Review Article

Nanoemulsion in Ophthalmics: A Newer Paradigm for Sustained Drug Delivery and Bioavailability Enhancement in Ophthalmic Manifestations

Rajesh Rao*, Satish Chandra Upadhyay, Manoj Kumar Singh
Sentiss Research Centre, Product Development, Sentiss Pharma, 261, Udyog Vihar, Phase- IV, Gurugram, Haryana, India.
***Corresponding author's E-mail:** rrao@sentisspharma.com, grajesh.rao@gmail.com

Received: 23-03-2018; **Revised:** 18-04-2018; **Accepted:** 03-05-2018.

ABSTRACT

Patient noncompliance to dosage regimen is one of the most challenging aspects to achieve therapeutic target for ocular diseases. Simplifying regimen characteristics for ophthalmic dosage forms by reducing frequency of dosing is one the prime alternative to achieve patient compliance. For ophthalmic dosage forms, precorneal, corneal and blood ocular barriers, in addition to frequent washouts, prevent the penetrability of therapeutic agents and hence multiple daily dosing is required. Multicomponent nanoemulsions are thermodynamically stable and easily manufactured systems that provide better penetrability and reduced frequency of dosing of formulations with improved solubility and stability. Also micellar characteristics of nanoemulsion systems mimic tears that enhances adherence of therapeutic agents to corneal tissues. Particle size (<200 nanometer) makes the system easy to sterilize by filtration and further helps with improved visibility compared to eye ointments and oleaginous formulations. Current review focuses nanoemulsion system for sustained drug release and enhanced bioavailability for better patient compliance in ocular therapeutics.

Keywords: Nanoemulsion, Ophthalmic, Sustained Drug Delivery, Micelles.

INTRODUCTION

Topical therapeutics to eyes is administered in form of eye drops, ointments, gels, ocuserts and soft contact lenses. Among all topical delivery systems, eye drops are effortless and most convenient mode of administration[1]. Eye drops are further classified as solutions and suspensions constituting more than 90% of currently accessible marketed ophthalmic formulations[1,2]. These conventional dosage forms have poor bioavailability due to precorneal loss, transconjunctival systemic absorption and drainage. Various anatomical barriers such as corneal epithelium (hydro-lipophilic nature) impede transport of both hydrophilic and lipophilic drugs[3]. Also, eye drops has major limitations of quick dilution and washing out. Due to these limitations only 5% of administered drug reaches the aqueous humor and most of the drugs are eliminated without absorption.

Eye ointments increases bioavailability of drug by increasing contact time however these formulations have drawbacks of blurring of vision and delayed onset of action[4]. Gels provide longer contact time (compared to ointments) with no blurring of vision but manufacturing cost of the formulations is relatively very high. Ocuserts are used for prolonged delivery of drugs with constant rate through membrane with minimal side effects; whereas, soft contact lenses deliver high concentration of antiviral, antibiotics and anti-glaucoma drugs. However patient compliance is major limitations for ocuserts and soft contact lenses [4-6].

Ocular parameter influencing topical bioavailability

Eye is separated from rest of the systemic access by blood retinal, blood-aqueous and blood-vitreous barriers making topical therapy most suitable for ocular manifestations[7,8]. The highly specialized ocular barriers control the inward and flow of compounds.

Precorneal parameters

Less capacity of cul-de-sac

Eye drops are instilled in cul-de-sac. Cul-de-sac has a maximum capacity of 30 µl in humans[9]. When the lower eyelid returns to its normal position the capacity of the conjunctival sac shrinks by 70% to 80% to less than 10 µl. further the capacity of cul-de-sac can be reduce by various pathological conditions such as cicatricial, allergic or inflammatory process and disabled patient. Moreover the capacity of cul-de-sac is reduced by blinking.

Elimination of drug from lachrymal fluid

At precorneal site drugs are mainly eliminated by solution drainage, lachrymation and nonproductive absorption to the conjunctiva[10]. Conjunctiva is thin membranous vascularised part that absorbs most of the topically applied drugs. For few drugs such as β-blockers conjunctival permeability coefficients are greater the corneal permeability coefficient causing absorption of drugs to systemic circulation.

At the time of application almost 30 µl of volume is instilled to eyes but instilled dose is rapidly removed from lachrymal drainage or through lachrymal drainage system until tear return to its normal volume i.e. 7µl. Tear turnover also plays a minor roles in clearance of drug leading to lesser corneal absorption. Also drug metabolism and drug protein binding into tears hinders absorption to an extent[11, 12-14].

Corneal parameter

Cornea provides major barriers for penetration of drugs into deeper tissues. Cornea functions as a trilaminar permeability barrier. The epithelium and endothelium being hydrophobic in nature are main barriers to hydrophilic molecules. Tight Junctions that are formed by apical corneal epithelial cells, limit drug absorption from the lachrymal fluid into the eye. The stroma is hydrophilic in nature. Hence these barriers provide major resistance for both hydrophilic and hydrophobic molecules[15].

Blood-ocular barriers

The blood-ocular barriers prevent access of hydrophilic drugs in aqueous humor. Retinal pigment epithelium (RPE) and tight walls of retinal capillaries form posterior barrier. This is a barrier between blood stream and eye. Distribution of drugs into retina is limited by the RPE and retinal endothelia[15].

Various delivery systems for improving topical bioavailability

Various ocular therapeutic systems have been tried to improve the ocular bioavailability of both hydrophilic and lipophilic drugs. However these systems are associated with limitations that make these formulations intricate for manufacturing and commercialization (Table 1).

Nanoemulsion system: a potential technique for ocular drug delivery

Nanoemulsions are thermodynamically stable dispersed, micro-heterogeneous, multi-component, surfactant containing optically isotropic, transparent or translucent clear system[61,62]. Nanoemulsions are acceptable as water-continuous ophthalmological carrier systems due to their dilution with physiological water giving extraordinary advantage for water insoluble, unstable drug for significant improvement in bioavailability and reduced frequency of dosing.

Nanoemulsions exhibit several advantages as drug delivery systems [63-65]

- ✓ Nanoemulsions are formed by self emulsification process and shelf life is not dependent on manufacturing process.
- ✓ Because of thermodynamic stability, nanoemulsions are easy to manufacture and hence no significant energy contribution is required for manufacturing.
- ✓ Nanoemulsions have low viscosity that helps in instillation of drugs to eyes. Further, viscosity of nanoemulsions can even be tailored using specific gelling agents like Carbopol®.
- ✓ Nanoemulsions act as 'super-solvents' of drug. Lipophilic or hydrophilic dispersed phase, (as in oil-in-water or water-in-oil nanoemulsion respectively), act as a reservoir of lipophilic or hydrophilic drug respectively. And solubility of drugs is further enhanced by micro-domains of different polarity within the same single phase solution.
- ✓ The mean diameter of nanoemulsion droplets is below 0.22 μm, hence nanoemulsion can easily sterilized by filtration.
- ✓ The use of nanoemulsion as delivery systems improve bioavailability and efficacy of drug, that further leads to reduction in total dose thereby minimizing side-effects.
- ✓ Nanoemulsion formulations penetrate more into deeper layers of ocular tissues than the native drug.
- ✓ Nanoemulsion is spread nicely on the cornea due to its low surface tension. It further improves mixing with the precorneal film constituents. Contact time between the drug and corneal epithelium is improved due to uniform spreading and mixing of nanoemulsion formulation in eyes. Also its micellar structure mimic tears, that further increases corneal adherence of the formulation.

Exploring nanoemulsion for sustained topical ocular delivery

In nanoemulsion system, drug gets partitioned between dispersed and continuous phases. Drug can be transported through the semi-permeable membrane if the nanoemulsion system comes in its contact. Drug releases from nanoemulsion system with pseudo-zero order kinetics. Drug release from nanoemulsion system also depends on volume of dispersed phase, partition coefficient and the transport rate of the drug.

Gallarate et al. (1993) prepared oil-in-water (O/W) nanoemulsion containing levobunolol. The study revealed a reservoir effect of drug in nanoemulsion showing prolonged drug release[66]. Naveh et al. (1994) developed a nanoemulsion formulation of pilocarpine using MCT, E-80 phospholipids, miranol MHT solution, α-tocopherol and water. The nanoemulsion formulation showed a prolonged hypotensive action in normotensive rabbits after topical administration. The formulation was found to be of substantial importance as aqueous pilocarpine solution is administered 3 to 4 times a day for treatment of glaucoma. Moreover the multiple dosing causes side effects such as miosis leading to blurring of vision and also thought to be cataractogenic. The formulation showed a prolonged hypotensive effect for 11 hour post instillation and it was increased to 29 hour during follow up[67]. Muchtar et al. (1997) prepared submicron O/W emulsion of indomethacin using purified phospholipids mixture, α-tocopherol, MCT and water. The *ex vivo* permeation studies indicated apparent corneal permeability coefficient of indomethacin incorporated in system is 3.8 times greater than that of marketed aqueous solution -Indocollyre®. The formulation shows purportedly better bioavailability and retention[68].

Table 1: Various delivery systems for improving topical bioavailability and problem associated:

S. No	Delivery system(s)	Advantage over conventional delivery system	Disadvantages	Ref.
1	**Ocular inserts**	• Increased ocular residence with controlled release • Reduction of systemic absorption • Reduced frequency of administration • Targeting of intraocular tissues through non-corneal route	• Difficulty in insertion • Irritation due to penetration enhancers	16-18
2	**Nano-suspensions**	• Can be commercialized easily with long term physical stability • Very good technique for sparingly water soluble drugs • Extended release, improved bioavailability with no toxicity	• Abrasion of grinding ball leading to high metal content of formulation	19-23
3	**Hydrogel systems**	• Controlled drug delivery using biodegradable polymers • Extended release	• Blurring of vision	24,25
4	**Liposomes**	• Controlled and sustained drug release • Improved ocular bioavailability by interaction between liposome and cells through surface absorption, endocytosis, lipid exchange between walls and merging of membrane. • Biodegradable, biocompatible and non-immunogenic.	• Very high manufacturing cost • Poor stability (phospholipids are prone to oxidative degradation). • Leakage and fusion of drugs	26-33
5	**Niosomes**	• Improved ocular absorption • More stable, flexible and achieves better entrapment of hydrophilic drugs. • Increased ocular bioavailability of drugs; surfactants act as penetration enhancers as they can remove the mucous layer and break junctional complexes. • Biodegradable, biocompatible, least toxic and non-immunogenic.	• Aggregation, fusion, leaching, or hydrolysis of encapsulated drug, thus reducing shelf-life of niosomal preparation • May be irritant to eye.	27,34,35
6	**Discomes**	• Better entrapment and bioavailability of hydrophilic drugs compared to niosomes.	• High manufacturing cost. • Discomes formulation can cause irritation to eyes.	27,36
7	**Solid Lipid Nanoparticles (SLNs)**	• High drug loading capacity for lipophilic and possibly hydrophilic drugs. • Suitable to sterilization by autoclaving. • Improved ocular bioavailability. • Prolong ocular retention time. • Sustained release.	• Drug expulsion after polymeric transition during storage • Hydrophilic drugs in SLN systems show burst effects.	27,37-39
8	**Polymeric nanoparticles**	• Improvement in ocular drug penetration with prolonged action • Use of biodegradable, biocompatible, nontoxic, non-immunogenic polymer • Nanocapsules more bio-available because of their bioadhesive properties.	• High production cost. • Aggregation, fusion, or leaching of encapsulated drug, thus reducing shelf-life of formulations	40-42
9	**Microspheres**	• Controlled delivery of drugs • Mucoadhesive property of microsphere helps in improved bioavailability. • Reduced toxicity.	• Burst effect. • Difficult to manufacture and high p cost.	43-45
10	**Lipid emulsions**	• Enhanced ocular penetration and bioavailability • Enhanced drug solubilization.	• Hydrophilic drugs cannot be incorporated into this system.	46,47
11	**In-situ gelling system**	• Prolong effect • Improved retention time.	• Blurred vision. • Sticking of eyelids.	1,6,48-51
12	**Contact lenses**	• Rate of drug delivery can be controlled	• May affect iris, conjunctiva and cornea	52-55

		• Single application of formulation can deliver drug for many days	• Long term use of contact lenses may cause decreased corneal keratocyte	
13	**Cyclodextrin Complexation**	• Better stability of formulations • Improved wettability, dissolution and stability with reduced side effects • Increased corneal permeability and increased bioavailability	• Cyclodextrins are toxic to eye at higher concentrations.	56-58
14	**Dendrimer**	• Improved efficacy of drug treatment • Improved penetration by altering corneal barrier	• Blurred vision • Possibilities to damage cornea, leading to loss of eyesight	27,59,60

Table 2: Nanoemulsion for topical ocular delivery

S.No	Drug	Solubility In water at 25°C (mg/ml)	Surfactants and co surfactants	Oil	Comment	Ref.
1.	Levobunolol	0.251	Lecithin, glycerol	Soybean oil	Increased *in vitro* permeability with a reservoir effect	66
2	Timolol	2.74	Lecithin	Isopropyl myristate	Bioavailability of nanoemulsion in aqueous humour was 3.5 times greater than Timolol alone	71
3	Indomethacin	3.11×10^{-3}	Phospholipids Miranol – MHT	MCT	Considerable increase in corneal permeability compared to Indocollyre® (marketed formulation) showing almost 4 times corneal permeability coefficient with no toxicity in *ex vivo* studies	68
4	Dexamethasone	0.08	Cremophor EL, Propyleneglycol,	Isopropyl myristate	Improved ocular bioavailability(almost three times compared to conventional dosage form) and sustained effect of drug with no ocular irritation	69
5	Chloramphenicol	2.5	Span20, Span80, Tween20, Tween80	Isopropyl palmitate and isopropyl myristate	Improved stability in nanoemulsion of conventional system as chloramphenicol is quite susceptible to degradation in conventional dosage form	72,73
6	Pilocarpine	31.3	Macrogol 1500-glyceroltriricinoleate, PEG 200, propylene glycol,	Isopropylmyristate	Improved ocular bioavailability to upto 1.68 times with sustained effect compared to aqueous solution with no ocular toxicity	70

Fialho and da Silva-Cunha (2004) prepared a topical O/W nanoemulsion for topical ocular administration of dexamethasone. The results have shown the sustained release of drug hence reducing frequency of administration[9,69]. Chan et al. (2007) formulated phase transition O/W nanoemulsion of pilocarpine. Sorbitan-mono-laurate and polyoxyethylene sorbitan-mono-oleate were used as non-ionic surfactant, ethyl-oleate as oil and water as aqueous component. All formulations showed a very good precorneal retention compared to pilocarpine in solution form. The miotic response was obtained after 130 min post administration of formulation. The nanoemulsion formulation showed a better hypotensive effect compared to pilocarpine solution[70]. Various nanoemulsion formulations for ocular use are listed in Table 2.

Nanoemulsion formulations have shown its reservoir effect and sustained release behavior in various other routes showing a potential candidate for sustained release. Dalmora et al. (2001) reported sustain release of piroxicam from nanoemulsion of piroxicam[74]. Kawakami et al. (2002) prepared nanoemulsion formulation of poorly water soluble drug (nitrendipine as model drug) and depicted sustained release of formulation in *in vitro* and *in vivo* studies[75,76]. Mehta et al. (2007) formulated rifampicin O/W nanoemulsion containing oleic acid, phosphate buffer (PB), Tween 80 and ethanol for oral delivery. *In vitro* dissolution studies showed a sustained release profile of drug[77].

CONCLUSION

Eye diseases are the major cause of blindness in human. A WHO study has indicated approximately 161 million visual impairment cases worldwide, out of which 37 million were blind[78]. Topical ocular delivery of drugs is pertinent for ocular manifestations and preferred over systemic route. Marketed ocular solutions and suspensions have considerable bioavailability issues with frequent dosing. Nanoemulsion is a thermodynamically stable and easily manufactured system that has huge potential in enhancing bioavailability and reducing frequency of administration.

Various surfactant, co surfactant, oily and aqueous phases are approved by various regulatory agencies including USFDA for ocular instillation. Amount of surfactant used in nanoemulsion systems is major limitation as formation of nanoemulsion system requires high concentration of surfactants. Use of non-ionic surfactants can resolve the issue as they have minimum toxicity. Formulation evaluation parameters such as refractive index, pH, osmolality and viscosity nanoemulsion systems can easily be estimated.

Nanoemulsion systems have been explored for ocular use in previous few decades. The inherent property of sustaining the drug release makes it more patient complaint. Use of a nanoemulsion system for topical ocular therapeutics can overcome the limitation of multiple daily dosing with enhanced bioavailability. Moreover the nanoemulsion formulations are easier to formulate, scale up and do not require sophisticated instrumentation.

REFERENCES

1. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R, Ophthalmic drug delivery systems--recent advances, Prog Retin Eye Res., 17, 1998, 33-58.
2. Saati S, Lo R, Li PY, Meng E, Varma R, Humayun MS, Mini drug pump for ophthalmic use. Trans Am Ophthalmol Soc., 107, 2009, 60-70.
3. Araujo J, Gonzalez E, Egea MA, Garcia ML, Souto EB, Nanomedicines for ocular NSAIDs: safety on drug delivery, Nanomedicine, 5, 2009, 394-401.
4. Ludwig A, The use of mucoadhesive polymers in ocular drug delivery, Adv Drug Deliv Rev., 57, 2005, 1595-639.
5. Joshi A, Microparticulates for ophthalmic drug delivery, J Ocul Pharmacol., 10, 1994, 29-45.
6. Nanjawade BK, Manvi FV, Manjappa AS, In situ-forming hydrogels for sustained ophthalmic drug delivery, J Control Release, 122, 2007, 119-34.
7. Cunha-Vaz JG, The blood-ocular barriers: past, present, and future, Doc Ophthalmol, 93, 1997, 149-57.
8. Tomi MK, Hosoya, The role of blood-ocular barrier transporters in retinal drug disposition: an overview, Expert Opin Drug Metab Toxicol, 6, 2010, 1111-24.
9. Jacobs G, Martens M, Beer JD, Selecting Optimal Dosage Volumes for Eye Irritation Tests in the Rabbit. Cut. & Ocular Toxicol, 6, 1987, 109-116.
10. Lee VH, Robinson JR, Mechanistic and quantitative evaluation of precorneal pilocarpine disposition in albino rabbits, J Pharm Sci., 68, 1979, 673-84.
11. Jtirvinena K, Javinen T, Urttia A, Ocular absorption following topical delivery. Ad. Drug Del. Reviews, 16, 1995, 39-43.
12. Patton TF, Robinson JR. Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes, J Pharm Sci., 65, 1976, 1295-301.
13. Patton TF, Robinson JR, Influence of topical anesthesia on tear dynamics and ocular drug bioavailability in albino rabbits, J Pharm Sci., 64, 1975, 267-71.
14. Thombre AG, Himmelstein KJ, Quantitative evaluation of topically applied pilocarpine in the precorneal area, J Pharm Sci., 73, 1984, 219-22.
15. Hornof M, Toropainen E, Urtti A, Cell culture models of the ocular barriers, Eur J Pharm Biopharm., 60, 2005, 207-25.
16. Hillman JS, Walker A, Davies EM, Management of chronic glaucoma with pilocarpine Ocuserts, Trans Ophthalmol Soc U K, 97, 1977, 206-9.
17. Hitchings R, Smith ARJ, Experience with pilocarpine Ocuserts. Trans Ophthalmol Soc U K, 97, 1977, 202-5.
18. Krieglstein GK, Pilocarpine-ocusert-p-40 in the handicapped glaucoma patient (author's transl), Klin Monbl Augenheilkd., 167, 1975, 55-61.

19. Patravale VB, Date AA, Kulkarni RM, Nanosuspensions: a promising drug delivery strategy, J Pharm Pharmacol., 56, 2004, 827-40.
20. Agnihotri SM, Vavia PR, Diclofenac-loaded biopolymeric nanosuspensions for ophthalmic application. Nanomedicine, 5, 2009, 90-5.
21. Pignatello R, Bucolo C, Spedalieri G, Maltese A, Puglisi G. Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application, Biomaterials, 23, 2002, 3247-55.
22. Pignatello R, Bucolo C, Ferrara P, Maltese A, Puleo A, Puglisi G, Eudragit RS100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen. Eur J Pharm Sci., 16, 2002, 53-61.
23. Pignatello R, Bucolo C, Puglisi G, Ocular tolerability of Eudragit RS100 and RL100 nanosuspensions as carriers for ophthalmic controlled drug delivery, J Pharm Sci., 91 2002, 2636-41.
24. Barbu E, Verestiuc L, Lancu M, Jatariu A, Lungu A, Tsibouklis J, Hybrid polymeric hydrogels for ocular drug delivery: nanoparticulate systems from copolymers of acrylic acid-functionalized chitosan and N-isopropylacrylamide or 2-hydroxyethyl methacrylate, Nanotechnology., 20, 2009, 225108.
25. Han J, Wang K, Yang D, Nie J, Photopolymerization of methacrylated chitosan/PNIPAAm hybrid dual-sensitive hydrogels as carrier for drug delivery, Int J Biol Macromol., 44, 2009, 229-35.
26. Bochot A, Fattal E, Gulik A, Couarraze G, Couvreur P, Liposomes dispersed within a thermosensitive gel: a new dosage form for ocular delivery of oligonucleotides, Pharm Res., 15, 1998, 1364-9.
27. Sahoo S, Dilnawaz KF, Krishnakumar S, Nanotechnology in ocular drug delivery, Drug Discov Today., 13, 2008, 144-51.
28. Carvalho E, De la Fuente LM, Seijo Rey B, Liposomes as ocular drug delivery systems, Arch Soc Esp Oftalmol.,79, 2004, 151-2.
29. Abdelbary G, Ocular ciprofloxacin hydrochloride mucoadhesive chitosan-coated liposomes. 2009.
30. Hosny KM, Ciprofloxacin as ocular liposomal hydrogel. AAPS, 11, 2010, 241-6.
31. Zhang J, Guan P, Wang T, Chang D, Jiang T, Wang S, Freeze-dried liposomes as potential carriers for ocular administration of cytochrome c against selenite cataract formation, J Pharm Pharmacol., 61, 2009, 1171-8.
32. Hathout R, Mansour MS, Mortada ND, Guinedi AS, Liposomes as an ocular delivery system for acetazolamide: in vitro and in vivo studies, AAPS PharmSciTech., 8, 2007, 1.
33. Cortesi R, Argnani A, Esposito E, Dalpiaz A, Scatturin A, Bortolotti F, Lufino M, Guerrini R, Cavicchioni G, Incorvaia C, Menegatti E, Manservigi R, Cationic liposomes as potential carriers for ocular administration of peptides with anti-herpetic activity, Int J Pharm., 317, 2006, 90-100.
34. Azeem A, Anwer MK, Talegaonkar S, Niosomes in sustained and targeted drug delivery: some recent advances, J Drug Target., 17, 2009, 671-89.
35. Abdelbary G, El-Gendy N, Niosome-encapsulated gentamicin for ophthalmic controlled delivery, AAPS PharmSciTech, 9, 2008, 740-7.
36. Vyas S, Mysore PN, Jaitely V, Venkatesan N, Discoidal niosome based controlled ocular delivery of timolol maleate, Pharmazie., 53, 1998, 466-9.
37. Seyfoddin A, Shaw J, Al-Kassas R, Solid lipid nanoparticles for ocular drug delivery, Drug, 17, 2010, 467-89.
38. Souto E, Doktorovova BS, Gonzalez-Mira E, Egea MA, Garcia ML, Feasibility of lipid nanoparticles for ocular delivery of anti-inflammatory drugs, Curr, 35, 2010, 537-52.
39. Attama A, Reichl AS, Muller-Goymann CC. Sustained release and permeation of timolol from surface-modified solid lipid nanoparticles through bioengineered human cornea, Curr Eye Res., 34, 2009, 698-705.
40. Singh K, Shinde HUA, Development and Evaluation of Novel Polymeric Nanoparticles of Brimonidine Tartrate, Curr Drug Deliv, 2010.
41. Nagarwal R, Kant CS, Singh PN, Maiti P, Pandit JK, Polymeric nanoparticulate system: a potential approach for ocular drug delivery, J Control Release., 136, 2009, 2-13.
42. Li S, Liu X. Development of polymeric nanoparticles in the targeting drugs carriers, Sheng Wu Yi Xue Gong Cheng Xue Za Zhi., 21, 2004, 495-7.
43. Giannola L, de Caro IV, Giandalia G, Siragusa MG, Cordone L, Ocular gelling microspheres: in vitro precorneal retention time and drug permeation through reconstituted corneal epithelium, J Ocul Pharmacol Ther., 24, 2008, 186-96.
44. Rathod S, Deshpande SG, Albumin microspheres as an ocular delivery system for pilocarpine nitrate, Indian J Pharm Sci., 70, 2008, 193-7.
45. Durrani A, Farr MSJ, Kellaway IW, Precorneal clearance of mucoadhesive microspheres from the rabbit eye, J Pharm Pharmacol., 47, 1995, 581-4.
46. Tamilvanan S, Benita S, The potential of lipid emulsion for ocular delivery of lipophilic drugs, Eur J Pharm Biopharm., 58, 2004, 357-68.
47. Yamaguchi M, Yasueda S, Isowaki A, Yamamoto M, Kimura M, Inada K, Ohtori A, Formulation of an ophthalmic lipid emulsion containing an anti-inflammatory steroidal drug, difluprednate, Int J Pharm., 301, 2005, 121-8.
48. Mundada A, Avari SJG, In situ gelling polymers in ocular drug delivery systems: a review, Crit Rev Ther Drug Carrier Syst., 26, 2009, 85-118.
49. Al-Kassas R, El-Khatib SMM, Ophthalmic controlled release in situ gelling systems for ciprofloxacin based on polymeric carriers, Drug Deliv., 16, 2009, 145-52.
50. Ma W, Xu DH, Nie SF, Pan WS, Temperature-responsive, Pluronic-g-poly(acrylic acid) copolymers in situ gels for ophthalmic drug delivery: rheology, in vitro drug release, and in vivo resident property. Drug Dev Ind Pharm., 2008; 34: 258-66.
51. Wu C, Qi H, Chen W, Huang C, Su C, Li W, Hou S Preparation and evaluation of a Carbopol/HPMC-based in situ gelling ophthalmic system for puerarin, Yakugaku Zasshi., 127, 2007, 183-91.
52. Xinming L, Yingde C, Lloyd AW, Mikhalovsky SV, Sandeman SR, Howel CA, Liewen L, Polymeric hydrogels for novel contact lens-based ophthalmic drug delivery systems: a review, Cont Lens Anterior Eye., 31, 2008, 57-64.
53. Gulsen D, Chauhan A, Ophthalmic drug delivery through contact lenses, Invest Ophthalmol Vis Sci., 45, 2004, 2342-7.

54. Gulsen D, Li CC, Chauhan A, Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery, Curr Eye Res., 30, 2005, 1071-80.

55. Kapoor Y, Thomas JC, Tan G, John A. Chauhan. Surfactant-laden soft contact lenses for extended delivery of ophthalmic drugs, Biomaterials., 30, 2009, 867-78,

56. Nijhawan R, Agarwal SP, Development of an ophthalmic formulation containing ciprofloxacin-hydroxypropyl-b-cyclodextrin complex, Boll Chim Farm., 142, 2003, 214-9.

57. Kaur I, Chhabra PS, Aggarwal D, Role of cyclodextrins in ophthalmics, Curr Drug Deliv., 1, 2004, 351-60.

58. Maestrelli F, Mura P, Casini A, Mincione F, Scozzafava A, Supuran CT, Cyclodextrin complexes of sulfonamide carbonic anhydrase inhibitors as long-lasting topically acting antiglaucoma agents, J Pharm Sci., 91, 2002, 2211-9.

59. Spataro G, Malecaze F, Turrin CO, Soler V, Duhayon C, Elena PP, Majoral JP, Caminade AM, Designing dendrimers for ocular drug delivery, Eur J Med Chem., 45, 2009, 326-34.

60. Yao W, Sun JKX, Liu Y, Liang N, Mu HJ, Yao C, Liang RC, Wang AP, Effect of poly(amidoamine) dendrimers on corneal penetration of puerarin, Biol Pharm Bull, 33, 2010, 1371-7.

61. Azeem A, Khan ZI, Aqil M, Ahmad FJ, Khar RK, Talegaonkar S, Microemulsions as a surrogate carrier for dermal drug delivery, Drug Dev Ind Pharm., 35, 2009, 525-47.

62. Subramanian N, Ghosal SK, Acharya A, Moulik SP, Formulation and physicochemical characterization of microemulsion system using isopropyl myristate, medium-chain glyceride, polysorbate 80 and water, Chem Pharm Bull (Tokyo)., 53, 2005, 1530-5.

63. Ansari M, Kohli JK, Dixit N, Microemulsions as potential drug delivery systems: a review, PDA J Pharm Sci Technol., 62, 2008, 66-79.

64. Lawrence M, Rees JGD, Microemulsion-based media as novel drug delivery systems, Adv Drug Deliv Rev., 45,2000, 89-121.

65. He C, He XZG, Gao JQ, Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs, Expert Opin Drug Deliv., 7, 2010, 445-60.

66. Gallaratea M, Gasco MR, Trottaa M, Chetonib P, Saettoneb MF, Preparation and evaluation in vitro of solutions and o/w microemulsions containing levobunolol as ion-pair International Journal of Pharmaceutics, 100, 1993, 219-225.

67. Naveh N, Muchtar S, Benita S, Pilocarpine incorporated into a submicron emulsion vehicle causes an unexpectedly prolonged ocular hypotensive effect in rabbits, J Ocul Pharmacol., 10, 1994, 509-20.

68. Muchtar S, Abdulrazik M, Frucht-Pery J, Benita S, Ex-vivo permeation study of indomethacin from a submicron emulsion through albino rabbit cornea, Journal of Controlled Release., 44, 1997, 55–64.

69. Fialho S, Silva-Cunha A, New vehicle based on a microemulsion for topical ocular administration of dexamethasone, Clinical and Experimental Ophthalmology., 32, 2004, 626–632.

70. Chan J, Maghraby GM, Craig JP, Alany RG, Phase transition water-in-oil microemulsions as ocular drug delivery systems: in vitro and in vivo evaluation, Int J Pharm., 328, 2007, 65-71.

71. Gasco M, Gallarate RM, Trotta M, Bauchiero L, Gremmo E, Chiappero O, Microemulsions as topical delivery vehicles: ocular administration of timolol, J Pharm Biomed Anal., 7, 1989, 433-9.

72. Lv F, Zheng FLQ, Tung CH, Phase behavior of the microemulsions and the stability of the chloramphenicol in the microemulsion-based ocular drug delivery system, Int J Pharm., 301, 2005, 237-46.

73. Lv F, Li FN, Zheng LQ, Tung CH, Studies on the stability of the chloramphenicol in the microemulsion free of alcohols, Eur J Pharm Biopharm., 62, 2006, 288-94.

74. Dalmora M, Dalmora ESL, Oliveira AG, Inclusion complex of piroxicam with beta-cyclodextrin and incorporation in cationic microemulsion. In vitro drug release and in vivo topical anti-inflammatory effect, Int J Pharm., 222, 2001, 45-55.

75. Kawakami K, Yoshikawa T, Moroto Y, Kanaoka E, Takahashi K, Nishihara Y, Masuda K, Microemulsion formulation for enhanced absorption of poorly soluble drugs. I. Prescription design, J Control Release., 81, 2002, 65-74.

76. Kawakami K, Yoshikawa T, Hayashi T, Nishihara Y, Masuda K, Microemulsion formulation for enhanced absorption of poorly soluble drugs. II. In vivo study, J Control Release., 81, 2002, 75-82.

77. Mehta S, Kaur KG, Bhasin KK, Analysis of Tween based microemulsion in the presence of TB drug rifampicin, Colloids Surf B Biointerfaces., 60, 2007, 95-104.

78. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP, Global data on visual impairment in the year 2002, Bull World Health Organ., 82, 2004, 844-51.

Source of Support: Nil, **Conflict of Interest:** None.