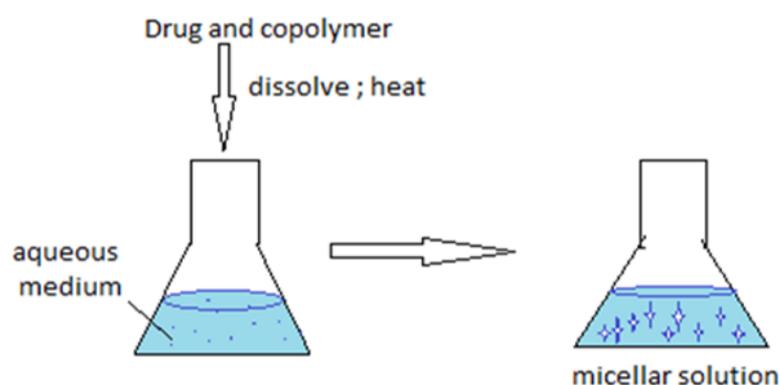
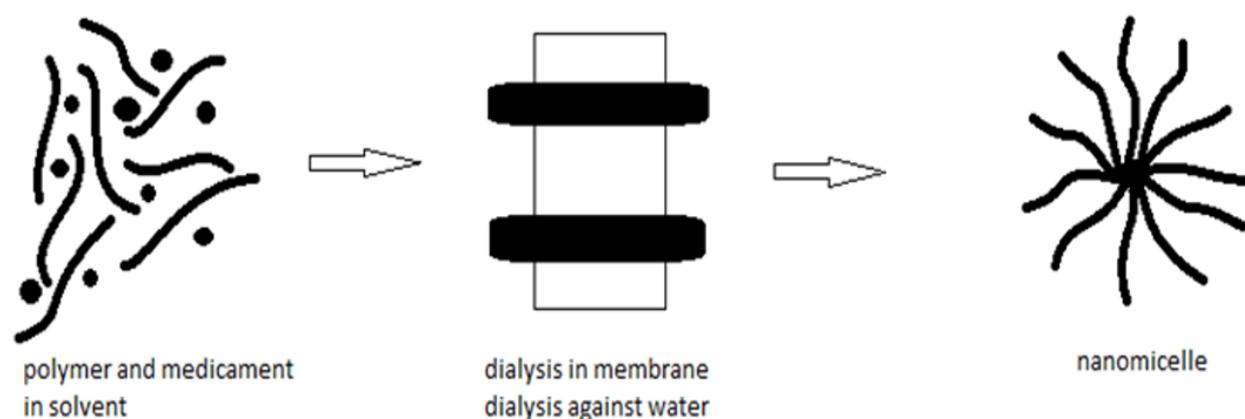
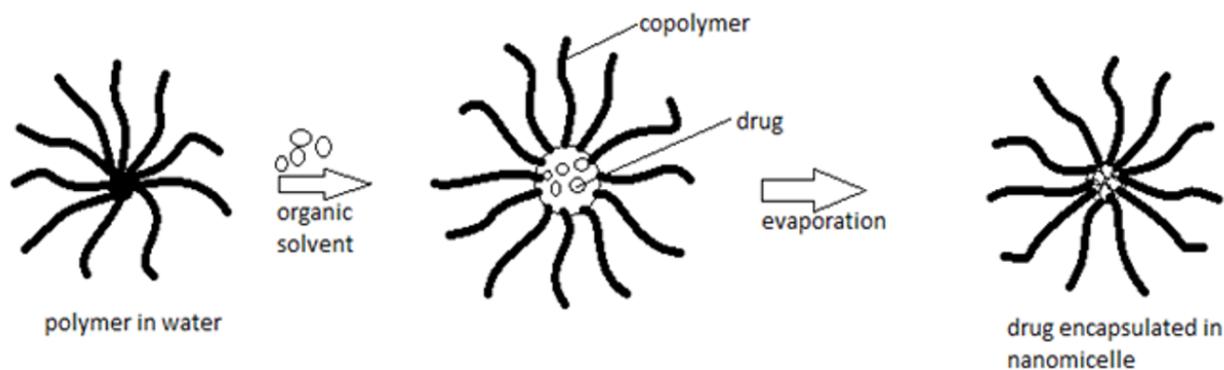
**Figure 1: Direct dissolution approach for the preparation of nano micelles****Figure 2: Dialysis technique for the preparation of nano micelles where in polymers and drugs are passed through the dialysis membrane.****Figure 3: (o/w emulsion method) depicts the method involved in the preparation of nano micelles**

Table 2: Recent developments in nano micelles as drug delivery systems used to deliver a drug into the eyes

Polymer or surfactant	Medicament	Size domain	Observation
Pluronicpolymer	Drug-Pilocarpine	23.3±0.5nm in water,30.3 ±0.3nm in 7.4 pH buffer	63.9% raise in Area under the curve alongst vital protracted miotic activity (Pepić et al., 2004).
Poloxamine (tetronic T1107)	Alpha tocopherol-drug	30.5-39.5nm	Nano micelles remained firm for days under 3-4°C (Ribeiro et al., 2013).
Poloxamine (tetronic T908, T1107, t1307)	Ethoxzolamide	Several faceted dispensation	Tuneable medicinal substance delivery profile attained by variegated nano micelle organization (Ribeiro et al., 2012).
m-Polyethyleneglycol+ hex poly(lactic acid)	Cyclosporine A	53±2nm	Improved penetrability across cornea (Tommaso et al., 2011, 2010, 2012a,b).
mPEG - PDLLA	Pirezepine HCl	PEG/PLA size (nm) 80/20 152.5 50/50 89.6	Intraocular drug extent inflated in rabbit scruti-nization – in vitro biocompatibility review on topical introduction (Tu et al., 2007).
Pluronic F127 with chitosan	Dexamethasone	25.4 – 28.9nm	Remarkable pharmacological reciprocation on instillation (Pepić et al., 2010).

Table 3: Developments been made in nano micelles for treating tuberculosis

Researchers	Drug	Polymer used	Evaluation
(Kumar et al., 2013)	Rifampicin	Stearic acid and the amine group of branched polyethylenimine adsorbed by covalent bond	The average size range of 218nm zeta potential = 16.7mv Drug loading efficiency = 99% Drug release = 85% for 24 hr In vitro cytotoxicity studies to check biocompatibility in which 80% of cells out of the population was found viable.
(Abdulla et al., 2010)	Rifampicin	Block copolymer of polyethylene oxide complexed withdistearoyl phosphatidyl-ethanolamine	Effectiveness of encapsulation was 83.5 – 103.9%

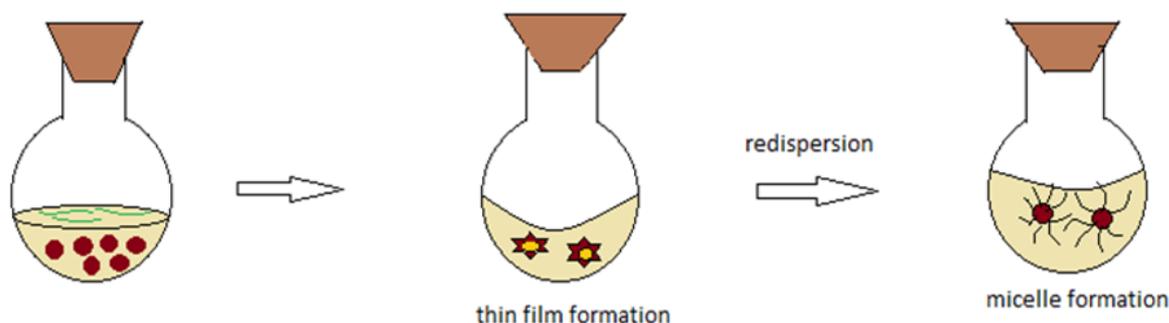


Figure 4: solution casting approach in which the thin film formation by polymer leads to micelle formation by redispersion



Figure 5: lyophilization technique where the solution is freeze-dried to obtain nano micelles which needs reconstitution

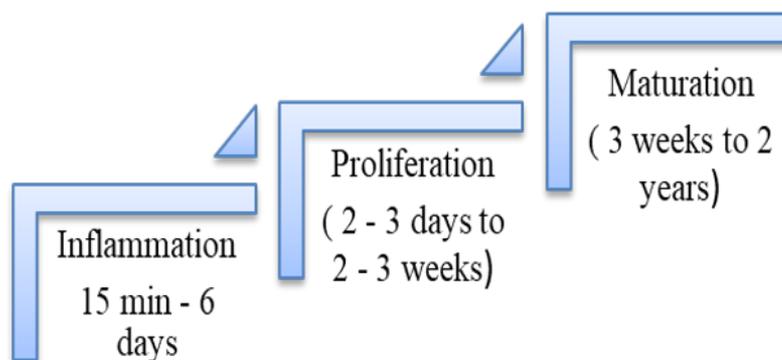


Figure 6: Three phases of wound healing

2018).

Increased tumour vaccination by in situ nano micelle - provoking microneedles

Resiquimod (R848) nano micelles are proven to increase the tumour vaccination *in situ*. Resiquimod is an imidazoquinoline derivative that falls under the category of an immunomodulator. Resiquimod exhibits specificity for a person’s toll-like receptor 7 and 8 conveyed on dendritic cells, macrophages, NK cells, and B-lymphocytes (Kim *et al.*, 2018).

Atherosclerosis

Iron oxide super paramagnetic Nano micelles, a de-novo magnetic probe, is the method of treatment employed.

Principle: Magnetic resonance imaging (MRI) (Groult *et al.*, 2014) The Nano probes act by passive accumulation in the process of engulfment

by the macrophages (Weissleder *et al.*, 2014).

Criteria for targeting atherosclerotic plaques,

1. PC-stabilised Nano micelle protein corona of ApoB-100, a protein responsible for plaque development (Shapiro and Fazio, 2017)
2. A greater degree of PC-PLC expression in atherosclerotic lesions
3. De-esterification amidst PC glycerol and phosphate moieties, which are mediated by natural PC-PLC (Exton, 1994), 89Zr, a radioelement, helps in the detection of the amount of Nano micelles in target tissues (Lechuga-Vieco *et al.*, 2018).

Nano micelle-in-nano fibre system providing long term dual controlled release in antibacterial medical dressings

Wound healing is a tidy clinical condition in which tissues respond to injury and self heals and can be disserted into 3 phases, as shown in Figure 6 (Lechuga-Vieco *et al.*, 2018; Fumakia and Ho, 2016; Ghavaminejad *et al.*, 2015).

Pluronic F127 micellar solution was prepared by the film dispersion hydration technique. AMX 40mg and pluronic F127 200mg were weighed and dissolved in 30ml methanol contained in 100ml flask, which was stirred up to 4hrs until a homogenous solution was formed. Eliminate excess organic solvent using a rotary evaporator maintained at 15rpm, 60°C to form a thin film. Reconstitute the film by 10ml deionized water and stir at 100rpm for 1.5hr and perform membrane filtration. Transfer this micellar solution to 5ml vials containing 2%w/w mannitol (lyoprotectant) and subject for freeze-drying. The next step is coaxial electrospinning maintained at 16kv voltage, 25±3°C, and 55±5% RH in order to enclose drug-carrying nano micelles in Nano fibres. Collect the fibres and vacuum dry for 24 hours.

Evaluation of nano micelle-in-nano fibre system,

1. ANOVA is employed for statistical analysis.
2. Encapsulation efficiency
3. Percentage of drug loading capacity
4. Antibacterial test (Yu *et al.*, 2019)

Osteoporosis

Osteoporosis is a bone disorder characterized by diminished bone formation, thus condensing the period of survival of bone cells (Riggs and Hartmann, 2003; Riggs *et al.*, 2002). This is caused by estrogenic deficiency. Raloxifene HCl (RH) nano micelles can be used to treat osteoporosis. The nano micelles were prepared using the Ipegal and condensed form of poly oxythylene. Nonyl-phenyl ether (C95H184O41) was used as a non-ionic, non-denaturing surfactant with HLB 17, relative mass 1981.99. Raloxifene HCl is a selective oestrogen-receptor modulator (SERM) - non-steroidal agonist (Hochner-Celnikier, 1999; Lewis and Jordan, 2005).

Tuberculosis

Tuberculosis is an infectious disease affecting the lungs. It is caused by Mycobacterium tuberculosis. The symptoms of TB may include weight loss, loss of appetite, coughing up blood or mucus, fatigue, fever, and night sweats. Nanomicelles of Rifampicin plays an important role in the treatment of tuberculosis. Table 3 shows the research work in Rifampicin nano micelles been made in the treatment of tuberculosis.

Anti-fungal activity

Amphoterecin B nanomicelles were prepared using polyethyleneoxide-b-p [6-HHA] and Polyethylene-b-p [HASA]. Analysed by chromatographic technique -HPLC (Adams *et al.*, 2003).

Antibiotics

Nanomicelles of Thiamphenicol (TAP) and its fluorinated derivative, florfenicol (FF), are employed in veterinary practice (Tao *et al.*, 2014). Polymers used was Chitosan-stearic acid (CS-SA), which serves as a carrier for the delivery of antibiotics.

CONCLUSIONS

Nanotechnology, a sophisticated area of great value and perspective, deals with the control, manipulation, synthesis, and biofunctionalization of structures/devices at the nanometre scale. Several pharmaceutical applications of Nano micelles are based on their specific physicochemical and biological properties regarding size (diameter), surface (porosity), pH, solubility, complexation (binding/ ligand capacity), bioavailability, toxicity, and cellular and molecular effects. Polymers play an important role in designing of nano micelles due to their widespread availability, renewability, low cost, versatility, biocompatibility, biodegradability, and lack of toxicity. Direct dissolution and solvent casting (freeze-drying, solution casting, and emulsification) are the main mechanisms applicable for the preparation of Nano micelles. In recent decades, interdisciplinary researches and instantaneous development of nanotechnology for diagnosis (imaging), drug delivery, and targeting of extremely serious disorders, such as cancer, Parkinson and Alzheimer diseases, chronic inflammations, ocular dysfunctions, and microbial/viral infections.

Current research is also focused on developing modern Nanosystems, including noisome, polymeric nanoparticles, Nanocomposite (colloidal) hydrogels, polymeric micelles, dendrimers, aptamers, capsosomes, Nano needles, molecularly imprinted polymers, stimuli-responsive polymers, therapeutic polymers (polymer-drug conjugates), and polymeric, artificial cells.

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