ejpmr, 2017,4(7), 813-819

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

NIOSOMES IN OCULAR DRUG DELIVERY

Gopa Roy Biswas* and Sutapa Biswas Majee

NSHM Knowledge Campus, Kolkata-Group of Institutions, Kolkata-700 053, West Bengal, India.

***Corresponding Author: Gopa Roy Biswas**

NSHM Knowledge Campus, Kolkata-Group of Institutions, Kolkata-700 053, West Bengal, India.

Article Received on 19/05/2017 **Article Revised on 09/06/2017** **Article Accepted on 28/06/2017**

ABSTRACT

The common principle behind the success of pharmacotherapy is that the suitable drug should be present in proper concentration at the site of action for a sufficient period of time. Drug delivery in ophthalmic treatment is very challenging because of the distinctive anatomy and physiology of eye containing different barriers like many layers of cornea, sclera and retina, blood retinal, lachrymal fluid-eye barrier and drug loss from the ocular surface. To overcome those obstacles, vesicular systems especially Niosomes, a non-ionic surfactant-based vesicle are preferred due to their stability and ability to promote drug absorption by modifying the permeability of the conjunctival and scleral membranes of ophthalmic region. They provide prolonged duration of action by preventing ocular metabolism in the lachrymal fluid. Niosomes have wide access in the treatment of inflammation, dry eye, allergy, ocular hypertension, and glaucoma. In addition, it has the advantage of drug to be administered in the form of a drop, which shows significant advancement in prolonging the preocular retention on the eye surface and improvement of transcorneal penetration of novel therapeutic agents.

KEYWORDS: Niosome, Vesicular system, Non-ionic surfactants, Glaucoma.

INTRODUCTION

Ocular drug delivery is one of the most interesting challenges to the pharmaceutical scientists because of significant and pharmacokinetically specific environment that exist in eye.

Eye is the most important and sensitive organ; in fact, it is the window of our soul. It is a unique organ from anatomical and physiological point of view. The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease .There should be clear understanding in disease pathogenesis to meet ophthalmic drug delivery challenges.[1] The conventional ophthalmic solution, suspension and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases. Successful delivery of drugs into the eye is quite complicated as the eye is protected by a series of complex defense mechanisms, which produces obstruction to achieve an effective concentration of the drug within the target area of the eye. Hence the challenge is to get around the shielding barrier of the eye without affecting any permanent tissue damage.[2]

Focusing on the above mentioned points, the development of a drug delivery is achieving importance in treatment of various ocular diseases. Ocular drug targeting has major merits like.

1. Enhancing drug permeation,
2. Improving bioavailability
3. To control the release of drug
4. To target drugs at active site

Although the Traditional ophthalmic dosage forms like solutions, suspensions; ointments are still acceptable, they are no longer sufficient to treat some of the ocular diseases like glaucoma due to poor bioavailability.[3; 4]

In conventional ophthalmic dosage forms, only 1-3 % of drug is generally absorbed through the cornea and it has to face precorneal loss due to tear formation, insufficient residence time in the conjunctival sac and non-productive absorption.[5] Inconvenience caused by conventional ocular dosage forms is also limited permeability that leads to lower absorption, lower bioavailability rapid elimination so that there will be frequent instillation. Drainage of drugs from nasolacrimal duct is also a major factor behind it.[6]

In most cases, ocular therapy is to administer the drugs into the cul-de-sac as many parts of the eye are relatively not accessible for systemically administered drugs.[7] The drugs may be delivered to the precorneal region for conjunctivitis and blepharitis, or to provide intra-ocular treatment via the cornea for diseases such as glaucoma and uveitis.[8] Similarly, interior segment of eye may get affected from keratitis, iritis, cataract and glaucoma; however diabetic retinopathy, viral and bacterial infections, malignancies, proliferative vitreal disorders as well as macular degeneration may occur generally in

anterior portion. The most convenient way to deliver drugs to the eye is in the form of drops. But the drops, instilled into the cul-de-sac are drained away very fast from the ocular cavity due to continuous tear flow and lachrymal nasal drainage. Hence only a small amount is available to exert therapeutic effect resulting in frequent dosing.[9] Cul-de-sac of the eye (the corners) normally can accumulate 7-9 µl of tear but can retain up to 20 to 30 µl if there is no blinking. But the volume of drops is approximately 50 µl. This also leads to rapid tear secretion deviating from its normal flow rate of 1 µl/min, and can causes subsequent drainage of eye drops.[10] For this elimination profile, the precorneal half life of drugs lies between 1-3 min. As a consequence, only the very small amount of the dosage actually penetrates through the cornea and is able to reach intraocular tissues.[11] In addition, the ocular residence time of conventional eye drops is limited to a few minutes due to lacrimation and continuous blinking; therefore the ocular absorption of a topically applied drug is reduced to approximately l-10%. The drug is mainly absorbed systemically via conjunctiva and nasal mucosa, which may result in some undesirable side effects. Even, ointment formulation does not minimize the repeated dosing significantly. Still these conventional ocular dosage forms cover nearly 90% of currently available marketed formulation.[12]

To overcome these problems, different approaches have been taken care of, such as in situ forming gel[13], micro- and nanocarrier systems, Inserts. There are several carriers such as immunoglobulin, microspheres, serum proteins and certain synthetic polymers and vesicular drug delivery systems.[14]

In recent years, vesicles have been chosen as the vehicle of choice in ocular drug delivery. Vesicular systems not only just provides prolonged and controlled action at the corneal surface but also help in controlled ocular delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface. Moreover, vesicles offer a promising gateway to fulfill the need for a convenient drop in ophthalmic drug delivery system, but will localize and maintain therapeutic activity at its site of action.[15]

Use of Niosomes instead of Liposomes – Reasons

Among the vesicular system liposomes, Niosomes can be useful in ophthalmic drug delivery. However liposome faces some problems. One of the most significant problems associated with the use of liposomes as adjuvant is the susceptibility of phospholipids to oxidative degradation in air.[16] The requirement is purified phospholipids and liposomes and they have to be stored and handled in an inert (e.g. nitrogen) atmosphere. Phospholipids are naturally available and extensive purification makes them costly.[17] Alternatively, phospholipids synthesis tends to be even more costly than using naturally occurring lipids. Whereas, Niosomes made of non ionic surfactants, are promising drug carriers and they possess greater stability. In comparison to liposome made off synthesised phospholipids, Niosomes are comparatively cheaper. Niosome production in large scale is comparatively simpler without the use of unacceptable solvents.[18]

Advantages of Niosome[19]

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems for therapeutic purpose may offer several advantages like.

1. They offer high patient compliance in comparison with oily dosage forms as these vesicle suspension is water–based vehicle.
2. A wide range of drug may be selected with a broad range of solubilities.
3. The characteristics of the vesicle formulation are variable and controllable by altering vesicle composition, size, lamellarity, surface charge and concentration can control the vesicle characteristics.
4. The vesicles can release the drug in a controlled manner.
5. They are osmotically active and stable; as a result the stability of entrapped drug get increased.
6. Handling and storage of surfactants in niosomes requires no special conditions.
7. They improve oral bioavailability of poorly absorbed drugs and enhance the permeation of it.
8. They can be made to reach the site of action by oral, parenteral as well as topical routes.

Niosome – a brief note

Niosomes are vesicles comprising non-ionic surface active agent bilayers, which serve as novel drug delivery systems. Their size lies in the nanometric scale which is formed on the admixture of non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Niosomes may be unilamellar or multilamellar depending on the methods of preparation. They are made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle while the hydrophobic chains face each other within the bilayer.[20] Hence, the vesicle entraps the hydrophilic drugs within the space enclosed in the vesicle while the hydrophobic drugs are embedded within the bilayer itself. The application of niosomal technology is to treat a number of diseases.

Niosomes size depends on the method of preparation. They can be formulated by different methods like thin film hydration, hand shaking, ether Injection, reverse phase evaporation, sonication, microfluidisation and trans membrane pH gradient. Niosomes vary widely by their properties depending both on procedure used for their production and composition of bilayer. However the principle is same (i.e.) formation of lipid phase followed by subsequent hydration on aqueous medium which leads to the formation of Niosomes. The formulated Niosomes are characterized by vesicle

diameter, entrapment efficiency, in-vitro drug release, zeta potential analysis and stability studies.[21]

Composition of Niosomes

They are consisted of two essential components like cholesterol and non ionic surfactants.

Cholesterol

Cholesterol is a waxy steroid metabolite found in the cell membranes. Cholesterol is used in Niosomes formation to impart rigidity and orientational order to the niosomal bilayer. Cholesterol and its derivatives are the most common additives found in niosomal systems. It forms the vesicles with non ionic surfactants, reduces agglomeration and provides greater stability. Cholesterol is also known to prevent gel to liquid phase transition of niosomal systems resulting in Niosomes with less leakage.[22]

Non-ionic surfactants

Non-ionic surfactants act as main component in Niosome formulations. Generally, they possess hydrophilic head group and a hydrophobic tail and possess high interfacial activity. The hydrophobic moiety may consist of 1/2/3 alkyl chains or per fluro group or in certain cases a single stearyl group. Sorbitan fatty acid esters are most commonly used surfactants found in literature. Most commonl Spans are Span 20, 40, 60, 65, 80, and 85. All of them have the same head group and different alkyl chain length. By increasing alkyl chain length leads to high entrapment efficiency of drug.[23]

Surfactants of non ionic groups like spans are available in different grades like span 20, span 40, span 60, span 80 and span 85. Similarly the surfactant of Tweens also has different grades such as Tween 20, Tween 40, Tween 60 and tween 80. Moreover the surfactant brij also has variety of grades such as brij 30, brij 35, brij 52, brij 58, brij 72 and brij 76.[24]

The formation of bilayer vesicles instead of micelles depends on the HLB value of the surfactant, the chemical structure of the components, and the critical packing parameter (CPP).[25] Nonionic surfactants are preferred due to less irritation caused by them and that ability decreases in order of cationic > anionic > ampholytic > nonionic. Niosomes >10 μm are suitable for drug administration to eye. Nonionic surfactants can be categorized according to the HLB system, the higher the percentage weight of polyethylene oxide in the molecule, the higher HLB value a surfactant holds and the more soluble in aqueous solution.[26]

Water-soluble surfactants like Tween 20, Tween 80, Cremophor EL, and poloxamer 108, and so forth entrapped in Niosomes an increased ocular bioavailability because surfactants act as penetration enhancers which can remove the mucus layer and break junctional complexes.[27]

Other additives: Charge inducers are one of the membrane additives which are often included in Niosomes because they increase surface charge density and prevent vesicles flocculation, aggregation and fusion. Dicetyl phosphate (DCP) and stearyl amine (SA) which induces negative or positive charge is examples of such membrane additives.[28]

Therapeutic Significance of Niosomes in Ocular Delivery: The eye is protected by three highly efficient mechanisms (a) an epithelial layer that is a formidable barrier to penetration (b) tear flow (c) the blinking reflex.[29] All the three mechanisms are responsible to inhibit proper drug penetration into the deeper layers of the cornea and the aqueous humour. There is also rapid wash out of drugs from the corneal surface due to lacrimal secretion. Various drug delivery strategies have been considered for numerous advantages over conventional ocular drug therapy but not overcoming of drawbacks like poor patient compliance and difficulty of insertion as in ocular inserts, tissue irritation, and damage caused by penetration enhancers, collagen shields and change in pharmacokinetic and pharmacodynamics of the drug, which is caused by altering the chemical structure of the drug (prodrug approach).[30] Niosomes can affect physical properties of drug products such as viscosity, film spreading, and film strength and improve the action.[31]

Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate are more promising in reduction of intraocular pressure as compared to marketed formulation (Dorzolamide).[32] The chitosan coated niosomal formulation of Timolol maleate (0.25%) can generate more effect for reduction of intraocular pressure if compared with marketed conventional formulation with less chance of cardiovascular side effects.[33]

The global burden of glaucoma has thrown a challenge to the researchers, ophthalmologists and general practitioners for detection, prevention and effectively treatment of this visual disability to makes safer ophthalmic drug delivery. Glaucoma is a disease with a characteristic of higher level of intraocular pressure (IOP) which might progressively impair visibility. [34] The average IOP of population is 15.5 ± 2.57 mmHg. The people whose IOP is 20.5 mmHg or higher could be suspected to have glaucoma and IOP over 24 mmHg is a definite case of that. The chronic glaucoma with open angle poses a major problem in today's scenario and it is the second leading cause of blindness all over the world**.** Its treatment requires a long term therapy by proper medication and Niosomes has been confirmed to be a useful vesicular system for the treatment of that.

Brimonidine tartrate is α2 adrenergic agonist is the drug of choice in open angle glaucoma. Nano-vesicles of brimonidine tartrate were prepared by Prabhu et al.

The *in vitro*, and *ex-in vitro* drug release studies of their experiment showed that there was slow and prolonged release of the drug. The IOP-lowering activity of Niosomes was found to be sustained for a sufficient period of time.[35] Allam et al studied on acyclovir loaded Niosomes and concluded that they are effective for the treatment of herpes simplex keratitis, a condition that can lead to blindness.[36]

Linezolid is a synthetic antibiotic, that has been incorporated to niosomal drug delivery by Lavanya et al and it has been reported that incorporation of Niosomes into in situ gels can improve the precorneal retention time leading to therapeutic efficacy of the drug. Niosomal in situ gel is used as an efficient vehicle to improve the patient compliance by reducing the frequency of administration and enhance ocular bioavailability of Linezolid.[37]

Karthikeyan and Pandey prepared diclofenac sodium containing Niosomes by using lipid film hydration technique. In vivo studies of that preparation exhibited that Span 60 based Niosomes can improve the ocular bioavailability of diclofenac sodium for the prolonged period of time and there were no ocular irritation effects.[38] Raghuwanshi et al[39] have investigated the Niosome encapsulated levofloxacin for ophthalmic delivery. In vitro studies indicated that niosomal formulations have exhibited a high retention of levofloxacin inside the vesicle and showed no sign of irritation. Saettone et al[40] reported that Niosomes promoted ocular absorption of cyclopentolate, an essential drug in pediatric eye examinations. Kaur et al[41] reported an improved ocular bioavailability of cyclopentolate encapsulated Niosome, with respect to reference buffer solution. It has been indicated that the above mentioned formulation can be used as an efficient vehicle for ocular drug delivery. Vyas et al[42] developed Timolol maleate loaded Niosomes for the treatment of ocular hypotensive activity and found satisfactory result. Guinedi et al [43] studied acetazolamide loaded niosomal formulation that showed a fairly high retention of drug inside the vesicles (~75%) at a refrigerated temperature for up to three months and also produced significantly less IOP than free drug. Aggarwal and Kaur[44] prepared mucoadhesive Timolol maleate (TM) loaded chitosan and carbopol coated Niosomes . In vitro studies indicated that the drug release is up to 10 h in a sustained manner, and they showed only limited systemic absorption and side effects. Niosomes Containing Flupirtine Maleate was studied by Patidar et al and reoported that Niosome formed from span 80 and cholesterol can prolong antinociception activity and improve the low corneal permeability for effective management of trigeminal neuralgia as compared to pure drug.[45]

Abdelbary and El-Gendy[46] reported that gentamicin sulfate loaded Niosomes can be used over a longer period of time when installed into eye. In vitro studies indicated a high retention of niosomal formulation inside the vesicles in sustained manner as compared to the drug solution and also observed no irritancy on albino rabbits. Aggarwal et al[47] found that an acetazolamide niosomal formulation exhibited the Cmax of the drug from the niosomal formulation was double than that of the drug suspension, Naltrexone hydrochloride loaded Niosomes prepared by Abdelkader et al. for the treatment of diabetic keratopathy . The formulation possessed better ocular tolerability and less ocular irritation.[48] Patidar and Jain[49] reported that flupirtine maleate loaded Niosomes can improve the low corneal permeability for effective management of trigeminal neuralgia.

Bioavailability of ofloxacin niosomal formulation prepared by Pandey et al was enhanced to 73.8%. *In vitro* studies revealed that those formulations had better residence time and longer duration of action.[50]

The above reports clearly indicates that in recent years, several researchers had evaluated the feasibility of Niosomes as an ophthalmic delivery system to prolong the preocular residence of ocular drugs , improve their bioavailability, long-term safety , stability. Some of the Niosomal formulations have been enlisted in Table: 1.Niosomal formulations can also be used to overcome solubility factor and increase retention through mucoadhesion.[43] They have the potential to target ocular tissues at high therapeutic value with several favourable biological properties like biodegradability, biocompatibility and mucoadhesiveness to fulfill the requirements.

Table: 1 Some drug –loaded Niosomes in ocular drug delivery

Drug incorporated in Niosomes	Surfactants used	Improvement
Atenol, Timolol, Betanol, Cyclosporine A	Brij 35, 78,98, 700	Increase in corneal permeability comparing with Conventional form
Cyclosporine A	Polysorbate 80, Polyoxyl 40 stearate , Polyoxyl 60 hydrogenated castor oil	Improvement in Corneal penetration
Pilocarpine	Pluronic F 127	Increase in miotic response in comparison with aqs solution
Gentamycin sulfate	Polysorbate 60,80 and Brij 35	Prolonging the drug release
Cyclopentolate	Polysorbate 20	Enhancement in occular penetration [41]
Timolol maleate	Solulan C-24, Span 60	Exhibited sustained , controlled manner in drug release [42]
Acyclovir	Span 20, 40, 60, 80	More effective in herpes simplex keratitis

Acetazolamide	Span 20,40, 60,80	Enhancement of bioavailability and lower IOP [32]
Briomodine tartarate	Span 20,40, 60,80	Improvement in bioavailability and increase in precorneal residence time [35]
Naltrxone hydrochloride	Span 20,40, 60,80	Better ocular tolerability and less irritation
Fluconazole	Span 20,40, 60,80	Increase in permeability
Flupirtine maleate	Span 20,40, 60,80	Increase in permeability
Diclofenac sodium	Span 20,40, 60,80	Non irritant [38]
Levofloxacin	Span 20,40, 60,80	Prolong drug release with less side effects [37]

CONCLUSION

Niosome based ophthalmic drug delivery has proved significant advancement in present day and found to posses future perspectives in relation to prolong the preocular retention on the eye surface and to improve the transcorneal penetration leading to a ideal novel drug delivery. The potential for availability of several nonionic surfactants can fulfil the purpose of controlled and sustained delivery to treat vision-threatening diseases as the Niosomes have the potential to target ocular tissues.

REFERENCES

1. Dhanapal R, Vijaya R J. OCULAR DRUG DELIVERY SYSTEM – A REVIEW. Int J Innov Drug Discov. 2012; 2(1): 4-15.
2. Shah S S, Denham L V, Elison J R, Bhattacharjee P S, Clement C, Huq T, Drug delivery to the posterior segment of the eye for pharmacologic therapy . Expert Rev Ophthalmol. 2010; 5(1): 75–93. doi: 10.1586/eop.09.70.
3. Holger A. Russ, Philippe Ravassard, Julie Kerr-Conte, Francois Pattou, Shimon Efrat..Epithelial-Mesenchymal Transition in Cells Expanded In Vitro from Lineage-Traced Adult Human Pancreatic Beta Cells, PLoS One, 2009. http://dx.doi.org/10.1371/journal.pone.0006417.
4. Przemysław B, Bożena K, Maciej G, and Janusz P. Ophthalmic Drug Dosage Forms: Characterisation and Research Methods. SCI WORLD J Journal. 2014, Volume 2014, Article ID 861904, 14 pages.http://dx.doi.org/10.1155/2014/861904.
5. Mishra M, editor. Handbook of Encapsulation and Controlled Release. CRC Press; 2015..DOI: 10.1201/b19038-57.
6. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmacol. 2013; 2(2): 47–64. doi: 10.5497/wjp.v2.i2.47.
7. Cholkar K, Patel S P., Vadlapudi A D, and Mitra A K.. Novel Strategies for Anterior Segment Ocular Drug Delivery. J Ocul Pharmacol Ther.2013; 29(2):106-127. doi: 10.1089/jop.2012.0200.
8. Kesavan K, Balasubramaniam J, Kant S, Singh P N, Pandit J K. Newer approaches for optimal bioavailability of ocularly delivered drugs: review. Curr Drug Deliv. 2011; 8(2): 172-93. DOI: 10.2174/156720111794479925.
9. Bhaskaran S,Lakshmi P K, Harish C G. Topical Ocular Drug Delivery-A Review. Ind J. Pharm. Sci. 2005; 67(4): 404-408.
10. James P M, Eduardo U, , Joel A D, Igor B A. , IMPACT OF EVAPORATION ON AQUEOUS TEAR LOSS. . Trans Am Ophthalmol Soc. 2006; 104: 121-128.
11. Rupenthal, I. D. and Alany, R. G. Ocular Drug Delivery. Pharmaceutical Sciences Encyclopedia. 2010; 19: 1-39. DOI: 10.1002/9780470571224.pse358.
12. Kompella U B, Kadam R S, Lee V H L. Recent advances in ophthalmic drug delivery. Ther Deliv. 2011; 1(3): 435–456. doi: 10.4155/TDE.10.40.
13. Carmona-Ribeiro A M, Carrasco L D M L. Novel Formulations for Antimicrobial Peptides. . Int J Mol Sci. 2014; 15(10): 18040–18083. doi: 10.3390/ijms151018040.
14. Sunil Kamboj, Vipin Saini, Nancy Magon1, Suman Bala, Vikas Jhawat. Vesicular drug delivery systems: A novel approach for drug targeting. Int J Drug Deliv. 2013; 5: 121-130.
15. Peter WJ Morrison & Vitaliy V Khutoryanskiy. Advances in ophthalmic drug delivery. Ther Deliv. 2014; 5(12): 1297-1315. DOI 10.4155/tde.14.75.
16. Nicholas J. D. Gower, Robert J. Barry, Matthew R. Edmunds,Lucy C. Titcomb and Alastair K. Denniston. Drug discovery in ophthalmology: past success, present challenges, and future opportunities. BMC Ophthalmology. 2016; 16(11). DOI: 10.1186/s12886-016-0188-2.
17. Melis Çağdaş, Ali Demir Sezer and Seyda Bucak. Liposomes as Potential Drug Carrier Systems for Drug Delivery. In: Ali Demir Sezer editor. Nanotechnology and Nanomaterials » "Application of Nanotechnology in Drug Delivery".2014.p. DOI: 10.5772/58459.
18. Manda R, SuthakaranR, Kaya V, Sreedevi B, Pravallika K. Non-ionic Surfactant Based Vesicle 'Niosome' as a Potential Ocular Drug Delivery System. World J Pharm Pharmaceut Sci. 2014; 3(11): 92-105.
19. Chandu V P, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: A Novel Drug Delivery System. Int J Novel Trend Pharm Sci. 2012; 2: 25-31.
20. Okore VC, Attama AA, Ofokansi KC, Esimone CO, Onuigbo EB. Formulation and evaluation of Niosomes. Indian J Pharm Sci. 2011; 73(3): 323-8. doi: 10.4103/0250-474X.93515.

21. Gannu P. Kumarn, Pogaku Rajeshwarrao. Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta Pharmaceutica Sinica B. 2011; 1(4): 208–219. http://dx.doi.org/10.1016/j.apsb.2011.09.002.
22. Rao R, Dahiya N K., Nanda S. Preparation and Characterization Techniques in Niosomal Vesicular Systems- A Review. J Pharm Biomed Sci. 2011; 5(20): 1-8.
23. Das K G, Ram A, R NIOSOME AS A NOVEL DRUG DELIVERY SYSTEM A REVIEW, Int J App Pharm. 2013; 5 (1): 1-7.
24. Chavda VP. Niosome: A Vesicular Weapon for Targeted and Controlled Drug Delivery. Indian Journal of Novel Drug Delivery. 2016; 8(3): 133-156.
25. Seleci D A, Seleci M, Walter J G, Stah F, Scheper T. Niosomes as Nanoparticular Drug Carriers: Fundamentals and Recent Applications. J Nanomat. 2016; 13 pages. Article ID 7372306http://dx.doi.org/10.1155/2016/7372306.
26. Sahoo R K, Biswas N, Guha A, Sahoo N, Kuotsu K. Nonionic Surfactant Vesicles in Ocular Delivery: Innovative Approaches and Perspectives. BioMed Res Intl.2014; 4: Article ID 263604, 12 pages http://dx.doi.org/10.1155/2014/263604.
27. Farhood Q K. Cycloplegic Refraction in Children with Cyclopentolate versus Atropine. J Clin Exp Ophthalmol. 2012; 3: 7.
28. González-Rodríguez ML, AM Rabasco. Charged liposomes as carriers to enhance the permeation through the skin. Expert Opinion on Drug Delivery.2011; 8(7): 857-871. doi: 10.1517/17425247.2011.574610.
29. Patel PB, Shastri DH, Shelat PK, Shukla AK. Ophthalmic Drug Delivery System: Challenges and Approaches. Systematic Reviews in Pharmacy.2010; 1(2): 113-120.
30. Cholkar K, Patel S P, Vadlapudi A D,. Mitra A K. Novel Strategies for Anterior Segment Ocular Drug Delivery. Journal of Ocular Pharmacology and Therapeutics.2012; 29(2): 106-123. doi: 10.1089/jop.2012.0200.
31. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery ,Saudi Pharmaceutical Journal . 2012; 20: 63–67.
32. Gandhi A, Sen S O, Paul A. Current Trends in Niosome as Vesicular drug delivery system. Asian J. Pharm Life Sci. 2012; 2(2): 339.
33. Pratt N L, Ramsay E N., Lisa M. Kalisch E, Nguyen T A, and Roughead E E. Association between Ophthalmic Timolol and Hospitalisation for Bradycardia. Journal of Ophthalmology.2015; 2015: Article ID 567387, 6 pages, http://dx.doi.org/10.1155/2015/567387.
34. Majeed M, Nagabhushanam K, Natarajan S, Vaidyanathan P , Karriuresh S K. Intraocular Pressure Lowering Activity of Ocufors® (forskolin 0.15% w/v ophthalmic solution) in Water Loaded New Zealand White Rabbits . Int J Pharm Bio Sci. 2014 Oct; 5(4): 328 – 336.
35. Occhiutto M L, Freitas F R,. Maranhao R C, Costa V P. Breakdown of the Blood-Ocular Barrier as a Strategy for the Systemic Use of Nanosystems. Pharmaceutics. 2012; 4(2): 252-275; doi:10.3390/pharmaceutics4020252.
36. Azher T N, Yin X T, Tajfirouz D, Huang A J W, Stuart P M. Herpes simplex keratitis: challenges in diagnosis and clinical management. Clin Ophthalmol. 2017; 11: 185–191.
37. Lavanya B, Indira S, Srinivas P. Formulation and Evaluation of Ocular Niosomal in situ gels of Linezolid. IJPSR.2014; 5(4): 1367-1375.
38. Karthikeyan D, Pandey V P.Study on ocular absorption of diclofenac sodium Niosome in rabbits eye. Pharmacology online. 2009; 1: 769–779.
39. Raghuwanshi N, Dikshit S, Sharma A, Upamanyu N, Dubey A,. Pathak A. Formulation and evaluation of Niosome-encapsulated levofloxacin for ophthalmic controlled delivery. Int J Adv Pharm Res. 2012; 3(5): 901–906.
40. Abdelkader H, Ismail S, Kamal A, Raid G. Design and Evaluation of Controlled-Release Niosomes and Discomes for Naltrexone Hydrochloride Ocular Delivery. J Pharm Sci. 2011; 100 (5): 1833–1846.
41. Chavda V P. Niosome: A Vesicular Weapon for Targeted and Controlled Drug Delivery. Ind J Nov Drug Deliv. 2016; 8(3): 133-156.
42. Khan R, Irchhaiya R. An Overview on Niosomes as Efficient Drug Ccarriers. Int J Pharm Bio Sci. 2017; 8(2): 106 -116.
43. Ranga Priya M, Natarajan R, Rajendran NN. Formulation and Evaluation of Zidovudine Loaded Niosomes. Res Rev J Pharmaceut Nano. 2013; 1(1): 12-18.
44. Marianecci C , Marzio L D, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S. Niosomes from 80s to present: The state of the art. Advances in Colloid and Interface Science. 2014; 205: 187–206.
45. Patidar S, Jain S. Non Ionic Surfactant Based Vesicles (Niosomes) Containing Flupirtine Maleate as an Ocular Drug delivery system. J. Chem. Pharm. Res. 2012; 4(10): 4495-4500.
46. Abdelbary G, El-Gendy N. Niosome-encapsulated gentamicin for ophthalmic controlled delivery. AAPS Pharm Sci Tech. 2008; 9(3): 740–747. doi: 10.1208/s12249-008-9105-1.
47. 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(1-2): 21–26. http://dx.doi.org/10.1016/j.ijpharm.2007.01.019.
48. Abdelkader H, Wu Z, Al-Kassas R, Alany R G. Niosomes and discomes for ocular delivery of naltrexone hydrochloride: morphological, rheological, spreading properties and photo-protective effects. Int J Pharm. 2012; 433 (1-2): 142–148. doi: 10.1016/j.ijpharm.2012.05.011.

49. Patidar S,Jain S.Non ionic surfactant based vesicles (Niosomes) containing flupirtine maleate as an ocular drug delivery system. J Chem Pharm Res.2012; 4(10): 4495–4500.
50. Vijay Prakash Pandey*, Karthikeyan Deivasigamani. Preparation and characterization of ofloxacin non-ionic surfactant vesicles for ophthalmic use. J Pharm Res. 2009; 2(8): 1330-1334.