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Nanomicelles: an emerging platform for drug delivery to the eye

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Delivery of pharmacologically active drugs at therapeutic concentrations to the target tissues with minimal/no toxicity to the healthy ocular tissues still remains a significant challenge for ocular pharmacologists. The complex anatomy and physiology of the eye restricts drug entry to the desired site of action, thus rendering it a highly protected organ [1]. Furthermore, existence of static and dynamic barriers, including the lipophilic corneal epithelium, hydrophilic corneal and scleral stroma, conjunctival lymphatics, choroidal vasculature and blood–ocular barriers, also pose a significant challenge for ocular drug absorption [2,3].

Topical administration (eye drops) is the most preferred, convenient and patient-compliant route of drug administration for treating ophthalmic disorders. Although highly desirable, ocular drug availability following topical drop instillation is very low. Several protective mechanisms severely limit ocular drug absorption. Such constraints to topical ocular drug-delivery include: high-resistance by drug absorption barriers, offered primarily by the corneal and conjunctival layers; rapid elimination from the cul-desac due to drainage of the instilled solutions; lacrimation, blinking and tear turnover; binding by the lacrimal proteins; metabolism of pharmacologically active drug by enzymes present in tears; limited corneal space and poor corneal permeability; and finally, removal of the therapeutic agent by highly vascularized ocular tissues such as conjunctiva, choroid, uveal tract and inner retina [4,5]. Topical administration is advantageous because of its ease of application, minimal risk of infection compared with implantation (during surgery) or any injection-based systems and their suitability to adjust dose [6]. Although a relatively small percentage (typically less than 5%) of topically applied dose reaches the anterior ocular tissues, topical formulations can be highly effective with high drug concentrations arising from highly soluble drug substances.

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Currently, many research groups in academia and industry are focused on developing topical formulations that could enable drug delivery to the anterior and particularly the posterior segments (back-of-the-eye). Currently, the treatment of posterior-segment diseases is significantly limited due to difficulties in delivering therapeutic drug concentrations to target tissues in the posterior chamber. Drug delivery into the vitreous by intravitreal injections is the current mode of treatment for these diseases. However, such a regimen is not patient compliant. Moreover, it is largely associated with a growing risk of tissue damage, infection and serious adverse effects. Therefore, a successful topical formulation enabling drug delivery to the front- and back-of-the-eye would redefine ocular drug delivery and provide opportunities to address large markets, including dry eye syndrome, glaucoma, age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy and other inherited retinal degenerative diseases [1,7–11]. Several drugs are currently available for effective treatment of ocular disorders. However, these potential therapeutic agents are often dropped from the initial screening portfolio due to failure in developing a suitable and efficient delivery system. Since many agents are very hydrophobic, the feasibility of generating aqueous formulations that can provide therapeutic levels in the ocular tissues is reduced. To overcome these issues, nanotechnology must make significant advances by offering smart drug-delivery systems such as nanomicelles for ocular delivery.

Nanomicelles are self-assembling nanosized (usually with particle size within a range of 10 to 100 nm) colloidal dispersions with a hydrophobic core and hydrophilic shell [12]. These are currently used as pharmaceutical carriers for solubilizing hydrophobic drugs. Hydrophobicity is considered a major limiting factor for formulating clear aqueous solutions with concentrations suff icient to attain therapeutic levels in ocular tissues. Nanomicelles solubilize hydrophobic drugs by entrapping the drugs within a mixed micellar hydrophobic core with a corona composed of hydrophilic chains extending outwards, resulting in a clear aqueous formulation [6]. Nanomicelles serve as excellent pharmaceutical carriers because of their ability to prevent or minimize drug degradation, lower adverse side effects and improve drug permeation through ocular epithelia with minimal or no irritation, ultimately leading to enhanced ocular bioavailability [3].

One such technology has been developed in our laboratory in association with Lux Biosciences Inc. It is a novel nanomicellar formulation of voclosporin, a calcineurin inhibitor, for the treatment of dry eye syndrome. The resulting mixed nanomicelles are formed from the combination of two non-ionic surfactants, D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) co-stabilized with octyl phenol ethoxylate (octoxynol-40) in a defined ratio [6]. The micelles were found to be very small in size (in nanometer range), and the resulting aqueous solution is completely homogeneous and perfectly clear in appearance. A noteworthy advancement of this formulation is that relatively high concentrations of drug could be achieved, such as, 0.2% formulation for the highly hydrophobic drug voclosporin. Besides establishing high drug levels locally, these nanomicelles are stable over prolonged periods of time when compared with the classic emulsions (a milky fluidic appearance). Topical instillation of this formulation achieved drug amounts higher than the therapeutic levels in the retina and choroid in the back-of-the-eye. An interesting observation was that no drug was detected in the lens or vitreous. This distribution pattern is absolutely necessary to circumvent the development of major side

effects such as cataract formation and intraocular pressure elevation, which often leads to discontinuation of the therapy. The nanomicellar solutions were well tolerated in patients and provide higher uptake in ocular tissues and glands.

Upon topical administration, therapeutic molecules can reach the back-of-the-eye by two pathways: the intraocular route through the cornea, aqueous humor, lens, vitreous humor and retina; and/or the conjunctival/scleral route around the conjunctiva, through the sclera, choroid and retina [11]. Intraocular delivery is often unsuccessful with hydrophobic drugs such as voclosporin and dexamethasone because the hydrophilic stroma can act as a rate-limiting barrier for transcorneal permeation [13]. Furthermore, the flow of aqueous humor in the anterior and posterior chambers in opposite directions may impede drug transport from the aqueous humor to the lens and, consequently, through the lens zonular spaces to the vitreous humor, thus rendering this pathway unfavorable. Alternatively, the conjunctival/scleral pathway appears to be more viable for delivery of hydrophilic drugs to the back-of-the-eye by facilitating passive diffusion through the scleral water channels/pores. Hydrophobic drugs encapsulated in nanomicelles form spherical structures of amphiphilic molecules in aqueous phase [14]. Hydrophilic corona facilitates permeation of these micellar nanocarriers through scleral aqueous channels/ pores (ranging from 30 to 300 nm in size) [15]. Subsequently, nanomicelles can endocytose onto the basolateral side of the retinal pigment epithelium. The therapeutic cargo is released inside the cell after vesicular fusion with the cell membrane. During transport, the corona of nanomicelles being hydrophilic may be able to evade drug washout into the systemic circulation by conjunctival/choroidal blood vessels and lymphatics.

In conclusion, nanomicelles possess the advantages of having a small size, exhibiting low toxicity, increasing the solubility of hydrophobic drugs and achieving therapeutic concentrations. The nanomicellar drug-delivery platform appears to be a potential pharmaceutical carrier for topical administration of hydrophobic drugs. Moreover, this technology can be highly patient compliant and may enable non-invasive drug delivery to back-of-the-eye disorders such as age-related macular degeneration, diabetic retinopathy, diabetic macular edema and posterior uveitis. It is highly anticipated that nanomicelles as potential drug-delivery systems may receive US FDA approval for human use in the near future. However, substantial progress still needs to be made in this field to achieve sustained drug release from the micelles relative to other larger particulate systems such as nanoparticles, microparticles and liposomes.

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Biographies

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