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Ophthalmic Delivery System for Dexamethasone: An overview

Preeti K Suresh* and Divya Dewangan

University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India.

ABSTRACT

Dexamethasone has been used by ophthalmologists with increasing frequency over the past 45 years, with the concomitant development of a diverse range of drop, ointment, subconjuctival, and oral preparations. Dexamethasone used to treat ocular inflammation is a lipophilic water-insoluble compound. The ocular bioavailability is seriously hampered by the low aqueous solubility. Common adjuvants to aqueous eye drop formulations can enhance ocular bioavailability by reducing the barrier function for example, the cornea (e.g. benzalkonium chloride and other surfactants) or by increasing the contact time of the drug with the eye surface (e.g. viscosity enhancers such as water-soluble polymers). This review will focus on the developments that promise a major impact on future ocular drug therapeutics: nanoparticles, gels, cubosomes, implants, microemulsions, inserts, contact lens, eye drops, liposomes, ointment as therapeutic approach in ophthalmology.

Keywords: ocular, Topical, Corticosteroid, Anti-inflammatory drugs.

INTRODUCTION

Dexamethasone has been one of the most frequently used topical ocular corticosteroids, which plays a long-lasting role in anti-inflammatory, anti-allergy and anti-shock activities. It is a synthetic, poorly soluble and crystalline corticosteroid. Dexamethasone reduces the intraocular inflammation as well as the breakdown of the blood ocular barrier in proliferative vitreoretinopathy (Zignania *et al*., 2000).

Topically administered corticosteroid therapy is indicated for some forms of conjunctivitis, dacryocystitis, episcleritis, keratitis, and anterior uveitis. The topical treatment of extra or intraocular diseases with eyedrops is the best accepted by patients. However treatment with eye drops usually entails coping with a poor bioavailability because the precorneal area, i.e., the site of drug action/absorption, is rapidly cleared of drugs by protective mechanisms of the eye, such as blinking, basal and reflex tearing, and nasolacrimal drainage. From here derives the need of frequent instillations, and hence the risk of side effects (Zambito *et al*., 2010). Currently available ophthalmic corticosteroids suitable for topical application include prednisolone acetate, dexamethasone alcohol, dexamethasone sodium phosphate, betamethasone, and hydrocortisone.

***Corrosponding author**

Preeti K Suresh
Email id: preeti_venugopalan@yahoo.co.in

Dexamethasone and betamethasone are approximately 5 to 10 fold more potent than prednisolone and 25 fold more potent than hydrocortisone (Zambito *et al*., 2010; Zhang *et al*., 2009).

Delivery of drugs to the posterior segment (retina, choroid, vitreous and optic nerve) is challenging due to the anatomic (cornea, conjunctiva, sclera) and physiologic barriers of the eye (Kristinsson *et al*., 1996). Current treatments of the posterior segment diseases using corticoid performed by direct injections of corticoid solutions or suspensions. However, direct injections of corticoids into the vitreous often require large boluses and repeated injections to ensure therapeutic levels over an extended period of time, leading to a reduction of patient compliance, or to an increased likelihood of complications. The controlled-release delivery of dexamethasone would allow a sustained delivery of the drugs, thus prolonging the duration of drug action, avoiding the need for frequent intraocular injections, and decreasing the risk of complications (Zhang *et al*., 2009).

Ophthalmic delivery system for dexamethasone in addition to factors concerning high tolerability and comfort is facing challenges. The first obstacle is general to all ocular products i.e. low ocular bioavailability of topically applied drugs and second is hydrophobic new chemical entity which usually lack suitable vehicle.

The emergence of new and innovative means for proving therapeutic efficacy suggests that a greater choice of dosage forms will be provided to physicians and patients in the next decade. Most of the formulation

efforts aim at maximizing ocular drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimizing precorneal drug loss.

This review will focus on the development that promises a major impact on future ocular drug therapeutics: nanoparticles, gels, cubosomes, implants, microemulsions, inserts, contact lens, liposomes, ointment, eye drops as therapeutic approach in ophthalmology.

OPTHALMIC DRUG DELIVERY SYSTEMS

EYE DROPS

The dexamethasone concentration in aqueous humor, vitreous, and serum of patients after repeated topical application of dexamethasone disodium phosphate was studied by Weijtens *et al.,* 2002. Dexamethasone disodium phosphate eye drops administered to most participants until the time of surgery and sample collection was 10. The mean dexamethasone concentration in the aqueous humor samples was 30.5 ng/ml, with time intervals between the last drop and sample collection ranging from 14 to 120 minutes. In the vitreous samples, the mean dexamethasone concentration was 1.1 ng/ml, with time intervals ranging from 21 to 128 minutes. In the serum samples, the mean dexamethasone concentration was 0.7 ng/ml with time intervals ranging from 3 to 101 minutes. The conclusion drawn from results were the penetration of dexamethasone into the vitreous after repeated drop application was negligible compared with previously tested administration routes (peribulbar or subconjunctival injection or oral administration) i.e. systemic uptake was low. Despite the frequent dosing schedule, the dexamethasone concentration in the aqueous humor was far lower than after a subconjunctival injection with dexamethasone disodium phosphate.

Loftsson *et al.,* 2007 investigated the effects of randomly methylated β-cyclodextrin (RMβCD) on dexamethasone delivery from aqueous eye drop solution into rabbit eyes and the results were compared with dexamethasone eye drops in aqueous 2-hydroxypropyl-β cyclodextrin (HPβCD) from previous study. The result illustrated that both the hydrophilic HPβCD and the lipophilic RMβCD enhanced topical dexamethasone delivery into the eye, but of the two, the lipophilic RMβCD resulted in higher dexamethasone concentrations.

OINTMENT

Lee *et al.,* 2006 reported the ocular hypertensive response to topical dexamethasone ointment in children, especially those 5 years old or younger. Dexamethasone ointment (Dexcosil®) was applied three times a day for the first week and twice a day for the second to third week postoperatively to children undergoing epiblepharon surgery. After dexamethasone ointment treatment, the cumulative percentage of eyes having intraocular pressure higher than 20 mmHg at days, 1, 7, 14, 21, 28 were 1.0, 29.2, 35.4, 36.5 and 50% respectively. The number of patients with an intraocular pressure higher than 20 mmHg in the study was 48 (50%).

GELS

Kim *et al*., 2008 investigated loading and release of different forms of dexamethasone in poly(hydroxyethyl methacrylate) gels. Three different derivatives of dexamethasone i.e., dexamethasone, dexamethasone 21-acetate, and dexamethasone 21-disodium phosphate were incorporated in the gel by soaking gels in drug solutions (soaking method) or by direct dissolution of the drug in the polymerizing mixture (direct entrapment method). The loaded drug was then released by soaking the drug-loaded gels in deionized water. Dynamic drug concentrations in the aqueous phase were monitored by both loading and release experiments. The equilibrium uptake in these experiments was utilized to determine the partition coefficients, and the dynamic data was fitted to a modified diffusion equation to determine the mean diffusivity, which includes contributions from both bulk and surface diffusion. Finally the transport model for the drugs was utilized to predict the bioavailability of the three forms of dexamethasone for drug delivery via poly(hydroxyethyl methacrylate) contact lens. The partition coefficients of dexamethasone and dexamethasone 21-acetate were about 40 and 80, respectively and independent of concentration. The partition coefficient of dexamethasone 21-disodium phosphate was concentration dependent as it decreased from about 30 to 3 as the concentration increased from 0.003 to 0.107 mg/ml.

INSERTS

Optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ophthalmic infections was developed by *Baeyens et al.,* 1998. In the case of external ophthalmic infections, repeated instillations of antibiotics are required to reach therapeutic level, above the minimal inhibitory concentration. An additional administration of a corticosteroid is often needed, in order to limit the precorneal damages caused by the infection. Repeated administration of a corticosteroid can increase intraocular pressure and thus lead to glaucoma. To overcome the disadvantages of separated and repeated instillations of two products and to avoid the side effects of dexamethasone, a soluble insert containing gentamicin sulfate and dexamethasone phosphate was developed. The system ensured the concomitant release of the two drugs during the first 10 h of 21 treatment, followed by an adequate concentration of gentamicin sulfate, above the minimal inhibitory concentration of 4.0 mg ml, during 50 h, due to a combination of gentamicin sulfate with cellulose acetate phthalate, which reduces the solubility of gentamicin and ensures prolonged release of gentamicin sulphate and dexamethasone phosphate for prolonged period of time.

IMPLANTS

Attia *et al*., 1988 reported the in vivo performance of [^{3}H] dexamethasone ophthalmic film

delivery system considering different base polymers and surfactant in the rabbit eye. Eudragit RSPM and Eudragit RL/RS 100 based films, as well as the cellulose acetate phthalate based film displayed an enhancement in the disposition of the drug in the aqueous humor at specific time intervals as compared to suspension. The work for the first time illustrated the potential of dosage form design in influencing not only the bioavailability but also the drug deposition. The results presented that ophthalmic film delivery systems may function as drug targeting agents, targeting the drug to the eye tissue.

Wadood *et al*., 2004 compared the safety and efficacy of the Surodex® dexamethasone anterior segment drug delivery system (Oculex Pharmaceuticals, Inc.) and dexamethasone 0.1% eye drops (Maxidex®) in patients with inflammation after cataract surgery. The implantation of Surodex® dexamethasone anterior segment drug delivery system with posterior chamber silicone IOL (SI-40NB ®, Allergan) had stable with no significant adverse effect.

Randomized clinical trial of Surodex steroid drug delivery system for cataract surgery, anterior versus posterior placement of two Surodex in the eye was investigated by Donald *et al*., 2001. Intraocular placement of two Surodex was a safe and effective treatment method to reduce intraocular inflammation after cataract surgery and clearly indicated its supremacy to eye drops in reducing inflammatory symptoms and aqueous flare as measured with the laser flare meter. No difference in efficacy between anterior chamber placement and ciliary sulcus placement of Surodex was detected.

CONTACT LENSES

The drug delivery duration for dexamethasone from contact lenses increased to more than a week by incorporation of Vitamin E (*Kim et al.*, 2010). The results showed that with about 30% of Vitamin E loading in the contact lens, the dexamethasone release time can be increased to 7 to 9 days which is a 9 to 16 fold increase compared to the dexamethasone release duration by pure contact lens without Vitamin E loading. *In vitro* studies explored the efficacy of Vitamin E loaded lenses for ophthalmic drug delivery and the results of the study strongly suggested that Vitamin E loaded contact lenses could be very useful vehicles for extended drug delivery of both hydrophobic and hydrophilic drugs. Also the novel approach of creating in situ transport barriers through loading of Vitamin E could be useful for extending release durations from other devices.

INTOPHORESIS

Behar-Cohen *et al.,* 1997 evaluated the efficacy of a coulomb controlled iontophoresis system in the local delivery of corticosteroids for the treatment of uveitis. The therapeutic efficacy of Dexamethasone administered by coulomb controlled iontophoresis was compared to systemic injection and to topical application with the iontophoresis apparatus in the absence of electrical current. The result showed that local administration of dexamethasone by coulomb controlled iontophoresis inhibited anterior and posterior signs of intraocular inflammation as effectively as systemic administration, with no effect on systemic effect.

APPLICATOR

Haller *et al*., 2009 evaluated the safety and performance of an applicator-inserted dexamethasone drug delivery system. Patients with clinically observable macular edema were randomized to receive 700 µg dexamethasone drug delivery system via a pars plana incisional placement or a 22-gauge applicator insertion. Both procedures were well tolerated and none of the patients in the applicator group required sutures to close the insertion wound. The result shows the occurrence of vitreous hemorrhage in two patients in the incisional group and none in the applicator group. Increases in intraocular pressure were less frequent in the applicator group than the incisional group. No cases of endophthalmitis or retinal detachment occurred in either group.

Haller *et al* reported the dexamethasone drug delivery system applicator system which allowed safe, effective, and sutureless intravitreal placement of 700 µg dexamethasone drug delivery.

MICROEMULSION

Fialho *et al.,* 2004 prepared new vehicle based on a microemulsion for topical ocular administration of dexamethasone using surfactant as Cremophor EL and cosurfactant propylene glycol. The pharmacokinetics of the system was studied in rabbits in order to determine its potential as an absorption promoter, and this was compared to a conventional dosage form of dexamethasone. The microemulsion developed produced a higher peak concentration of the drug (1.86 µg/mL) when compared with conventional dosage form. Such a formulation offers the possibility of decreasing the number of applications, per day of eye drops.

NANOPARTICLES

Nanoparticle drug delivery offers advantages that allow a more targeted drug delivery and controllable release of the therapeutic compound. The study by Zhang *et al.,* 2009 investigated the tolerance and pharmacokinetics of dexamethasone loaded poly (lactic acid–co-glycolic acid) nanoparticles (DEX-NPs) in rabbits after intravitreal injection that provided a more efficient means for improving the retention of the drug in the vitreal cavity, and allowed for sustained release of dexamethasone for at least 50 days in the rabbit eyes, during which relatively constant drug levels in the vitreous were obtained for about 30 days.

The optimized dexamethasone encapsulation within biodegradable poly(d,l-lactide-coglycolide) (PLGA) nanoparticles by solvent evaporation method for intravitreal injection have been developed by Gomez-Gaete *et al.,* 2007. The influence of several parameters on dexamethasone encapsulation was investigated such as the type of organic solvent and polymer, the dexamethasone initial mass, the evaporation rate of the

solvent, the continuous phase saturation and the incorporation of a lipid in the polymer. The highest drug loading was obtained using 100 mg PLGA 75:25 in a mixture of acetone-dichloromethane 1:1 (v:v) and 10 mg of dexamethasone. The drug was completely released from this optimized formulation after 4 h of incubation at 37 °C. Differential scanning calorimetry and X-ray diffraction demonstrated that the drug was molecularly dispersed within the nanoparticles whereas the non-encapsulated dexamethasone crystallized. The results demonstrated the feasibility of encapsulating dexamethasone and its subsequent delivery.

Rafie *et al.,* 2010 investigated the in vivo effects of a new smart polymer loaded with dexamethasone on inflamed rabbit eye. N-isopropylacrylamide, vinyl pyrrolidone, and methacrylate were used as monomers to prepare polymeric micelles in the presence of N,N-methylene bis-acrylamide and triethyleneglycol dimethacrylate as cross-linking agents. These micelles were characterized on their physicochemical properties using a particle size analyzer, FT-IR, and ^{1}H NMR. Dexamethasone-containing nanosuspensions consisting of temperature- and pH-sensitive micellar nanoparticles were prepared. To evaluate the efficacy of the novel ocular drug delivery the novel micellar nanoparticles, uveitis was induced by intravitreal injection of the endotoxin within the rabbit eyes. Clinical distinctions for the inflammation within eyes were performed using Hogan's classification method and statistically analyzed using independent student t-tests and Mann–Whitney U-tests. Topical administration of prepared nanosuspensions clearly reduced uveitis symptoms, which were qualified with Hogan scoring. Statistical analysis represented that both of the nano formulations significantly reduced inflammation ($p < 0.05$) during 48 hr after LPS injection.

CUBOSOMES

The self-assembled liquid crystalline nanoparticles i.e cubosomes, were investigated as an ocular drug delivery system by Li *et al.,* 2010. The apparent permeability coefficient of dexamethasone formulated in cubosomes was significantly enhanced. In addition, the cubosomes (10% oil) with low viscosity were retained in the preocular region much longer. Consequently, the ocular bioavailability of dexamethasone has been greatly improved.

In vitro, the apparent permeability coefficient of dexamethasone administered in cubosomes exhibited a 4.5 fold (F1) and 3.5 fold (F2) increase compared to that of dexamethasone sodium phosphate eye drops. Preocular retention studies revealed that the retention of cubosomes was significantly longer than that of solution and carbopol gel, with $AUC_{0\rightarrow180\ min}$ of RhB cubosomes being 2–3-fold higher than that of the other two formulations. In vivo pharmacokinetics in aqueous humor was evaluated by microdialysis, which indicated a1.8 fold (F1) increase in$AUC_{0\rightarrow240\ min}$ of dexamethasone administered in cubosomes relative to that of dexamethasone phosphate eye drops, with about an 8-fold increase compared to that of dexamethasone suspension. Corneal cross-sections after incubation with dexamethasone cubosomes demonstrated an unaffected corneal structure and tissue integrity, which indicated the good biocompatibility of dexamethasone cubosomes (Li *et al.,* 2010).

CONCLUSION

The complexity of the eye in terms of anatomic barriers and lacrimal drainage presents a number of unique challenges for ocular drug delivery. In this scenario, drug delivery to the posterior part of the eye becomes all the more challenging due to the anatomical and physiological barriers that separate the posterior and anterior segments. Systemic use of glucocorticoids cause a series of adverse and toxic effects as withdrawal symptoms, suppression of hypothalamus-pituitary axis, electrolyte imbalance. These needs have generated interest and development in the novel techniques of ophthalmic drug delivery systems that can increase bioavailability, prolong action, minimize local and systemic side effects and achieve better patient compliance.

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