

OCULAR DRUG DELIVERY SYSTEMS: A REVIEW

LAURA MACOVEI^{1,3#}, ALINA GHEORGHE^{1,2*}, SPERANTA SCHMITZER^{1,2#}, MARIAN BURCEA^{1,2#}, MATEI MOROSANU²

¹“Carol Davila” University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021, Bucharest, Romania

² Emergency Ophthalmology Hospital Bucharest, 1 Lahovari Square, 010464, Bucharest, Romania

³“Carol Davila” Central Military Emergency Hospital, 010825, Bucharest, Romania

*corresponding author: alina.gheorghe.g@gmail.com

#Authors with equal contribution.

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Abstract

The unique ocular route of drug administration comes with its own challenges, as novel nanotechnology based drug delivery systems and implants are being developed in order to overcome the drawbacks associated with conventional methods. Although, eye drops are convenient, safe, immediately active, patient compliant and non-invasive, the drug must be transported across several barriers, as most of the topically administered dose is lost rapidly within five to six minutes after administration due to reflux blinking and nasolacrimal drainage. Devices such as punctual plugs are used to prolong the retention time and increase the absorption of eye-drops, by blocking the nasolacrimal drainage system. Drug loaded nanoparticles have been developed in order to increase drug retention time, permeation and ocular bioavailability and intravitreal implants provide localized, controlled and sustained drug release over an extended period of time, with reduced side effects and enhanced ability to circumvent the blood retina barrier.

Rezumat

Calea unică oculară de administrare a medicamentelor are numeroase provocări, astfel încât sunt dezvoltate sisteme noi de eliberare a principiilor active, bazate pe nanotehnologii, precum și diverse implante, pentru a depăși obstacolele asociate metodelor convenționale. Deși picăturile oftalmice sunt conveniente, sigure, neinvazive, acționează imediat și produc o bună complianță terapeutică, substanța trebuie să străbată mai multe bariere oculare protective, astfel încât majoritatea dozei administrate topic se pierde rapid în primele 5 - 6 minute din cauza clipitului reflex și a drenajului nazolacrimal. Dispozitive precum dopuri lacrimale sunt folosite pentru a prelungi timpul de retenție și a îmbunătăți absorbția picăturilor, blocând sistemul de drenaj lacrimo-nazal. Au fost dezvoltate nanoparticule încărcate cu principii active medicamentoase pentru a îmbunătăți timpul de retenție al substanței, permeația și biodisponibilitatea oculară, în timp ce implantele intravitreene furnizează o eliberare localizată, controlată și susținută a medicamentului pentru o perioadă extinsă de timp, cu efecte adverse reduse și capacitate sporită de traversare a barierei hemato-retiniene.

Keywords: ocular drug delivery systems, novel approaches, nanotechnology, implants

Introduction

The eye can be the site of many diseases (some of which sight-threatening) and taking into account its unique anatomy and physiology, treating these various diseases has always been a challenge for physicians and the pharmaceutical industry, especially when considering the route of drug administration. Topical eye-drops are widely used and usually the preferred type of medication administered regarding the anterior segment of the eye. However, these drugs do not usually reach the retina, vitreous or choroid, for which there are other preferred routes of drug administration, as novel technologies are being developed.

Current drug delivery systems

Eye drops

Topical instillation is the elected route of drug administration regarding the anterior part of the eye

and although eye drops are useful, safe and act immediately, the drug must be transported across several barriers (tear film, cornea and conjunctiva) that protect the eye from exogenous substances and external stress [1, 2].

Most of the topically administered dose, regardless of the instilled volume, is lost rapidly within the first six minutes after administration because of the reflux blinking or nasolacrimal drainage. Only 20% (approximately 7 μ L) is retained in the conjunctival pocket and just 1 - 3% actually reaches the intra-ocular tissue [1-4].

Various additives (such as viscosity enhancers, permeation enhancers and cyclodextrins) and ophthalmic vehicles (suspensions, emulsions and ointments) may be used to increase retention time, permeation and ocular bioavailability [1, 2].

Viscosity enhancers (such as hydroxy methyl cellulose) have been proven to enhance the precorneal retention

time. Preservatives, chelating agents, bile salts and surface active agents act as permeation enhancers, by improving the corneal uptake and bioavailability of the drug [1, 5].

Cyclodextrins are agents that can encapsulate hydrophobic drug molecules in a hydrophilic aqueous solution, acting as carriers and while the lipophilic cell membrane absorbs the drug, it does not allow passage of the cyclodextrins, which were reported to produce an optimal drug bioavailability at concentration levels of less than 15% [1, 5-9].

Emulsions

An emulsion is an oil-in-water or water-in-oil formula that enhances the drug's solubility, it's precorneal residence time and permeation across the cornea, increasing the release time and bioavailability [1, 5, 10-13]. AzaSite[®], Refresh Endura[®] and Restasis[™] are such examples [1, 5, 14-16].

Recently, Tajika *et al.* suggested in their study that an emulsion based formula of [3H]-difluprednate, a prednisolone derivate, can be used for treating anterior ocular inflammation at concentration levels of 0.05%, with small amounts of the drug even reaching tissues such as vitreous, retina and choroid in rabbit eyes following not only single, as well as multiple topical drop instillation [1, 5, 17].

Liu *et al.* showed that azithromycin acted better as an emulsion (using lipid sources such as soybean lecithin or stearylamine as additives and carriers) when compared to an aqueous solution, with parameters such as chemical stability, precorneal retention time, drug release time and bioavailability being improved, as the pharmacokinetics of tear elimination after topical instillation shows, also in the rabbit eye [1, 5, 18].

Similarly, Shen *et al.* attempted to improve the bioavailability and reduce ocular irritation of flurbiprofen as an active pharmaceutical ingredient, by combining a derivate (flurbiprofen acetyl) with castor oil (a lipidic excipient) and tween-80 (a stabilizer) to form an emulsion. Aqueous humor pharmacokinetic studies were conducted after topical drop instillation in male New Zealand Albino rabbits [1, 5, 19].

Other researchers have studied the efficacy of polymers such as chitosan or hydroxypropyl methyl cellulose ether as coating agents for emulsions, as an indomethacin emulsion demonstrated better pre-corneal residence time and bioavailability when coated by chitosan. Concentrations levels were assessed in the conjunctiva, cornea and aqueous humor following tear fluid pharmacokinetic studies conducted in rabbits following topical instillation [1, 5, 20-22].

Ointments

An Ophthalmic ointment is a carrier system for topical application that has demonstrated increased bioavailability and sustained drug release. These are comprised of solid and semisolid hydrocarbon molecules (paraffin) and have a melting point of 34°C, the physiological ocular temperature [1, 5, 23-27].

Fukuda *et al.* studied the intraocular dynamics of ophthalmic ointments based on vancomycin (an antibiotic with high activity against methicillin and cephem resistant *Staphylococcus aureus* and anaerobic and aerobic gram positive bacteria) in rabbits and demonstrated higher corneal concentration levels in eyes with induced *Bacillus subtilis* corneal infection than in the normal control group eyes, with higher than minimum growth inhibitory concentration levels regarding methicillin and cephem resistant *Staphylococcus aureus* (MRSA) maintained for as much as 240 minutes after topical administration [1, 5, 28]. The reason for the observed effect relies on breaks within the ocular barriers which seem to improve drug permeation in unhealthy eyes, as improved outcomes based on increased permeability in healthy ocular tissues are yet to be projected [1, 5, 29].

Eguchi *et al.* concluded 0.3% to be an adequate and effective concentration level of vancomycin for MRSA keratitis resolution after topical application of liquid paraffin and Vaseline based ointments in rabbit model eyes [1, 5, 30].

Suspensions

A suspension is a non-invasive topical drop drug carrier system known for its improved duration of action and drug contact time. They carry the drug as a dispersion of divided insoluble active pharmaceutical ingredients (API) in an aqueous solvent. The suspension particles are being retained in the conjunctival pocket, with duration of action being particle size dependent [1, 5, 31-33].

TobraDex[®], containing both dexamethasone and tobramycin is a widely used anti-inflammatory and anti-infective suspension. Recent attempts have been made in order to reduce its viscosity by using xanthan gum to form ionic interactions with tobramycin, as bactericidal activity, tear film kinetics, tissue permeation and patient compliance all improved. Higher tissues concentrations of the active pharmaceutical ingredients, as well as higher effectiveness against *Staphylococcus aureus* and *Pseudomonas aeruginosa* were observed [1, 2, 5, 34-37].

Novel approaches

In order to overcome drawbacks associated with conventional formulations (such as systemic complications due to increased systemic API availability following chronic administration and adverse reactions induced by preservatives), novel strategies for ocular drug delivery are currently being researched and developed [1].

Devices

Contact lenses

Soft contact lenses can be used as drug delivery systems by immersing it in a solution of a given drug, as ocular tissue-drug contact time, flux across the cornea, as well as bioavailability increase, less

of the drug being lost to lacrimal drainage, some studies show [1, 5, 38-40]. Vistakon Pharmaceuticals have conducted a clinical trial that tried to prevent allergic conjunctivitis in contact lens wearers by using a pre-soaked contact lens that released ketotifen, an antihistamine drug, following application [2, 41, 42]. Kim *et al.* observed that dexamethasone had higher bioavailability when released from contact lenses compared to eye drops [43].

The contact lenses can be modified in order to immobilize drugs on their surface, as research shows and drugs can be entrapped using liposomes or micelles that are dispersed in the contact lens material, "smart" particles limiting drug release to the eye only based on factors such as pH or temperature in order to avoid drug loss during storage, as particle-laden contact lenses have been developed [1, 2, 5, 44, 45].

Gulsen *et al.* demonstrated the extended release of lidocaine from nanoparticle-loaded contact lenses over a period of 8 days [1, 5, 46, 47].

Molecular imprinted contact lenses have demonstrated higher drug loading capacity and provided sustained drug delivery regarding timolol [1, 5, 48].

Research is being developed for ion ligand-containing polymeric hydrogel and drug plate or drug solution combined piggyback contact lenses as well [2, 49, 50].

Cul-de-sac inserts

Ocusert[®] is a *cul-de-sac* insert that contains an internal layer of pilocarpine (an ocular hypotensive drug) in alginate gel within di-(ethylhexyl)phthalate as a release enhancer, between 2 external layers of ethylene-vinyl acetate copolymer and although it provides a uniform and controlled release (20 or 40 µg per hour for a week) of the active pharmaceutical ingredient, the difficulty of insertion, the device ejection and ocular irritation have limited its use due to the unsatisfactory control in intraocular pressure (IOP) [2, 51-53].

Lacrisert[®] is a water-soluble *cul-de-sac* hydroxypropyl cellulose insert developed for moderate and severe dry eye syndrome and although it does not contain preservatives, it has yet to be successfully applied [54].

The reluctance to abandon the traditional drug carrier systems and occasional device ejection have led to the commercial failure of these systems, as no further activities exist at present [2].

Punctual plugs

Punctual plugs are used to increase the retention time and thus the absorption of eye-drops, by blocking the nasolacrimal drainage system, as a decrease in IOP by approximately 2 mmHg was observed in plugged eyes compared to unplugged eyes following topical instillation of ocular hypotensive eye-drops [2, 55-57].

QLT Inc. (Vancouver, Canada) and Vistakon Pharmaceuticals, LLC have developed latanoprost and bimatoprost containing punctual plugs as delivery systems and despite a retention rate of 81%, a dose-

response for IOP reduction has yet to be observed [2, 58].

Episcleral and subconjunctival implants

LX201 is an episcleral implant composed of a silicone matrix designed to continuously deliver potentially therapeutic cyclosporine levels to the lacrimal gland for a keratoconjunctivitis model in preclinical studies using rabbits and dogs [2, 59, 60].

3T Ophthalmics have developed a drug-filled silicone episcleral implant that provides high drug levels in the retina and posterior vitreous following scleral diffusion in animal studies, as clinical trials for retinoblastoma are planned [2, 61, 62].

Pfizer, Inc. has developed a subconjunctival insert composed of a poly (DL-lactide-co-glycolide) (PLGA) tube that contains a latanoprost-core. It releases its active pharmaceutical ingredient across the permeable end of the tube for a duration of 3 - 6 months. The release rate is regulated by the internal diameter of PLGA tube [2, 63].

Microelectromechanical systems (MEMS) are drug delivery devices made of parylene (biocompatible and flexible) that can be used by implanting their reservoir in the subconjunctival space, while a cannula is placed through an incision into the anterior or posterior segment of the eye. Electrolysis (driven by battery and wireless inductive power transfer) generates pressure inside the reservoir pushing the drug through the cannula, as water is transformed into hydrogen and oxygen gas due to the electrochemically-induced phase change. This allows a precise delivery of the desired dosage volume, overcoming the limits of the previous generation of manually-controlled MEMS consisting of variations regarding drug-release duration and force applied for depressing of the reservoir. MEMS device allows refilling with drug solution, providing long-term drug therapy which avoids repeated surgeries. Timolol or travoprost loaded MEMS have generated a continuous reduction in IOP for 8 hours in dogs, as no complications were observed after 3 months following subconjunctival device implantation with an anterior chamber placed canula. MEMS drug delivery devices are currently being investigated for the treatment regarding chronic and refractory ocular diseases, including glaucoma and age related macular degeneration (AMD) [2].

Nanotechnology based ocular drug delivery systems

Liposomes

A liposome is a vesicle composed of lipid layers (phospholipids, lipid conjugated polymers, and cholesterol) that entrap both lipophilic and hydrophilic drug molecules in an aqueous phase [64-66].

The fluidity of lipid bilayers (biodegradable in nature), surface charge (lipid dependent) and size are properties of liposomes that enhance corneal adhesion and drug penetration, especially when enhancing polymers and bio-adhesives are added to the formulation [64, 67].

In rabbit eyes, due to electrostatic interaction between the liposomes and the negatively charged corneal surface, the acyclovir concentration and absorption through cornea at two and a half hours following topical administration of cationic liposomes was higher than in the case of anionic liposomes and free acyclovir, as aqueous humor concentrations show [1, 68].

Chitosan coated coenzyme Q₁₀ liposomes demonstrated an increase by almost 5 times regarding the precorneal residence time in the rabbit eye, proving the importance of mucoadhesive additives [1, 69].

Dong *et al.* used silk fibroin (a mucoadhesive material) coated, ibuprofen loaded liposomes to enhance drug retention and release time, as no toxicity was reported in human corneal epithelial cells [64, 70].

Huang *et al.* used a formulation based on betaxolol hydrochloride and montmorillonite for the treatment of glaucoma [64, 71].

Prostaglandins such as latanoprost have been used as stable liposomal formulations for ocular drug delivery in order to lower intraocular eye pressure in glaucoma *via* subconjunctival injection, while sodium hyaluronan, sodium hydroxide solution and sodium citrate were used as glycosaminoglycan- coated metallic nanoparticles *via* topical instillation to treat the dry eye [64, 72-75].

The administration of a rho-kinase inhibitor in association with latanoprost has led to increased treatment compliance and a further decrease in intraocular pressure (IOP) [76].

Tears again[®] is a spray that uses phospholipid liposomes in order to treat dry eye syndrome [1, 77, 78].

Liposomes provide sustained drug release by improving the vitreal half-life of drugs, protecting them from degradation and clearance, as studies conducted for fluconazole and tacrolimus show [1, 79-82].

Various effects associated with intravitreal instillation such as endophthalmitis, vitreous haemorrhage, and retinal detachment are minimized, as liposomes exert targeted drug delivery at the location of action and overcome the low bioavailability associated with topical instillation [64, 83].

Vallejo JC *et al.* used triamcinolone acetonide loaded liposomes for vitreous cavity and retina delivery in rabbit eyes, as no increase in intraocular pressure was observed [64, 84].

Li *et al.* demonstrated the sustainable drug release and low toxicity of a chitosan coated, triamcinolone acetonide loaded liposome used to treat macular oedema [64, 85].

Visudyne[®] uses verteporfin (a photosensitizer) loaded liposomes for photodynamic therapy regarding subfoveal choroidal neovascularization in AMD, presumed ocular histoplasmosis and pathological myopia [1, 86].

Nanoparticles

Lipid nanoparticles. Nanoparticles are drug loaded nanocapsules (drugs enclosed inside a polymeric shell) or nanospheres (drugs uniformly distributed throughout

a polymeric matrix) composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, PLGA, polylactic acid (PLA) and polycaprolactone, ranging in size from ten to one thousand nanometres [1, 87-96]. Due to their small size and lipophilic nature, nanoparticles provide high ocular drug uptake by easily crossing barriers, with increased corneal absorption, providing high retention time and bioavailability at the ocular site, with sustained and targeted drug release that provide a high drug loading capacity and long term stability [64, 97-100]. They produce low toxicity and irritation levels due to their high biocompatibility and infrequent administration. They also provide sustained drug release based on particle size, large particles being less susceptible for rapid clearance and even providing transscleral delivery of the drug to the posterior tissues [1, 64, 101-104]. Furthermore, muco-adhesives such as chitosan, polyethylene glycol (PEG) and hyaluronic acid can be added in order to improve precorneal residence time, corneal permeation, bioavailability and drug release by overcoming the rapid elimination from the conjunctival pocket, as studies conducted on natamycin, melatonin and ofloxacin show [1, 64, 105-108].

Singh *et al.* used isoniazid loaded nanoparticles to demonstrate the high corneal permeation and retention of such formulas that provide a long drug half-life, as aqueous humor concentrations show [64, 109].

Ahmad and co-workers developed an etoposide loaded nanoparticle by melt-emulsification and ultrasonication technique with high penetration ability and entrapment efficiency that provided good drug concentration levels at the ocular site, maintaining the desired dose without any serious effect [64, 110].

Tatke and associates prepared triamcinolone acetonide loaded gellan gum combined nanoparticles by hot homogenization and ultrasonication technique for deep ocular tissue penetration [64, 111].

Some studies demonstrated sustained drug release following intravitreal injection of nanoparticles, as retinal pigmented epithelium and vitreous levels show, with negatively charged particles penetrating the entire retinal structures and reaching the external layers due to interaction between their anionic surface and the Müller cells as some drugs even reached the choroid through the disruption site of the retinal pigmented epithelium (RPE) and Bruch's membrane in laser photocoagulated retinas, providing hope for the inhibition of choroidal neovascularization in age related macular degeneration [1, 112-115].

Inorganic nanoparticles. An inorganic nanoparticle is comprised of an inorganic core (such as quantum dots, gold, iron oxide or silica) and an organic (or metal) shell that protects the core in order to prevent drug degradation. The large surface area, high physical stability, great catalytic properties and intrinsic beneficial properties (such as antiangiogenic and anti-inflammatory properties in some cases) of these particles provide

high compatibility and specificity in biological functions, as some ocular disorders (such as glaucoma, retinal diseases, age related macular degeneration, corneal fibrosis, retinoblastoma and ocular inflammation) have been well treated using inorganic nanoparticles as drug delivery systems [64, 116-118].

Li *et al.* used an amfenac-loaded polycatechin-capped gold nanoparticle that provided anti-inflammatory and anti-oxidative effects with no toxicity following drop instillation in dry eye treatment [64, 119].

Wang and co-workers proposed an N-acetyl carnosine loaded gold nanoparticle, obtained using *Coccinia grandis* bark extract for cataract treatment that provided high bioavailability and biocompatibility with no significant cytotoxic effect [64, 110].

Maulvi and co-workers combined timolol loaded gold nanoparticles with contact lenses in order to treat glaucoma, with results showing a considerable decrease in IOP levels due to increased drug delivery at the desired site following high uptake without swelling and optical transmittance problems of the contact lenses [64, 120].

Kim and co-workers developed a brimonidine loaded amino-functionalized mesoporous silica nanoparticle for the management of glaucoma that provided a substantial decrease in IOP due to an increase in drug residence time at the corneal site that led to high bioavailability following topical administration in the rabbit's eye [64, 121, 122].

Nano-micelles

A polymeric micelle is a nanoscopic core covered by a shell structure formed by amphiphilic copolymers used to solubilize therapeutic agents into clear aqueous solutions. They are effective in transporting hydrophobic drugs and protein across biological membranes by enhancing drug stability, bioavailability and regulating drug release pattern. The high drug encapsulation capability, small size, ease of preparation and hydrophilic nano-micellar corona allow the drug to be retained in the systemic circulation for longer periods of time and accumulate at the location of the diseased tissue *via* enhanced permeation and retention (EPR) effect, with minimum non-specific accumulation of the drug in healthy tissues. Proper engineering techniques and selection of surfactant/polymer may aid in delivery of drugs to both posterior and anterior eye segments [1, 64, 123].

Civiale *et al.* used nano-micelles loaded with dexamethasone for anterior segment delivery demonstrating higher ocular drug bioavailability compared to dexamethasone suspension, as concentration time profiles following aqueous humor sampling in rabbits shows [1, 124].

Li and co-workers proved the high corneal permeation and anti-inflammatory properties of diclofenac loaded micelles in rabbit eyes, as no irritation was observed [64, 125].

Xu and his co-workers used nifedipine loaded PLA-PEG nano-micelles to constrain extracellular calcium ion influx as anticataract activity, as high drug bio-compatibility and bioavailability were observed [64, 126]. Liaw *et al.* efficiently transferred plasmid DNA with pK12-Lac Z-PM gene for corneal delivery of keratin 12 and keratocan promoters by topical drop administration in mouse and rabbit eyes following endocytosis and particle size dependent paracellular transport of polymeric micelles [1, 127, 128].

Studies show that voclosporin, dexamethasone and rapamycin loaded nano-micelles were able to deliver therapeutic drug concentrations to posterior eye tissues post topical drop instillation, as their hydrophilic corona and small size helped them to evade the ocular barriers and produce low irritation and good tolerability [1, 129].

Ideta *et al.* used fluorescein isothiocyanate-labelled poly-L-lysine loaded nano-micelles *via* intravenous administration of the drug to treat neovascularization located in the posterior segment of the eye, as elevated retina-choroid drug concentration levels were detected up to 7 days following single administration [1, 130]. This high cytotoxic effect of dendritic photosensitizer (DP) loaded nano-micelles following light irradiation has been utilized for the photodynamic treatment of exudative AMD, as photocoagulation was induced in rat eyes following intravenous injection and DP accumulation at the choroidal neovascular site [1, 131].

Niosomes

Niosomes are bi-layered, biodegradable and non-immunogenic vesicles of 10 nm to 01 μ m composed of non-ionic surfactants that can carry both hydrophilic and lipophilic compounds in aqueous compartments. They have a long storage time (shelf-life), enhanced therapeutic effectiveness and reduced side effects due their low systemic absorption [64, 85, 132].

Niosomes are available as drops for topical instillation used for treating ocular hypertension, dry eye, glaucoma, as well as eye infections. The enhanced precocular retention time and drug absorption result in a sustained and prolonged discharge at the location of action, as inhibition of ocular metabolism in by lachrymal fluid and reduced systemic drainage provide an extended duration of action [64, 133].

Allam and co-workers demonstrated the enhanced antibacterial activity of a vancomycin niosomal gel against MRSA in rabbits [64, 134].

Nabarawi with his co-workers developed natamycin (NAT) loaded niosomes in ketorolac tromethamine (KT) gels with increased penetration rates and enhanced effectiveness against fungal keratitis following topical administration, as accelerated photoactivated chromophore collagen cross-linking could be a solution for infectious keratitis or corneal ulcer resistant to antimicrobial and antifungal therapy [64, 135, 136].

Dendrimers

A dendrimer is a branched, nanosized and star shaped polymeric drug carrier system available in many

different molecular weights with different terminal end functional groups that can incorporate both hydrophobic and hydrophilic drugs [1, 137-140].

Vandamme *et al.* demonstrated the increased ocular residence time, enhanced ocular bioavailability and better therapeutic outcomes of Poly (amidoamine) (PAMAM) dendrimers as an ophthalmic vehicle for drug delivery, as higher miotic and mydriatic activity in Albino rabbits was observed after co-administration of PAMAM dendrimers with pilocarpine nitrate and tropicamide [1, 138, 141].

The subconjunctival administration of glucosamine and glucosamine 6-sulfate loaded dendrimers in rabbit model eyes of filtration surgery regarding glaucoma have demonstrated significant inhibition of pro-angiogenic and pro-inflammatory responses with reduced formation of scar tissue [1, 142].

Hydro-gels

Hydrogels are polymeric, cross-linked solutions and undergo sol-gel phase transition induced by UV irradiation or changes in ions, temperature and pH and to form viscoelastic gels. For ocular delivery, thermosensitive polymers are mixed with drugs to form micellar aggregates that are temperature dependent and gellify at physiological temperature due to packing or aggregation [1, 64, 143-145].

The sustained drug release, prolonged corneal drug contact time, infrequent need of applications, decreased side effects and high ocular bioavailability suggest that thermosensitive gels could be a promising option for drug delivery regarding chronic ocular diseases [1].

Thermosensitive hydro-gels have been shown to produce higher drug concentration levels in the anterior chamber relative to eye drops, as studies based on dexamethasone loaded PLGA-PEG-PLGA (poly-(DL-lactic acid co-glycolic acid)-polyethylene glycol-poly-(DL-lactic acid co-glycolic acid)) polymers in rabbit model eyes demonstrate [1, 146].

Rieke *et al.* have reported the sustained drug release of an ovalbumin loaded biodegradable and thermosensitive triblock copolymer to the choroid and retina in the rat eye following subconjunctival administration [1, 147].

Liu and co-workers used a poly(ethylene glycol)-co-(l-lactic acid) diacrylate/N-isopropyl acrylamide (PEG-PLLA-DA/NIPAA) thermosensitive biodegradable hydrogel to deliver aflibercept in order to treat ocular neovascularization in a precise, safe and also effective manner [64, 148].

Nanosuspensions

Nanosuspensions are heterogeneous colloidal systems (10 to 1000 nm in size) stabilized by surfactants and used as carriers for hydrophobic drugs with poor solubility in lacrimal fluids [64, 149-151].

Their increased precorneal residence time and enhanced ocular bioavailability are some advantages, as they easily cross ocular barriers (due to their size) and produce less irritation [1, 152].

Efforts have already been made towards improving ocular parameters such as bioavailability of glucocorticoids by formulating them as nanosuspensions, as current use of these drugs requires frequent administration at high doses which induce the formation of cataract and optic nerve damage [1, 153, 154].

Güven and co-workers have demonstrated the high entrapment efficiency, high drug loading percentage and persistent drug release of an olopatadine hydrochloride loaded nanosuspension used for treating allergic eye disease [64, 155].

Verma and co-workers designed an itraconazole loaded chitosan nanosuspension with good permeation, increased aqueous saturation solubility and effective *in vitro* discharge of the drug in the goat's cornea [64, 156].

Nanoemulsions

A nanoemulsion is a colloidal dispersion found to possess kinetic and thermal stability. The interaction with the lipid layer of the tear film enhances the ocular residence time, as sustained drug release is provided due to high corneal permeation and penetration [64, 157-159].

Mahboobian and co-workers demonstrated the high corneal penetrating properties of a brinzolamide loaded nanoemulsion for the treatment of glaucoma [64, 160]. Shah *et al.* tested the bioavailability of a moxifloxacin loaded nano-emulsion, as high concentration levels at the target site were reported, with therapeutic effects being produced even at low dosing levels [64, 161].

Implants

Intraocular implants are injected into the vitreous *via pars plana* incision in order to provide a localized, controlled and sustained drug release over an extended period of time, with reduced side effects and enhanced ability to circumvent the blood retina barrier [1, 162-164].

Non-biodegradable implants are able to release the drug for extended periods of time due to their release kinetics and are made of ethylene vinyl acetate (EVA), polyvinyl alcohol (PVA) and polysulfone capillary fibre (PCF) polymers [1, 162, 164]. They require surgical removal after drug depletion and complications such as endophthalmitis, pseudo-endophthalmitis, vitreous haze, vitreous haemorrhage, cataract development and retinal detachment have limited their applications [1].

Biodegradable implants provide sustained drug release, are highly biocompatible and do not require surgical removal. They are made of PLA, polyglycolic acid (PGA), PLGA, and polycaprolactones polymers [1, 162]. Vitrasert[®] is an intraocular non-biodegradable implant composed of a 4.5 mg tablet of ganciclovir surrounded by EVA/PVA that slowly and passively releases the drug by diffusion through a small opening in EVA at the base of the device over a period of five to eight months, without systemic toxicity in order to treat cytomegalovirus retinitis [1, 2, 162, 164-167].

Retisert® is a non-biodegradable silicone laminated PVA implant approved by the FDA (Food and Drug Administration) for the treatment of chronic uveitis, as it provides the sustained release of fluocinolone acetonide for up to three years and although it effectively controls inflammation, reduces uveitis recurrences and improves visual acuity, cataract formation and elevated IOP have limited its application [1, 164, 165, 168, 169]. Iluvien® is a non-biodegradable, fluocinolone acetonide loaded, rod-shaped intravitreal implant made of polyimide and PVA developed in order to treat diabetic macular oedema (DME) that provides sustained drug delivery for up to three years, as higher percentages of patients whose visual acuity improved by at least 15 letters at 24 months were noted when compared to the control groups, some clinical trials show [2, 170, 171]. Dry age-related macular degeneration (AMD), wet AMD and macular oedema secondary to retinal vein occlusion (RVO) could also benefit from the application of Iluvien® [2, 172-174].

I-vation™ is a triamcinolone acetonide loaded, non-biodegradable titanium intravitreal implant coated with poly(methyl-methacrylate) and EVA predicted to provide sustained drug delivery for at least two years, as clinical trials regarding patients with DME that demonstrate an improvement in visual acuity and a decrease in macular thickness are currently being conducted [2, 175, 176].

Ozurdex® is an FDA approved biodegradable implant comprised of a PLGA polymer matrix that provides the release of dexamethasone for up to six months, as an improvement in visual acuity regarding macular oedema (caused by with either central or branch retinal vein occlusion), diabetic retinopathy, Irvine-Gass syndrome and posterior non-infectious uveitis was noted [1, 2, 164, 177].

Brimonidine tartrate loaded PLGA intravitreal biodegradable implants are being tested in phase II clinical studies regarding dry AMD and also phase I/II clinical trials regarding Retinitis Pigmentosa by Allergan, Inc., as the neurotrophins (including the ciliary neurotrophic factor and the brain-derived neurotrophic factor) released by this α_2 adrenergic agonist have the potential to prevent the apoptosis of photoreceptors and/or RPE [2, 178-183].

Injectable Particulate Systems

Using Verisome™ (a translucent liquid) technology as a drug delivery platform, Icon Bioscience, Inc. have developed a triamcinolone acetonide loaded solution (IBI-20089), that becomes a milky, slightly opaque gel when mixed with saline. It is administered as an intravitreal injection in biodegradable benzyl benzoate and supposed to last for up to 1 year, as phase I studies for cystoid macular oedema associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) demonstrate a decrease in mean central subfield optical coherence tomography (OCT) thickness, with the substance being tested

alongside ranilzumab for neovascular AMD [2, 184-186].

Cardillo *et al.* demonstrated the superior long-term pharmacologic performance of intravitreal injected triamcinolone acetonide loaded PLGA microspheres compared to naked triamcinolone acetonide injected eyes regarding patients with diffuse DME, as a marked decrease of the retinal thickness as well as an improvement in visual acuity were observed, as no complications were noted [2, 187].

Cortiject® is a dexamethasone palmitate (a corticosteroid prodrug) loaded preservative-free emulsion. It is composed of an oily carrier and a phospholipid as a surfactant that provides a sustained drug release of over 6 - 9 months, as the dexamethasone palmitate undergoes de-esterification and activation following intravitreal injection, with phase I studies for DME being conducted [2, 188, 189].

Visudyne® is a verteporfin (a photosensitizer) loaded intravenous liposomal formulation proposed for photodynamic therapy regarding presumed ocular histoplasmosis, pathological myopia or subfoveal choroidal neovascularization secondary to wet AMD [2, 190]. The encapsulated verteporfin accumulates in the vascular endothelial cells or into tumour cells via low density lipoprotein (LDL) receptor-mediated endocytosis, as phosphatidylglycerol (a negatively charged phospholipid) is a major constitute of Visudyne® formulation [2, 191].

Free verteporfin uptakes in neovascular tissues or in tumour cells after release in the blood flow from liposomes and associates with plasma LDL [2, 192].

Microneedles

Using microneedles, drugs can be deposited into the sclera or the suprachoroidal space, as diffusion into deeper ocular tissues such as choroid and retina may provide therapeutic effects for diseases such as AMD, diabetic retinopathy and posterior uveitis. This minimally invasive technique reduces the risks and complications associated with intravitreal injections, as microneedles only penetrate the superficial sclera, avoiding damage to the retina, vitreous, or choroid [1, 193].

Jason *et al.* demonstrated the high drug deposition of sulforhodamine coated microneedles following scleral injection in cadaver eyes [1, 194]. Jiang *et al.* [195] and Patel *et al.* [196] made attempts to infuse drug solutions, microparticles and nanoparticles into the sclera and the suprachoroidal space of human cadaver eyes and although results demonstrated the safeness and sustained drug release of the strategy, drugs may not reach the inner retinal tissues [1].

Iontophoresis

During iontophoresis, a weak direct current that drives charged molecules across the sclera is applied in order to deliver the drug into the vitreous, retina and choroid. The procedure requires an electrode to be placed elsewhere on the body in order to complete the

circuit. It is non-invasive in nature and avoids the risks and complications associated with surgical implantation or intravitreal injections [2].

In the rabbit, corneal dexamethasone levels were up to 30 fold higher following a single transcorneal iontophoresis for one minute (1 mA) in comparison to topical eye-drop instillation [2, 197]. EGP-437 is a dexamethasone phosphate compound currently undergoing clinical trials for the treatment of dry eye syndrome and anterior uveitis [2, 198-200].

Conclusions

While the reluctance to abandon the traditional drug carrier systems and occasional device ejection have led to the commercial failure of some systems, others have demonstrated to provide a localized, controlled and sustained drug release over an extended period of time, with reduced side effects and enhanced bio-availability.

Drug loaded nanoparticles have demonstrated to increase retention time, permeation and ocular bio-availability and seem to provide the solution to overcome the drawbacks associated with conventional eye-drops, while implants are proving to be promising for the posterior tissues. Nonetheless, more studies need to be conducted in order for the novel drug delivery systems to be established as a definite first choice option.

Conflict of interest

The authors declare no conflict of interest.

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