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Review article

Drug-loaded nanocarriers for back-of-the-eye diseases- formulation limitations

Yoav Hamdi [a], Frederic Lallemand [b], Simon Benita [a, *]

[a] The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University, Jerusalem, Israel
[b] Santen Pharmaceutical Co. Ltd., France

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ABSTRACT

The main therapeutic advances in ophthalmology have been made in diseases affecting the posterior eye segment that are presently increasing and can lead to partial or complete blindness if untreated. Therapy is based on efficient hydrophilic macromolecules which can only be injected in the vitreous every month. However, frequent intravitreal injections have been associated with injection-related adverse events such as retinal detachment and endophthalmitis. Many intravitreal formulations based on liposomes, nanoemulsions and nanoparticles have been proposed to sustain drug release for a prolonged period of time, thereby alleviating repeated injections which otherwise exacerbate the clinical condition. Despite extensive efforts and significant investments, there is still no nanodelivery system in clinical trials even in the early stages for such a purpose. We will focus on three major obstacles; the limitation of the drug dose imposed by the small volume required to be injected in the vitreous (50 μl), the drug loading capacity of the nanocarriers, and the complexity of the industrial production of the nanocarriers. New therapies have appeared but there is still a lot of room for improvement as several unmet medical needs prevail and need to be addressed in order to ameliorate efficacy, safety and usability of these treatments.

1. Introduction

The rising demand for therapies and treatments for eye disorders and diseases is causing the ophthalmic drug market to rapidly expand. Being no longer a niche market it is predicted that the overall world market for ophthalmic drugs will reach $22 billion in 2015 and will continue to rise significantly [1]. There is an increase in prevalence of eye disorders due to ageing of the population, and the incidence increase in diabetes and obesity leading to a high socio-economical burden [2]. Despite the relative direct access to the eye, it is not easy to treat eye diseases because it is a privileged organ and as such it is highly protected by biological barriers which impede the passage of drugs, either dissolved or dispersed in liquid formulations, to be instilled on the eye irrespective of the targeted tissue. Depending on the location of the ocular pathologies, drugs either need to be retained on the cornea and/or conjunctiva or cross these barriers to reach the internal structures of the eye. Therefore, different therapeutic and delivery strategies are being adopted depending on whether the drug needs to reach the anterior segment of the eye to treat ocular infections, inflammations, dry eye syndrome, and glaucoma or the posterior segment to treat ocular infections, inflammation, age-related macular degeneration (AMD) and retinal disorders. Despite the barriers and hurdles such as the rapid renewal rate of the outer layers of the lachrymal fluid (1–3 μl/min) together with the blinking reflex which severely limits the residence time of drugs in the precorneal space (<1 min) rendering the ocular bioavailability of the instilled drugs very poor with less than 5% of the instilled drug dose [3], therapeutic progress has been made in ocular diseases of the anterior segment. Such progress was rendered possible thanks to the emergence of nanotechnology which proposed ingenious miniscule delivery systems specifically designed to overcome the permeability drawbacks imposed by eye-associated anatomical and physiological barriers.

* Corresponding author.
E-mail address: simonb@ekmd.huji.ac.il (S. Benita).

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Indeed, many ocular nanocarriers (liposomes, nanoemulsions and nanoparticles) exhibit the capacity of transporting a multitude of drugs, mostly lipophilic and in some cases also hydrophilic including macromolecules. These nanocarriers can protect labile drugs from degradation and increase the residence time of the active molecules on the ocular surface by strengthening their interactions with the corneal and conjunctival epithelia resulting in a marked improvement of their ocular bioavailability [4–7]. Unfortunately, such nanodelivery systems have not yet facilitated the transport of hydrophilic macromolecules from the anterior to the posterior segment of the eye. For the time being, the only therapeutic possibility is to inject the macromolecule formulations into the vitreous to elicit a positive and beneficial outcome.

1.1. Therapeutic advances in the anterior eye segment diseases using nano-delivery systems

It has recently been shown and reviewed that specific developed nanocarriers can interact with the ocular mucosa, thereby increasing the retention time of the associated drug onto the eye, as well as its permeability across the corneal and conjunctival epithelium [8]. The readers are referred to a comprehensive review that comparatively analyzes the mechanism of action and specific potential of the most studied nano drug-delivery carriers. In addition, the authors present the success achieved using a number of nanotherapies for the treatment of the most prevalent ocular pathologies, such as infections, inflammation, dry eye, glaucoma, and retinopathies [9]. It is interesting to note according to Reimondez-Troitino and colleagues [10] that most of the marketed formulations are drug-free nanoemulsions that have been approved for the treatment of dry eye. Drug-free liposomal eye sprays are also commercially available for dry-eye therapy including TearMist® (Schalcon), DryEyesMist® (Schalcon) and Optix-Actimist®(Optima Pharmazeutische). As yet, there is no commercial nanoparticle (NP)-based nano-delivery system even for improved treatment of the surface of the eye although some PII clinical trials are under way and such nanocarriers are expected to reach the market in the future [9,10]. Recently, an additional delivery system based on the cationic nanoemulsion of cyclosporine A received approval of the Marketing Authorization Application (MAA) for Ikervis® (Santen SAS, France) from the European Commission. Ikervis® is approved for treatment of severe keratitis in adult patients with dry-eye disease, which has not improved despite treatment with tear substitutes. Indeed, more and more new nanotechnology-based formulations exhibiting safety, efficacy and affordability are being marketed in major pharmaceutical markets because of increasing prevalence of eye disorders occurring in the anterior segment (Table 1). It should further be stressed that nanotechnology is not limited to liposomes, nanoemulsions and NPs but includes also nanotubes, micelles, dendrimers, and nanoconjugates, collectively referred to as nanomedicines [11,12].

1.2. The therapeutic concerns of posterior eye segment diseases

The main dramatic therapeutic advances in ophthalmology have been made in diseases affecting the posterior eye segment that are presently increasing at an alarming rate, representing more than 50% of the most enfeebling ocular diseases [13]. Furthermore, most of these diseases lead to partial or complete blindness if left untreated [14]. The diseases of the back of the eye include the three most common neovascular diseases, AMD, diabetic retinopathy (DR), and retinopathy of prematurity [15] in addition to viral retinitis, choroid neovascularization, proliferative vitreoretinopathy, posterior uveitis, retinal vascular occlusions, and so on. The development of intravitreal therapies targeting VEGF such as ranibizumab (Lucentis® Novartis), bevacizumab widely used off-label in ophthalmology (Avastin® Roche), pegaptanib (Macugen® Pfizer) and aflibercept (Eylea® Regeneron) was a major breakthrough in the treatment of ocular neovascular disorders. However, these therapies also have drawbacks. Besides the risks related to intravitreal injection of the formulation into the eye, which will be elaborated later, there are also relevant systemic risks described in detail in a recent review [15], that stem from antibodies which exit the eye and enter into systemic circulation [16]. The small but prolonged suppression of the plasma VEGF level which may result is postulated to lead to an increased risk of cardiovascular diseases such as stroke and thromboembolic events [16,17]. Furthermore, because VEGF also plays an important protective role in the retinal tissue itself [18], broad and rigorous VEGF knockout in the retina can lead to severe side effects: defects in the retinal pigment epithelium (RPE)–choroid complex or the loss of interaction between the RPE and photoreceptors' outer segments [19]. Additionally, VEGF deprivation results in a reduction of endothelial cell fenestrations in the choriocapillaris [20], which can in turn induce endothelial wall thickening and lead to decreased nutritional support for the photoreceptors and RPE [19]. This is also the reason why the therapy with anti-VEGF antibodies increased the development of foveal and non-foveal geographic atrophy in a number of patients with neovascular AMD [21].

Those recent advanced ophthalmological therapies are based on the administration of hydrophilic macromolecules, mainly monoclonal antibodies, which cannot for the time being reach the target tissue via a non-invasive administration because the delivery of such exogenous large molecules to the intraocular tissues including the retina is significantly limited [22]. Thus, the pharmacological treatment of these diseases requires a direct and local application of the active principles to the posterior eye segment at a therapeutic concentration by means of intravitreal injections. Indeed, intravitreal drug delivery has been one of the most popular routes for the administration of hydrophilic macromolecules intended for the

Table 1
Commercial ocular nano delivery systems currently on the market.

Product	Company	Active ingredients	Nanocarrier type	Size range (nm)	Application	Status
Cationorm®	Santen SAS	Oil	Cationic nanoemulsion	100–200	Mild dry-eye syndrome	USA* & Europe
Lipimix™	Tubilux Pharma	Oil	Anionic nanoemulsion	150–250	Dry-eye syndrome	USA & Europe
Durezol®	Alcon Labs	Difluprednate	Neutral nanoemulsion	60–200	Ocular Inflammation	USA
Restasis®	Allergan	CsA	Anionic nanoemulsion	50–200	Dry eye syndrome	USA
Ikervis®	Santen SAS	CsA	Cationic nanoemulsion	100–300	Severe keratitis in dry-eye patients	Europe
Lipomill®	Schalcon Clear Vision	Sod. Hyal. + Chamomile	Liposome dispersion	150–250	Dry-eye syndrome	Europe
Optix-Actimix®	Optima Pharmazeutis.	Vit. A & E	Liposome dispersion	50–200	Dry-eye syndrome	Europe
TearMist®	Tesco stolen	Sod. Hyal.	Liposome dispersion	50–200	Eye lubrication	Europe

CsA = Cyclosporin A; Sod. Hyal. = Sodium Hyaluronate, * sold under the brand name Retaine MGD by Ocusoft in the USA, Ambisome® (amphotericin B in liposomes, Astellas for the treatment of severe mycoses) is also used for intraocular administration (off-label).