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OPTHALMIC DRUG DELIVERY SYSTEM FOR ANTIBIOTHERAPY

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ABSTRACT :

One of the most challenging tasks faced by the pharmaceutical scientists is th ophthalmic drug delivery. In the last fifty years, ophthalmic drug delivery research has made much progress, challenging scientists about the advantages and limitations of this drug delivery approach. Their aim is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Therefore, to sustain drug levels at the target site for a sufficient time. Opthalmic drug delivery has proved significant advancement for future point of view. This article evaluates a variety of ophthalmic drug delivery systems. Topical eye drops are the most commonly used formulation in ocular drug delivery. Despite the good tolerance for patients, this topical administration is only focus on the anterior ocular diseases and had a high precorneal loss of drugs due to the tears production and ocular barriers. Antibiotics are popularly used in solution or in ointment for the ophthalmic route. However, their local bioavailability needs to be improved in order to decrease the frequency of administrations and the side effects and to increase their therapeutic efficiency. For this purpose, sustained release forms for ophthalmic delivery of antibiotics were developed. This review briefly describes the ocular administration with the ocular barriers and the currently topical forms. It focuses on experimental results to bypass the limitations of ocular antibiotic delivery with new ocular technology as colloidal and in situ gelling systems or with the improvement of existing forms as implants and contact lenses. Nanotechnology is presently a promising drug delivery way to provide protection of antibiotics and improve pathway through ocular barriers and deliver drugs to specific target sites.

Keywords : antibiotics; ocular drug administration; nanoparticles; drug delivery

INTRODUCTION :

They are specialized dosage forms designed to be instilled onto the external surface of the eye (topical) , administered inside (intraocular) or adjacent (periocular) to the or used in conjuction with an ophthalmic device. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments. But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lacrimal nasal drainage. Ophthalmic drug delivery presents major challenges for pharmaceutical and medicinal sciences. For several decades, progress has been achieved to improve the currently dosage forms. Ocular diseases are complicated to treat, and ocular forms need to be safe, non-allergic for the patient and sterile. Topical forms represent 90% of the marked formulation[1]. The tear fluid turnover, the nasolacrimal drainage, the corneal epithelium and the blood-ocular barriers are decreasing the local bioavailability of drugs and residence time on the ocular surface in topical application. Only 5%–10% of the drug crosses the corneal barriers. Anterior segment diseases as blepharitis, conjunctivitis, scleritis, keratitis and dry eye syndrome are resolved with topical or periocular administration. The delivery of drug to the posterior segment of the eye for glaucoma, endophthalmitis or uveitis and to the anterior segment has the same issue of poor bioavailability of the drug and barriers. However, intraocular administration might be preferred despite its risk of complication.[2]

In addition, compared to the oral route, ocular drug delivery provided equivalent or better bioavailability in the eye.[3]Approaches have been made for the improvement of the bioavailability of the drug, the controlled release and the improvement of the therapeutic effect.[4] Antibiotics are group of medicines popularly used in ophthalmic delivery due to the multiples ocular diseases (microbial keratitis, conjunctivitis, Meibomian gland dysfunction and dry eye). Infectious disease is one of the most public health challenge.[5] Antibacterial therapies can be administrated in the eye by topical, subtenon, intraocular or subconjunctival administration. Tetracyclines, fluoroquinolones, aminoglycosides and penicillins are examples of antibiotics commonly used in the treatment of eye infections.[6]

The antimicrobial resistance is the ability of bacteria to resist to the effect of an antibiotic administration. This limitation of efficacy is caused by the misuse of antibiotic, the overuse of this group of medicine and the adaptation of the bacteria to the effect. In fact, ophthalmic antibiotic delivery aims to decrease the frequency of administration and dosing by improving the current forms and developing new ones. New ocular drug delivery forms are various; they included in situ gelling systems, liposomes, nanoparticles, niosomes, nanoemulsions and microemulsions. They are suitable for hydrophilic or lipophilic drugs, have the capacity of targeting a specific site and can be administrated in different routes. With the appropriate excipients, in situ gelling systems are able to increase the precorneal residence time and decrease the loss of drug due to the

tear. Different polymers, methods of preparation and compositions allow the nanoparticles to respond to a need for mucoadhesion, topical, periocular or intraocular administration, and to obtain a stable, effective and non-irritating formulation for the patient.

The objective of this is to review the antibiotic formulations for an ophthalmic administration. First the ocular anatomy and physiology and the ocular barriers were described. Topical forms such as eye drops, ointments, hydrogels, contact lenses and ophthalmic inserts are developed in a second part to introduce the ocular administration and explain the currently marketed dosage form. Finally, recent advances on ocular antibiotic administration are reviewed. In vitro and in vivo studies explored the efficacy of antimicrobial formulations. Different compositions and forms are developed to improve the bioavailability of antibiotics, increase the residence time in the eye and the therapeutic response.

Ideal characteristics of ophthalmic drug delivery system[7] :

• Good corneal penetration.

• Maximizing ocular drug absorption through prolong contact time with corneal tissue.

• Simplicity of instillation for the patient.

• Reduced frequency of administration.

• Patient compliance.

• Lower toxicity and side effects.

• Minimize precorneal drug loss.

• Nonirritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking).

• Should not cause blurred vision.

• Relatively nongreasy.

• Appropriate rheological properties and concentrations of the viscous system.

Fomulation :

Improvement of Drug Dissolution and Stability Using Cyclodextrins :

Cyclodextrins (CD) were discovered in the 1900 and more recently used in ocular drug delivery. They are cyclic oligosaccharides with an inner lipophilic cavity and a hydrophilic outer surface. They are used as solubilizer, drug stabilizer, permeation enhancers, separation agent in HPLC or catalyst and additives. These excipients increase solubility and stability of drugs, prevent side effects as irritation and discomfort.[8] Cyclodextrins should be non-irritating, non-toxic, well tolerated, inert and enhance permeability of the drug through the corneal mucosa. CD can be used in particles (nanosphere, microsphere, liposome).[9] Hydroxylpropyl-β-cyclodextrin (HPβCD) was used to create a complex with ciprofloxacin in order to formulate eye drops. The inclusion complex showed a better stability, an ocular tolerance and a higher biological activity in comparison to marketed eye drops and simple aqueous solutions.[10] The same combination increased the solubility of ciprofloxacin from 3-fold at pH 5.5 and 2-fold at pH 7.4. The authors noticed that the complex at pH 5.5 had a higher stability after two months of storage than the

complex at pH 7.4. The stability of the drug increased with the HPβCD and the complex improved the in vitro release of the drug.[11] Novel βCD polymers are incorporated at complexes with rifampicine, novobycin or vancomycin into a hydrogel showed a slower release of the drug compared to the dextrose-based gels. The study demonstrated that the larger and more hydrophilic drugs had release profiles less altered than small hydrophobic drugs.[12]

Contact Lens for Antibiotic Delivery **:**

Contact lenses were used as drug reservoir or support for the active ingredient in antibiotic ocular delivery. Initially, they are used as ophthalmic system to correct vision. The scleral RPG (Rigid Gaz Permeable)) lenses trap a tear reservoir, which can be used as a drug container. It prevents tear evaporation or adhesion from mucus filament in the cornea, has a potential cornea healing or hydrates the cornea in severe case of dry eye disease.[13] It prevents eyes of the patient from exposure to their irregular cornea and the reservoir can contain some artificial tears needed to lubricate the surface of the eye. In the toxic epidermal necrosis and Steven-Johnson syndrome, wearing scleral lens improves the relieving symptoms. The liquid reservoir of this lens can contain some drug as topical corticosteroids and cyclosporine.[14] More recently, a study describes the in vivo release of ofloxacin from a scleral lens in rabbit with keratitis. This preclinical study assesses local tolerance and intraocular diffusion of the antibiotic administrated by a contact lens. The authors found a higher level of drug in aqueous humor and cornea than those reported with other administration route. [15]

Ocular Inserts for Antibiotic Delivery **:**

Ocular insert is solid or semi-solid preparation placed in the cul-de-sac to deliver a controlled flow of drug. The use of ocular insert for antibiotic delivery was also described in the literature. In 1980, some researchers studied the in vitro and the in vivo release of antibiotics such as erythromycin and erythromycin estolate from matricial ocular inserts. They discovered that when the water content of the hydrogel insert is more than 30%, the elution rate of a low aqueous solubility drug is constant.[16] In the same time, drug-inserts with copolymers of N-vinylpyrrolidone tested completely suppressed the chlamydia trachomatis infection in the monkey eyes.[17] In a study, macrolide antibiotics (erythromycin) and penicillin were evaluated as a potential ocular drug delivery system in an antibiotic-impregnated collagen insert. The system with the erythromycin and the soluble collagen produced the most interesting system due to his sustained drug delivery.[18] To treat external ophthalmic infections, a combination of the aminoglycoside, gentamicin sulfate, and dexamethasone phosphate in a soluble insert was developed. The matricial insert was composed of HPMC, ethylcellulose and carbomer. This new form prolonged the release of gentamycin above the minimum inhibitory concentration value (MIC) of 4μg·mL−1 for nearly 50 h. The dexamethasone side effects caused by repeated instillation were avoided and the compliance improved.[19]

In Situ Gelling Systems for Antibiotic Delivery :

Some antibiotics were studied in different in situ gelling systems during the past two decades to improve patient compliance by:

prolonging and controlling drug release, prolonging corneal contact time and enhancing ocular bioavailability. Different in situ gelling systems are used in ocular drug delivery as the thermosensitive, the ion-activated and the pH sensitive gelling system.

Different concentrations of active substance in the formulation allowed screening the efficiency on referential bacteria as Staphylococcus aureus, Pseudomonas aeruginosa or Escherichia coli. In a study, various concentrations of clarithromycin or levofloxacin in ophthalmic gels were tested. Two drops of each gel were administered four times per day during 4 days. The 0.25% clarithromycin ophthalmic gel had a better action again Staphylococcus aureus than the 0.1% clarithromycin ophthalmic gel.[20]

Different excipients are used for the formulation of in situ gelling systems in order to control the mucoadhesion force and the viscosity of the formulation. HPMC is a viscosity enhancer commonly employed in gel formulation. The combination of alginate as ionic-induced gelation agent and HPMC with gatifloxacin demonstrated a higher efficacy than the alginate alone. The mixture could be used as an in situ gelling system to improve compliance of patient and increase ocular bioavailability.[21] These conclusions were confirmed by a recent study testing HPMC and sodium alginate in a pH induced gelation system developed for a ciprofloxacin ocular gel.[22] In some cases, the addition of HPMC and methylcellulose is used to increase the viscosity of the gel and decrease the concentration of carbomer in the formulation. This pH or ionic sol-in-gel transition system with ciprofloxacin, used in corneal ulcer and corneal infection, allowed prolonging the antimicrobial effect against bacteria for instance Escherichia coli, Staphylococcus strains and Pseudomonas aeruginosa.[23]

Colloidal Systems for Antibiotic Delivery :

Colloidal systems are popularly employed in the development of formulation for the treatment of ocular diseases (Table 3). They have many advantages; prolonging the residence time of the drug on the surface of the eye, sustained release, increasing the bioavailability of the drug. The dosages' forms

included microemulsions, nanoemulsions, nanoparticles, liposomes or niosomes (Figure1).[5,24]

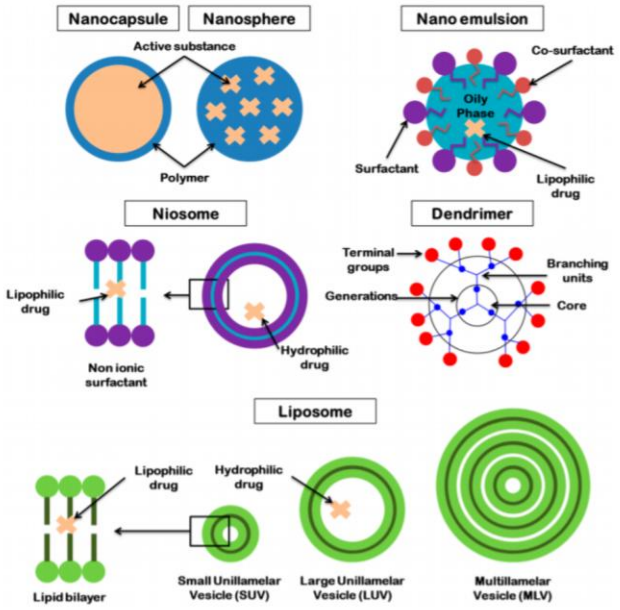

Figure 5. Schema of micro- and nanostructure intended for ocular drug delivery.

Microemulsions for antibiotic delivery :

Microemulsions are colloidal systems kinetically stable. They are used for their ability to deliver both lipophilic and hydrophilic drugs and to increase the bioavailability of active substances. Tween® 80 (polyoxyethylene sorbitan monooleate) and Span® 20 (sorbitan monolaurate) are mainly used as a non-ionic surfactant and co-surfactant for microemulsion formulation. Tween® 80 is recognized as a practically non-irritating and non-toxic surfactant for ophthalmic use.[25]

. Lv et al. studied the stability of microemulsion containing 0.3% of chloramphenicol for the treatment of trachoma and keratitis. The organic phase is composed of butanol, isopropyl palmitate and isopropyl myristate and the aqueous phase is composed of water. They concluded with an improvement of the stability of the drug after three months compared to classical chloramphenicol eye drops. Chloramphenicol was in hydrophilic shells of microemulsion drops.[26] This improvement of stability was confirmed by another study using microemulsion for the ocular delivery of moxifloxacin for the treatment of bacterial keratitis. Droplet sizes were below 40 nm and exhibited a sustained drug release profile. The in vivo study showed a greater antimicrobial activity on bacterial keratitis in rabbit eyes than the commercial eye drops.[27]

Nanoemulsions for Antibiotic Delivery **:**

Many studies describe the use of nanoemulsion in ocular administration. Their small size and god tolerance by the patient are advantages for an effective treatment. Unfortunately, this form is sparsely described in the literature in association with antibiotics. Researchers explored a mucoadhesive cationic nanoemulsion of dexamethasone and polymyxin B. The innovation was in the use of a positively charged drug and preservatives to achieve mucoadhesion of cationic emulsion. The lipid phase was composed of dexamethasone 0.5% (w/w), Lipoid® S100-Eutanol® G (30%:70%) (soy phosphatdylcholine-octyldodecanol) (BASF Corporation, Ludwigshafen, Deutschland)) and the aqueous phase contained polymyxin B 0.1% (w/w), cetylpiridium chloride 0.01% (w/w) and glycerol 2.6% (w/w). The pH of the formulation was 5.31, droplets size was below 200 nm, and zeta potential ranged from 11 to +9 mV and the emulsion was stable after six months at room temperature and +4◦C. The in vitro study demonstrated the non-cytotoxicity of the nanoemulsion and its ocular potential application as viable alternative to commercial solutions.[28]

Nanoparticles and Microparticles for Antibiotic Delivery *:*

Nanoparticles were explored in many cases of eye diseases. With their ability to cross the ocular tissues[29] without any influence on cornea, iris or retina, they are promising technology for increasing the therapeutic efficacy of ophthalmic therapies.[30]

Das et al. studied polymeric nanoparticles composed of Eudragit® RL100 and prepared by the nanoprecipitation method for ophthalmic delivery of amphotericin B against Fusarium solani. The particles had a size ranged from 130 to 300 nm, a positive zeta potential and encapsulation efficiency from 60% to 80%. They showed no signs of eye irritation and were stable for two months at +4◦C and room temperature.[31] Other authors confirmed this conclusion. The combination of Eudragit® RL100 and Pluronic® F108 (BASF Corporation,

Ludwigshafen, Deutschland) formulated small positive particles (below 500 nm) with no significant chemical interaction between the polymer and the drug. They noticed that changing the pH of the external phase of nanoparticle suspension increased the encapsulation efficiency of sulfacetamide.[32]

Ibrahim et al., developed Eudragit® RL100 / RS100 nanoparticles of coated with hyaluronic acid as bioadhesive polymer, to extend the release of gatifloxacin and prednisolone (glucocorticoid) compared to the free drug and to improve the patient compliance. The authors demonstrated that the increase of drugs:polymers ratio improved the drug encapsulation efficiency and the increase of Eudragit® RS100 amount decreased the release efficiency values. The particles had a size ranged from 315 nm to 473 nm and showed better bioavailability of drugs in the aqueous humor and corneal tissue than the marketed eye drops.[33]

Liposomes for Antibiotic Delivery :

Phosphatidylcholine (egg and soy) (PC) and cholesterol (CH) are lipids popularly used in liposomes preparation. To provide long-term drug delivery without avoiding systemic drug exposure, a study explored a ciprofloxacin hydrochloride liposomal system. Different molar concentrations of CH were studied, and it appeared that this parameter influenced the particle size, the drug entrapment efficiency and its release. The sizes of the particles ranged from 2.5 to 7.2 µm. Ciprofloxacin had a fast release profile during the first hours, then the drug release followed the Higuchi diffusion model. The authors showed that the drug release was controlled by the drug concentration during the first 10 h and, after 10 h, by the concentration of CH.[34] More recently, Chetoni et al. compared the efficacy of distamycin a liposomes to a simple solution, for Herpes simplex virus treatment. The combination of PC and CH was used. Using PC/CH liposomes, the authors showed that the ocular tissue toxicity was reduced with this formulation and that the ocular bioavailability and retention into the cornea were increased.[35]

Another study investigated the influence of different molecular weights and concentrations of chitosan for the coating of ciprofloxacin liposomes. Despite a lower encapsulation efficiency of the drug, coated liposomes improved ocular penetration and antimicrobial activity of ciprofloxacin. In vitro studies showed that the formulation inhibited the growth of Pseudomonas aeruginosa in rabbit's eyes for 24 h. In addition, a higher concentration and molecular weight of chitosan increased the mucoadhesion properties of the liposomes.[36] More recently, a study with the combination of chitosan, liposomes and ciprofloxacin hydrochloride concluded to the improvement of the bioavailability of the drug. The liposomes were composed of PC, CH at different ratio and stearylamine. Optimized formulation obtained with a ratio PC:CH of 10:0 showed the better entrapment efficiency of ciprofloxacin of 39% and an in vitro release after 8 h of 79%.[37]

To increase the contact time between the drug and the surface of the eye, the liposomal gels showed great potential. MLV were formulated with lecithin and PC in a bioadhesive poyl(vinyl alcohol) and polymethacrylic acid gel. This formulation aimed to minimize the dilution effect of tear in the conjunctival sac and ensured a steady and prolonged drug release. The liposomal encapsulation of the ciprofloxacin extended the in vitro release of the antibiotic.[38]

Niosomes for Antibiotic Delivery :

Antiglaucoma therapy requires a continuous and chronic administration of antibiotics. To improve the low corneal penetration and bioavailability of drugs in conventional ocular forms, azetazolamide-niosomes were tested as ocular drug delivery vesicles. Span® 40 or 60 and CH were used in different molar ratios. The results showed that the ratio 7:6 (Span® 60:CH) made MLV and had the higher entrapment efficiency. The formulation showed a high retention of drug with 75% of active substance in the vesicles after 3 months at +4◦C. The intraocular pressure (IOP) was measured to establish the treatment efficacy due to the antimicrobial activity of acetazolamide. There was a better decrease of IOP with the niosomes compared to the free drug solution. The most effective molar ratio was 7:4 (Span® 60:CH) with a prolonged decrease of IOP. In addition a reversible irritation in the rabbit's eyes was noted with no major change in ocular tissues.[39]

Another study explored acetazolamide-niosomes coated with Carbopol® (bioadhesive effect) for a glaucoma treatment. The low solubility (0.7mg/mL) and low permeability coefficient of the drug require frequent administration. They compared the coated niosome with an aqueous suspension with 1% w/v of Tween® 80 as dispersing agent. They demonstrated a concentration of acetazolamide in the aqueous humor (determined by a microdialys method) two fold higher with niosomes than using aqueous suspension and a longer effect; 6 h for the niosomes against 3 h for the aqueous suspension.[40]

Gentamicin is a water-soluble antibiotic which was studied in a niosomal system with Tween® (60 or 80) or Brij 35, CH and dicetylphosphate. With in vitro drug release, the study demonstrated a higher drug concentration inside the vesicles and slower drug release compared to the aqueous solution. They observed that the size of vesicles depended of amount of cholesterol and surfactant type. The molar ratio of 1:1:0.1 (Tween® 60:CH:dicetylphosphate) had the higher entrapment efficiency (92%) and the higher release rate of drug 8 h after administration (66%) with no sign of ocular irritation.[41]

More recently, a study confirmed this conclusion. Ciprofloxacin-niosomes were developed with different concentrations of Span®, Tween® and CH to treat conjunctiva and corneal ulcer. They obtained a ranged size from 8.6 to 61.3 µm and an entrapment efficiency of 74% and demonstrated that the MIC values with niosomes were 2-fold higher compared to the free ciprofloxacin. In addition, the authors concluded of the higher release of drug for the combination of Span® and Tween®.[42]

Table 3. Example of colloidal system for ocular drug delivery of antibiotics.

Formulation	Antibiotic	Anterior (AS) or posterior (PS) Seg	Disease Targeted	Reference

		ment		
Microemulsions	Chloramphenicol	AS	Trachoma	[26]
		AS	Keratitis	[27]
	Moxifloxacin		Bacterial keratitis	
Nanoemulsions	Polymixin B	AS	Opthalmic infection	[28]
Nanoparticles	Tobramycin	AS + PS	Bacteria infection *Pseudomonas aeruginosa*	[43]
	Levafloxacin	AS		[44]
			Bacteria infection *S. aureus and E. coli*	
Liposomes	Ciproflox acin	PS	Bacterial endophthalmitis	[45]
	Distamycin A	AS	Herpes simplex virus	[35]
Niosomes	Acetazolamide	AS	Glaucoma	[39]
	Ciproflox acin	AS	Conjunctiva	[42]

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS[46-51] :

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.

2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.

4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.

5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.

6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.

7. To provide better housing of delivery system.

Conclusions

Topical eye drops represent 90% of all ocular dosage forms. In recent years, medical and pharmaceutical researchers have made major advances in the field of ophthalmic administration and in ocular drug delivery systems. New ocular drug delivery systems have great potential to improve drug bioavailability in the eye. Limitations of the ocular barriers are major issues to solve for an optimal formulation. Active substance limitations are decreased with the choice of an adaptable form and composition. Patient compliance improves with a tolerable and non-irritating formulation; this parameter is primary for an acceptable administration.

This review showed various development studies of ocular delivery forms. Many studies explored the possibility to decrease

the side effects of ocular barrier to prolong ophthalmic residence of the drugs in the eyes, to improve the bioavailability of the active substances and to enhance ocular penetration. Various antibiotics with different characteristics were tested with different delivery systems in order to improve their ophthalmic bioavailability. Antibiotic administration required optimal antimicrobial efficacy. These drugs are used in eye surgeries, anterior segment and posterior segment diseases. Some improvements to limit the impact of the antibiotic's disadvantages on the eye are under study and under development. Existing forms and new shapes make it possible to increase the ocular therapy efficacy. In the next few years, drug development allowing local action without the need for systemic passage will decrease the frequency of administration, dosage of the drug and improve patient compliance.

Reference :

1. Gan, L.; Wang, J.; Jiang, M.; Bartlett, H.; Ouyang, D.; Eperjesi, F.; Liu, J.; Gan, Y. Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. Drug Discov. 2013, 18, 290–297.

2. Le Bourlais, C.; Acar, L.; Zia, H.; Sado, P.A.; Needham, T.; Leverge, R. Ophthalmic drug delivery systems—Recent advances. Prog. Retin. Eye Res. 1998, 17, 33–58.

3. Achouri, D.; Alhanout, K.; Piccerelle, P.; Andrieu, V. Recent advances in ocular drug delivery. Drug Dev. Ind. Pharm. 2013, 39, 1599–1617.]

4. Yellepeddi, V.K.; Palakurthi, S. Recent advances in topical ocular drug delivery. J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther. 2016, 32, 67–82.

5. Kalhapure, R.S.; Suleman, N.; Mocktar, C.; Seedat, N.; Govender, T. Nanoengineered drug delivery systems for enhancing antibiotic therapy. J. Pharm. Sci. 2015, 104, 872–905.

6. Sharma, S. Antibiotic resistance in ocular bacterial pathogens. Indian J. Med. Microbiol. 2011, 29, 218–222.

7. Keister JC, Cooper ER, Missel PJ, Lang JC, Huger DF. Limits on optimizing ocular drug delivery. J Pharm Sci 1991;80:50-3.

8. Shimpi, S.; Chauhan, B.; Shimpi, P. Cyclodextrins: application in different routes of drug administration. Acta Pharm. Zagreb Croat. 2005, 55, 139–156.

9. Tiwari, G.; Tiwari, R.; Rai, A.K. Cyclodextrins in delivery systems: Applications. J. Pharm. Bioallied Sci. 2010, 2, 72.

10. Nijhawan, R.; Agarwal, S.P. Development of an ophthalmic formulation containing ciprofloxacin-hydroxypropyl-b-cyclodextrin complex. Boll. Chim. Farm. 2003, 142, 214–219.

11. Bozkir, A.; Denli, Z.F.; Basaran, B. Effect of hydroxypropyl-beta-cyclodextrin on the solubility, stability and in-vitro release of ciprofloxacin for ocular drug delivery. Acta Pol. Pharm. 2012, 69, 719–724.

12. Thatiparti, T.R.; von Recum, H.A. Cyclodextrin complexation for affinity-based antibiotic delivery. Macromol. Biosci. 2010, 10, 82–90.

13. Pullum, K.W. The unique role of scleral lenses in contact lens practice. Contact Lens Anterior Eye 1999, 22, S26–S34.

14. Tougeron-Brousseau, B.; Delcampe, A.; Gueudry, J.; Vera, L.; Doan, S.; Hoang-Xuan, T.; Muraine, M. Vision-related function after scleral lens fitting in ocular complications of stevens-johnson syndrome and toxic epidermal necrolysis. Am. J. Ophthalmol. 2009, 148, 852–859.e2.

15. Laballe, R.; Vigne, J.; Denion, E.; Lemaitre, F.; Goux, D.; Pisella, P.-J. Preclinical assessment of scleral lens as a reservoir-based ocular therapeutic system. Contact Lens Anterior Eye J. Br. Contact Lens Assoc. 2016, 39, 394–396.

16. Ozawa, H.; Hosaka, S.; Kunitomo, T.; Tanzawa, H. Ocular inserts for controlled release of antibiotics. Biomaterials 1983, 4, 170–174.

17. Hosaka, S.; Ozawa, H.; Tanzawa, H.; Kinitomo, T.; Nichols, R.L. In vivo evaluation of ocular inserts of hydrogel impregnated with antibiotics for trachoma therapy. Biomaterials 1983, 4, 243–248.

18. Punch, P.I.; Costa, N.D.; Edwards, M.E.; Wilcox, G.E. The release of insoluble antibiotics from collagen ocular inserts in vitro and their insertion into the conjunctival sac of cattle. J. Vet. Pharmacol. Ther. 1987, 10, 37–42.

19. Baeyens, V.; Kaltsatos, V.; Boisramé, B.; Varesio, E.; Veuthey, J.-L.; Fathi, M.; Balant, L.P.; Gex-Fabry, M.; Gurny, R. Optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ophthalmic infections. J. Controlled Release 1998, 52, 215–220.

20. Wang, J.; Li, X.; Xiong, L.; Sun, N. Different concentrations of clarithromycin ophthalmic gel for rabbits corneal ulcers induced by Staphylococcus aureus. Yan Ke Xue Bao 2008, 24, 18–22.

21. Liu, Z.; Li, J.; Nie, S.; Liu, H.; Ding, P.; Pan, W. Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin. Int. J. Pharm. 2006, 315, 12–17.

22. Carlfors, J.; Edsman, K.; Petersson, R.; Jörnving, K. Rheological evaluation of Gelrite® in situ gels for ophthalmic use. Eur. J. Pharm. Sci. 1998, 6, 113–119.

23. Al-Kassas, R.S.; El-Khatib, M.M. Ophthalmic controlled release in situ gelling systems for ciprofloxacin based on polymeric carriers. Drug Deliv. 2009, 16, 145–152.

24. Ameeduzzafar; Ali, J.; Fazil, M.; Qumbar, M.; Khan, N.; Ali, A. Colloidal drug delivery system: Amplify the ocular delivery. Drug Deliv. 2014, 23, 700–716.

25. Ammar, H.O.; Salama, H.A.; Ghorab, M.; Mahmoud, A.A. Nanoemulsion as a Potential Ophthalmic Delivery System for Dorzolamide Hydrochloride. AAPS PharmSciTech 2009, 10, 808–817.

26. Lv, F.-F.; Zheng, L.-Q.; Tung, C.-H. Phase behavior of the microemulsions and the stability of the chloramphenicol in the microemulsion-based ocular drug delivery system. Int. J. Pharm. 2005, 301, 237–246.

27. Bharti, S.K.; Kesavan, K. Phase-transition W/O Microemulsions for ocular delivery: Evaluation of antibacterial activity in the treatment of bacterial keratitis. Ocul. Immunol. Inflamm. 2016, 1–12.

28. Li, X.; Müller, R.H.; Keck, C.M.; Bou-Chacra, N.A. Mucoadhesive dexamethasone acetate-polymyxin B sulfate cationic ocular nanoemulsion–novel combinatorial formulation concept. Int. J. Pharm. Sci. 2016, 71, 327–333.

29. Almeida, H.; Amaral, M.H.; Lobao, P.; Frigerio, C.; Sousa Lobo, J.M. Nanoparticles in Ocular Drug Delivery Systems for Topical Administration: Promises and Challenges. Curr. Pharm. Des. 2015, 21, 5212–5224.

30. Zhou, H.-Y.; Hao, J.-L.; Wang, S.; Zheng, Y.; Zhang, W.-S. Nanoparticles in the ocular drug delivery. Int. J. Ophthalmol. 2013, 6, 390–396.

31. Das, S.; Suresh, P.K.; Desmukh, R. Design of Eudragit RL 100 nanoparticles by nanoprecipitation method for ocular drug delivery. Nanomedicine Nanotechnol. Biol. Med. 2010, 6, 318–323.

32. Mandal, B.; Alexander, K.S.; Riga, A.T. Sulfacetamide loaded Eudragit® RL100 nanosuspension with potential for ocular delivery. J. Pharm. Pharm. Sci. Publ. Can. Soc. Pharm. Sci. Soc. Can. Sci. Pharm. 2010, 13, 510–523.

33. Ibrahim, H.K.; El-Leithy, I.S.; Makky, A.A. Mucoadhesive nanoparticles as carrier systems for prolonged ocular delivery of gatifloxacin/prednisolone bitherapy. Mol. Pharm. 2010, 7, 576–585.

34. Mehanna, M.M.; Elmaradny, H.A.; Samaha, M.W. Ciprofloxacin liposomes as vesicular reservoirs for ocular delivery: Formulation, optimization, and in vitro characterization. Drug Dev. Ind. Pharm. 2009, 35, 583–593.

35. Chetoni, P.; Monti, D.; Tampucci, S.; Matteoli, B.; Ceccherini-Nelli, L.; Subissi, A.; Burgalassi, S. Liposomes as a potential ocular delivery system of distamycin A. Int. J. Pharm. 2015, 492, 120–126.

36. Mehanna, M.M.; Elmaradny, H.A.; Samaha, M.W. Mucoadhesive liposomes as ocular delivery system: Physical, microbiological, and in vivo assessment. Drug Dev. Ind. Pharm. 2010, 36, 108–118.

37. Abdelbary, G. Ocular ciprofloxacin hydrochloride mucoadhesive chitosan-coated liposomes. Pharm. Dev. Technol. 2011, 16, 44–56.

38. Budai, L.; Hajdú, M.; Budai, M.; Gróf, P.; Béni, S.; Noszál, B.; Klebovich, I.; Antal, I. Gels and liposomes in optimized ocular drug delivery: Studies on ciprofloxacin formulations. Int. J. Pharm. 2007, 343, 34–40.

39. Guinedi, A.S.; Mortada, N.D.; Mansour, S.; Hathout, R.M. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int. J. Pharm. 2005, 306, 71–82.

40. Aggarwal, D.; Pal, D.; Mitra, A.K.; Kaur, I.P. Study of the extent of ocular absorption of acetazolamide from a developed niosomal formulation, by microdialysis sampling of aqueous humor. Int. J. Pharm. 2007, 338, 21–26.

41. Abdelbary, G.; El-Gendy, N. Niosome-encapsulated gentamicin for ophthalmic controlled delivery. AAPS PharmSciTech 2008, 9, 740–747.

42. Akbari, V.; Abedi, D.; Pardakhty, A.; Sadeghi-Aliabadi, H. Release studies on ciprofloxacin loaded non-ionic surfactant vesicles. Avicenna J. Med. Biotechnol. 2015, 7, 69–75.

43. Chetoni, P.; Burgalassi, S.; Monti, D.; Tampucci, S.; Tullio, V.; Cuffini, A.M.; Muntoni, E.; Spagnolo, R.; Zara, G.P.; Cavalli, R. Solid lipid nanoparticles as promising tool for intraocular tobramycin delivery: Pharmacokinetic studies on rabbits. Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm. Verfahrenstechnik EV 2016, 109, 214–223.

44. Baig, M.S.; Ahad, A.; Aslam, M.; Imam, S.S.; Aqil, M.; Ali, A. Application of Box-Behnken design for preparation of levofloxacin-loaded stearic acid solid lipid nanoparticles for ocular delivery: Optimization, in vitro release, ocular tolerance, and antibacterial activity. Int. J. Biol. Macromol. 2016, 85, 258–270.

45. Wiechens, B.; Krausse, R.; Grammer, J.B.; Neumann, D.; Pleyer, U.; Duncker, G.I. Clearance of liposome-incorporated ciprofloxacin after intravitreal injection in rabbit eyes. Klin. Monatsbl. Augenheilkd. 1998, 213, 284–292.

46. Gazayerly, E.L., Omaima. N. and Hikal. A H., Int. J. Pharm. 1997; (158); 121.

47. Chien YW: Ocular drug delivery and delivery systems, special edition, 269-296.

48. Greaves JL and Wilson CG: Treatment of diseases of the eye with mucoadhesive delivery systems. Advance Drug Delivery Review 1993; 11: 349– 383.

49. Robinson JC: Ocular anatomy and physiology relevant to ocular drug delivery, Ophthalmic Drug Delivery Systems, New York, A.K. Mitra Edition, 1993, 29–57.

50. Huang AJW, Tseng SCG and Kenyon KR: Paracellular permeability of corneal and conjunctival epithelia. Investigation Ophthalmology of Visual Sciense 1989; 30: 684–689.

51. Haeringen NJV: Clinical biochemistry of tears. Survival Ophthalmology 1981; 5 : 84– 96