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A REVIEW ON IMPACT OF NANOMICELLE FOR OCULAR DRUG DELIVERY SYSTEM

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Amphiphilic block copolymer micelles, Drug delivery vehicles, Cross - linking, Polymeric nano-micelle

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ABSTRACT: In this article, we have reviewed several features of nanomicelles relating to their general properties, preparation and characterization techniques, and their applications in the areas of ocular drug delivery system. Nanomicelles can be rummage-sale as 'smart drug carriers' for targeting certain areas of the eye by making them stimuli-sensitive or by attachment of a specific ligand molecule onto their surface. In present scenario, the major challenge for the researchers is ocular drug delivery system as eye is the most sensitive organ in our body. Topical eye drop is the best suited way for delivery of drugs for the treatment of anterior segment of the eye. Delivery of the drugs to the targeted areas is restricted by the various barriers and even the amount instilled do not remain there for a long duration of time. In the past many years scientist are working on providing the masses the way for delivering drug in a novel, safe and patience compliance manner. The aided the basic delivery by providing the administration through various permeation enhancers and viscosity modifiers. Widely studied subjects in nanoscience technology is related to the conception of supramolecular architectures with well-defined structures and functionalities. Nanomicelles have congregated considerable attention in the field of drug and ocular drug delivery due to their exceptional biocompatibility, low toxicity, enhanced blood circulation time.

INTRODUCTION: Any vision intimidating ocular diseases such as age-related macular degeneration (AMD), diabetic retinopathy, glaucoma, and proliferative vitreoretinopathy may affect in blindness [1]. Ocular drug delivery specifically to the intraocular tissues remains a thought-provoking task due to the incidence of various physiological barriers. Even so, recent progressions in the field of nanomicelle-based novel drug delivery system could fulfil these unmet requirements [2].

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Nanomicelle consists of amphiphilic molecules that self-assemble in aqueous media to form organized supramolecular structures. Micelles can be prepared in various sizes (10-1000 nm) and shapes conditional on the molecular weights of the core and corona forming blocks. Nanomicelle have been an attractive carrier for their potential to solubilize hydrophobic molecules in aqueous solution [3].

In addition, small size in nanometer range and highly adjustable surface properties have been reported to be advantageous in ocular drug delivery. In this review, various factors influencing rationale design of nanomicelle formulation and disposition are discussed along with case studies. Despite the progress in the field, influence of various properties of nanomicelle such as size, shape, surface charge, rigidity of structure on ocular disposition need to be studied in further

details to develop an efficient nanocarrier system [4]. The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment.

Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.

All forms of conjunctivitis - including bacterial, viral, allergic and other types - involve inflammation of the transparent, mucous membrane covering the white part of the eye. Effective intraocular drug delivery poses a major challenge due to the presence of various elimination mechanisms and physiological barriers that result in low ocular bioavailability after topical application. Over the past decades, polymeric micelles have emerged as one of the most promising drug delivery platforms for the management of ocular diseases affecting the anterior (dry eye syndrome) and posterior (age-related macular degeneration, diabetic retinopathy and glaucoma) segments of the eye. Promising preclinical efficacy results from both *in-vitro* and *in-vivo* animal studies have led to their steady progression through clinical trials.

The cohesive nature of these polymeric micelles results in enhanced contact with the ocular surface while their small size allows better tissue penetration. Most importantly, being highly water soluble, these polymeric micelles generate clear aqueous solutions which allows easy application in the form of eye drops without any vision interference. Enhanced stability, larger cargo capacity, non-toxicity, ease of surface modification and controlled drug release are additional advantages with polymeric micelles [5].

Finally, simple and cost-effective fabrication techniques render their industrial acceptance relatively high.

This review summarizes structural frameworks, methods of preparation, physicochemical properties, patented inventions and recent advances of these micelles as effective carriers for ocular drug delivery highlighting their performance in preclinical studies.

Drug Absorption in the Eye: It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye and by other concomitant factors, for example:

- Drainage of the instilled solutions
- Lacrimation and tear turnover
- Metabolism
- Tear evaporation
- Non-productive absorption/adsorption
- Limited corneal area and poor corneal

The drainage of the administered dose via the nasolacrimal system into the nasopharynx and the gastrointestinal tract takes place when the volume of fluid in the eye exceeds the normal lacrimal volume of seven to 10 microliters. Thus, the portion of the instilled dose (one to two drops, corresponding to 50 - 100 microliters) that is not eliminated by spillage from the palpebral fissure is drained quickly and the contact time of the dose with the absorbing surfaces (cornea and sclera) is reduced to a maximum of two minutes [6].

The lacrimation and the physiological tear turnover (16% per minute in humans in normal conditions) can be stimulated and increased by the instillation even of mildly irritating solutions. The net result is a dilution of the applied medication and an acceleration of drug loss [7].

It is now definitively established that the rate at which instilled solutions are removed from the eye varies linearly with instilled volume. In other words, the larger the instilled volume, the more rapidly the instilled solution is drained from the precorneal area.

Novel Delivery Systems:

Nanomicelle: Micelles consists of amphiphilic molecules that, generally, self-assemble in aqueous media to form organized supramolecular structures. Micelles are formed in various size (10-1000 nm) and shapes (spherical, cylindrical, star-shaped, etc.) depending on the molecular weights of the core and corona forming blocks. The self-assembly takes place above acertain concentration, referred to as critical micelle concentration (CMC) [8].

The force driving the self-assembly and maintenance of supramolecular assembly is hydrophobic interactions of core forming blocks, for typical micellar structures. The corona-forming block is water soluble that renders micelles soluble in the aqueous phase. Taking the advantage of hydrophobic core, the nanocarriers can be utilized to enhance the water solubility of hydrophobic molecules.

Classification of Nanomicelle: Nanomicelles investigated for ODD thus far be divided into three broad categories, *i.e*.,

- Polymeric Nanomicelle
- Surfactant Nanomicelle
- Polyion Complex Nanomicelle

Polymeric Nanomicelle: Polymeric nanomicelle are formed by amphiphilic polymers with distinct hydrophobic and hydrophilic segments. The polymer self-assemble to form micelles in aqueous solution, where in water insoluble segment forms the core and hydrophilic segment forms the corona. In some cases, the self-assembly is not spontaneous and micelle formation is assisted by additional means, such as temperature [9].The self-assembly occurs above the CMC. The hydrophilic segments forming corona aid the solubilization of the entire supramolecular structure. Polymeric micelles are characterized by their low CMC in addition to excellent kinetic and thermodynamic stability in solution. Ideally, the polymers utilized to prepare nanomicelles should be biodegradable and/or biocompatible [10].

The most widely studied core-forming polymers are:

- poly(lactide)
- poly(propylene oxide) (PPO)
- poly(glycolide)
- poly(lactide-co-glycolide) and
- poly(ϵ-caprolactone) (PCL)
- Poly(ethylene glycol) (PEG)

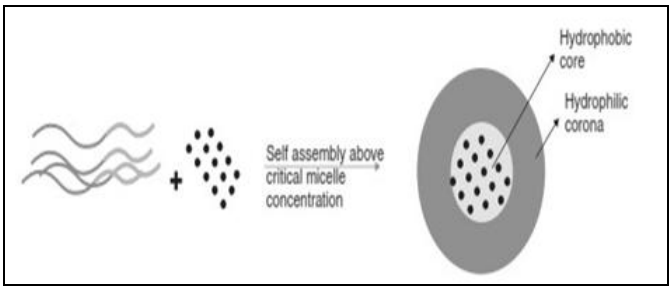

FIG. 1: SHOWING FORMATION OF POLYMERIC OR SURFACTANT NANOMICELLE

Surfactant Nanomicelle: Amphiphilic molecules having a hydrophilic head and hydrophobic tail is commonly referred to as surfactants. Hydrophilic head of surfactant molecules can be dipolar/ zwitterionic, charged or anionic/cationic or neutral /non-ionic [11].

Commonly used surfactants for nanomicellar formulation are:

- Sodium dodecyl sulphate (SDS, anionic surfactant)
- Dodecyl-trimethylammonium bromide (DTAB, cationic surfactant)
- Ethylene oxide (N-dodecyl; tetra, C12E4)
- Vitamin E TPGS [d-alpha tocopheryl polyethylene glycol (PEG) 1000 succinate]
- Octoxynol-40 (non-ionic surfactants)
- Dioctanoylphosphatidyl choline (zwitterionic surfactants)

A hydrophobic tail commonly comprises of a long chain hydrocarbon and rarely includes a halogenated/oxygenated, hydrocarbon/siloxane chain. Micelles are formed when surfactants are dissolved in water at a concentration above CMC [12]. A balance between intermolecular forces such as Vander Waal interactions, hydrogen bonding, hydrophobic, stearic and electrostatic interactions are vital for nanomicellar formulation. The shape of nanomicelle *i.e*. spherical, cylindrical or planar/ discs/bilayers depends on the non-covalent aggregation of surfactant monomers. Alteration in the chemical structure of surfactant and conditions such as surfactant concentration, pH, temperature, ionic strength may determine the shape and size of nanomicelle [13].

Poly-ionic Nanomicelle: Poly-ion complex (PIC) micelles have been widely investigated as nanocarrier system for gene and antigen oligonucleotide delivery. PIC micelles have been explored extensively for the delivery of ionic hydrophilic therapeutics. This special class of micelles is formed by electrostatic interactions between poly-ion copolymers (comprised of the neutral segment and ionic segment) and oppositely charged ionic species. The block copolymer is water soluble with very narrow poly dispersity. A neutral segment of the block copolymer is usually PEG, whereas the ionic segment is neutralized by oppositely charged species to form a hydrophobic core.

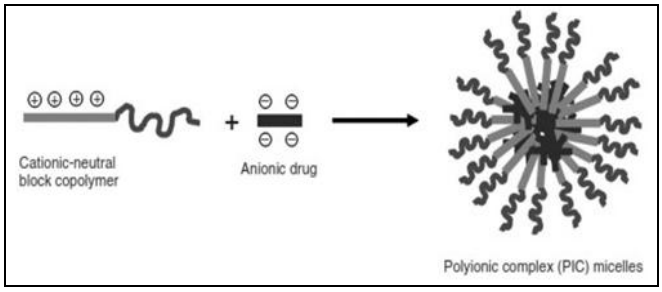

FIG. 2: SHOWING THE FORMATION OF PIC NANO-MICELLE

Method of Formation of Nano-micelle:

Prodrug Method: Synthesizing a prodrug of the drug of interest and encapsulating in a micelle is useful for sustained drug release. In this approach, a prodrug that is most compatible with the micelle forming amphiphilic molecule is desirable [14]. Prodrug release from the micelles and prodrug conversion to the drug are the two limiting processes controlling drug release in this approach. One such example is paclitaxel palmitate, a paclitaxel prodrug, which was synthesized and encapsulated in PEG-b-polycaprolactone (PEG-b-PCL) (Mw of PEG:5000, Mw of PCL: 10,500) micelles [15]. The mean diameter of these micelles was about 27 - 44 nm. The prodrug micelles released the prodrug over 14 days compared with 1-day release with the plain drug.

Drug Polymer Conjugate: This is one of the most effective ways to sustain drug release from a micellar delivery system. This approach typically involves forming a conjugate of the drug with the hydrophobic part of an amphiphilic polymer and then forming micelles out of this conjugate [16]. Such a formulation will add two steps for the release of the drug. First, the drug is released from the polymer through enzyme hydrolysis or other means of breakdown and second, the drug is released *via* diffusion of the drug out of the micelles, with the former typically being the rate-limiting step [17]. A major advantage of this method is that the drug remains in the micelle for a long period of time due to conjugation.

Novel Polymers: This is the most common approach used to prepare sustained release micelles. Polymers with very low CMC (< 0.1 µg/ml) can be used for prolonging the circulation time before the micelle degrades [18]. Upon intravenous injection, the micelles undergo dilution in the body. If the CMC of the micelles is high, the concentration of the polymer or surfactant falls below the CMC upon dilution and hence, the micelles dissociate [19]. Therefore, a higher concentration of the polymer or surfactant has to be used to prepare the micelles so that they withstand the dilution up to 5 L in the blood.

Block Copolymers with Lipids: Block copolymers between a polymer and a lipid are one useful approach in preparing micelles. It has been shown that increasing the length of the hydrophobic portion of a micelle will lead to a decrease in its CMC [20]. Lipids are more hydrophobic than most polymers and hence, a micelle made with a lipid as its hydrophobic part might lower the CMC. Hence, using fatty acyl chains as hydrophobic segments in an amphiphilic copolymer might be a useful approach. Di-stearoylphosphatidyl ethanolamine (DSPE) has been used as the hydrophobic block in a diblock copolymer with hydrophilic polyethylene oxide (PEO) to form 22 nm micelles.

Block Copolymer with Cyclodextrin: This involves non-covalent interactions between a macromolecular polymer, which works as a host, and a small polymer molecule, which works as a guest. One such attempt was made using alpha-cyclodextrins as the hydrophilic macromolecular host and PCL (Mw = 37,000) as the hydrophobic guest molecule [21]. Using this approach, supra-molecular polymeric micelles with a mean diameter of 30 nm were made.

Di-block Copolymer Micelle: Using a polymer that physically interacts with the drug can result in

drug retention and sustained release of the drug from such polymer micelles. If the drug can form hydrogen bonds with the core of the micelle, then the release obtained from the micelle will be much more sustained. In this, a polymer participates in hydrophobic interaction with the drug and can also sustain the release of the drug from the micelle [22]. If the polymer hydrophobically interacts with the drug, then the hydrophobic core of the micelle resists the migration of the drug from the core to the media, thus resulting in sustained drug release. This means that the release is affected not only by micelle properties but also by polymer and drug properties.

Tri-block Copolymer Micelle: Flower-like micelles can be formed with a tri-block copolymer with small hydrophobic ends and a long hydrophilic midsection. When dissolved in water, such polymer molecules assemble to form flower-like micellar structure. These flower-like micelles can dissolve the drug in the hydrophobic core and sustain drug release for long periods of time [23]. Sustained, the zero-order release has been reported using PLA-PEO-PLA (Mw of PEO = 8900 Da; Mw of PLA= 4100-6500 Da) triblock flower-like micelles (mean diameter of approximately 7-13 nm) for sulindac (20 days) and tetracaine (10 days).

Pluronics: Paclitaxel-loaded Pluronic micelles of 150 nm in diameter were prepared from Pluronic P105 polymer. The pharmacokinetics and bio distribution of paclitaxel was studied in rats following intravenous administration [24]. The half-life and AUC of the drug in micelle formulation were 4.0 and 2.2 fold higher, respectively, when compared with plain.

Uni-molecular Micelle: Formation of a uni-molecular micelle also helps sustain release of very fast-acting drugs. The uni-molecular micelle is made from a polymer that has several hydrophilic and hydrophobic portions and forms a single molecular micelle. Hence, by definition, uni-molecularmicelles do not have a clear CMC. Lipids and PEG like hydrophilic polymers can be conjugated to form such unimolecular micelles [25]. One such polymer is core (Laur) PEG, which, when formed into unimolecular micelles, prolongs the release of lidocaine to about 20 h from less than 10 h observed for the plain drug. The core (laur) PEG polymer consists of a core of lauroyl ester of mucic acid (19,000 Da) and a shell of mPEG-5000. The unimolecular micelles formed had a mean diameter of 50 nm [26].

Multi-arm Block Copolymers: Synthesizing multi -arm block copolymers can also be useful to overcome the stability problem of regular micelles. For instance, star-shaped or multi-armed micelles can be formed with an amphiphilic block copolymer with multiple hydrophilic blocks and a single hydrophobic block [27]. These polymers can form micelles if the number of arms is high enough. One such polymer is H40-PLA-mPEG (Mw = 108,516 Da; Mw = 148,678 Da). H40 is a polyol that contains 64 hydroxyl groups and is hydrophilic. This means that the multi-arm copolymer has two hydrophilic portions and one hydrophobic region. This polymer was used to form micelles containing 5-FU (5-fluorouracil). The micelles sustained 5-FU release for up to 80 h, unlike aplain drug, which was released completely in 4 h. The CMC of this polymer was found to be 4.5µg/ml and the mean diameter of the micelles was 74 nm [28].

Graft Polymers: Graft polymers have recently attracted significant attention in preparing micelles. Cellulose graft polymers can be used to form micelles for sustained drug release [29]. The cellulose portion of the polymer can be the hydrophilic part, with any hydrophobic segment conjugated to it to form an amphiphilic graft polymer [30]. Cellulose-g-PLLA (MW of cellulose = 1.2 × 10 of PLLA = 11,000 g/mol) polymer has been used for the sustained delivery of prednisone acetate. Delivery of prednisone acetate was sustained up to more than a week with the use of these micelles.

Oligopeptides: Polymers have some degree of toxicity even if they are biocompatible. Therefore, there is a need to synthesize materials that are more biocompatible for the preparation of micelles and incorporation of drugs. Oligopeptides can be very useful amphiphilic molecules for the preparation of micelles [31]. Hydrophobic residues, such as alanine, can be used to synthesize the hydrophobic block and hydrophilic residues like histidine or lysine can be used to synthesize the hydrophilic block. Such molecules can be used as amphiphilic molecules to formulate micelles.

Reverse Micelles: Reverse micelles are especially useful for administration in oily vehicles. Usually, the nutrients required for comatose patients are given as oily injections. Moreover, USP injections of steroids can also be made as oily injections. Reverse micelles can prove to be useful for the co-administration of hydrophilic drugs in such injections [32]. Some biocompatible oils are also used as vehicles for oral delivery. Thus, reverse micelles may be useful in the oral delivery of some drugs by dispersion of micelles in oily vehicles. Reverse micelles may be particularly useful for protein delivery.

Multi-layer Micelle with Layer by Layer Assembly: Multi-layer micelle assembly can be used to achieve the greater sustained release of drug frommicelles than any other techniques. Micelles can be formed from an H-bond acceptor and any bond donor can be added to the micellar shell [33]. Then, the micelles can be arranged layer by layer on a support to form a microsized film containing several layers of drug-loaded micelles. The H bonding can be tailored to be broken under desired conditions to release the micelles.

Reverse Thermo Responsive Polymers: These polymers have special properties. They exist as a solid at room temperature but at higher temperatures such as the body temperature, these polymers form gel-like structures. This property can be used to form micelles, which will form a gel-like structure at body temperature [34]. These structures can lock the drug in the core, resulting in a sustained release of the drug. These polymers, however, are complicated to synthesize and very long release times have not been reported.

Micelles Coated on Metal Stents: Metallic stents are in use for patients suffering from cardiovascular problems. If such patients need to be given medication, the stents can be a good source for drug release. Drug-eluting stents have been long investigated for the treatment of lesions and other cardiovascular problems [35]. Drug-loaded micelles can potentially be coated on stents to achieve sustained drug release in patients. In this approach, the stent will perform the function it is supposed to perform, that is, widening the coronary arteries. Second, such a coated stent will release the drug of choice into circulation or arterial walls in a sustained manner. The stents can be appropriately heparinized and chemically treated so that they last for prolonged periods.

Advantages of Nanomicelle:

- Maintenance of optimum therapeutic concentration of drug in the blood or cell [36].
- Elimination of frequent dosing and better patient compliance.
- High drug encapsulation capability, ease of preparation, small size and hydrophilic nanomicellar corona generating an aqueous solution [37].
- The micellar formulation can enhance the bioavailability of the therapeutic drugs in ocular tissues, suggesting better therapeutic outcomes.
- Nanocarriers can be used to specifically target the small pores, lower pH, and higher temperature of tumors, they have the potential to lower the toxicity of many chemotherapy drugs [38].
- Nanomicelles offer unique advantages such as simplicity, ease of manufacturing and reproducibility at small and bulk scale.

Disadvantages of Nanomicelle:

- Despite extensive expertise with nanomicelle, they are not broadly used in commercial products, mainly because there is the possibility that:
- Drug loaded nanomicellar formulations encounter rapid tear dilution upon their topical administration [39].
- Premature drug release and lack of sustained/controlled release [40].
- Costly as compared to other formulations [11].
- Poor scale-up for the purposes of manu-facturing.
- In the case of change of therapy the new drug cannot be given the next moment, we have to wait for the complete removal of the previous dose that is instilled [22].
- The eye being one of the most sensitive parts of the body cannot be given any formulation without proper testing and evaluation so this makes it a quiet hectic job as acharacterization of nanomicelle is a very tough task [18].

Socio-economic Advantages:

- Polymeric nanomicelle composed amphiphilic block or grafted copolymers have shown much advantage in drug delivery systems and attracted lots of interest due to its solubilisation low toxicity a long circulation passive targeting against tumor.
- Surfactant and polymeric micellar nanocarriers provide an amendable means to improve drug solubilisation, develop clear aqueous formulations and deliver drugs to anterior and posterior ocular tissues.
- Nanomicelle have played a major role in alzheimer's disease through interaction with beta-amyloid and mitigation of beta sheet formation, aggregation and neurotoxicity.
- Mixed nanomicelle with phospholipid have increased drug absorption.
- Nanomicelle aided dual drug delivery for the treatment of cytotoxicity.
- Nanomicelle are used for providing efficient antigen delivery for helping the body to face resistance through PIC.
- Improved oral delivery of drugs like glycyrrhizin.
- Nanomicelle are used for preparation of cyclodextrin copolymers for biomedical imaging.
- Nanomicelle are used for the treatment for lung cancer.
- Nanomicelle are used for treatment of major disorders of eye like AMD, diabetic retinopathy and glaucoma.
- High drug loading through nanomicelle for drug delivery to brain mainly for steroids is rendered.
- Major advantage is through reverse nanomicelle technology of imbibing water molecule in lipid membrane.

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