VESICULAR OCULAR DRUG DELIVERY SYSTEM: PRECLINICAL AND CLINICAL PERSPECTIVE OF DRUGS DELIVERED VIA NIOSOMES

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ABSTRACT
An eye is the most precious and easily accessible organ of the body. It possesses easy route to local drug delivery and is a way to non-invasive clinical treatment of ocular diseases. Ocular delivery in spite of possessing various advantages has the limitation of poor bioavailability and low permeability across the cornea thus, limiting the efficacy of drugs. Therefore, various carrier systems have been developed to overcome these limitations. Most recently, niosomes have been developed as efficient vesicular carrier for ophthalmic drug delivery. Large numbers of drugs of various therapeutic categories have been incorporated in these vesicles. These systems exhibited enhanced permeability required for the treatment of ocular diseases, initiating a new era in vesicular research for ocular delivery. Various reports show promising future of niosomes for topical, transdermal, ocular delivery of various therapeutically active agents more effectively and providing better in vivo data thus suggesting the need of the clinical testing of these carriers for their widespread utility. So, to evaluate its safety and efficacy, various preclinical and clinical studies were conducted. The present review focuses on the preclinical and clinical perspective of delivery of various drugs through niosomal vesicular carriers illustrating enhanced safety and efficacy by designing these carriers.

Key words: Corneal permeability, Drug delivery, In Vivo study, Niosomes, Ocular, Vesicles.

INTRODUCTION
Eye is considered as the window of our soul. It is a unique organ of our body anatomically as well as physiologically. It possesses easy access to local drug delivery and is a way to non-invasive clinical treatment of ocular diseases. Topical drug delivery is ought to be the most preferable route to eyes as the systemically acting drug are not readily accessible through it. But this route becomes complicated by the effective removal processes of the eye which removes the foreign particles and also by the precorneal barrier which includes blinking reflex, tear turnover and low permeability across the cornea (Rathore KS et al., 2009). About 5% of dose instilled into the eyes reaches the intraocular tissues due to various factors like pre-corneal drainage and less permeability of corneal epithelium cells. The systemic route can overcome this but due to the presence of blood-aqueous barrier and blood-retinal barrier, it ultimately leads to high loading dose at the target site. The high dose and dosing frequency causes unavoidable systemic side effects like stomach upset and disturbed GI motility (Modi KA et al., 2012). The main purpose of pharmacotherapeutics is to achieve the effective drug concentration, at the desired site of action for a sufficient time period to elicit the desired pharmacological response. Ocular dosage forms possessed poor bioavailability due to the production of tears, transient residence time and impermeability across corneal
epithelium (Kaur et al., 2012). To treat ocular diseases, topical and localized approaches in the form of solution, suspensions and ointments are more preferred in the treatment of ocular diseases but they suffer from the drawback of poor ocular bioavailability (Sahoo et al., 2008).

In ocular drug delivery system, scientist faced many challenges due to unique anatomical and physiological structure of eye. There are two barriers namely, static and dynamic barriers that limit the ocular drug delivery. Static barrier is composed of different segments of eye such as cornea, sclera, retina and blood-retinal barriers whereas dynamic barriers consists of choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution. These barriers ultimately affect the bioavailability of various drug delivered via this route. In the new era, various new concepts of drug delivery such as iontophoresis, liposomes, niosomes, bioadhesive gels, ocular insert, contact lenses etc has been developed to overcome the problems related with these barriers. These formulation based approaches have considered to be sufficient enough in achieving the maximum drug concentration at specific site of eye for the targeted drug delivery. Ocular drug delivery system possessed major disadvantage of rapid and extensive elimination of conventional eye drops after instillation from the eye, which results in the loss of drug. Only limited amount drug penetrates into the corneal layer and reaches the internal tissue of eye. The main region of drug loss includes lachrymal drainage and drug dilution by tears. This in turn reduces the ocular bioavailability of drug and leads to unwanted toxicity and adverse effects (Sikander et al., 2012).

Ocular drug delivery systems are designed to treat the eye diseases locally and are thereby developed to overcome all the disadvantages of conventional dosage forms such as ophthalmic solutions. The eye drop dosage form though easy to instil but suffers from the drawback that the majority of the drug present in get immediately diluted in the tear film as soon as the eye drop is instilled into the cul-de-sac and is rapidly drained away from the precorneal cavity by constant tear flow. Therefore, only 1.2% of the instilled dose is available to the aqueous humour. Frequent dosing frequency of drugs thus, becomes necessary to achieve the therapeutic concentration at the targeted site which often results in corresponding increase in local and systemic side effects. So, various Novel ophthalmic drug delivery systems have been developed and still are in progress to overcome all the disadvantages of conventional ophthalmic dosage forms (Ratnam et al., 2011). The main motive behind the development of novel drug delivery system to the eye is to improve the ocular dosage forms that have been developed so far and thereby improving the therapeutic efficacy (Prabhu et al., 2010).

In this new era of research, the drug delivery through vesicles has gained lot of attention due to its prominent advantage in improving bioavailability and reducing dose frequency (Modi KA et al., 2012). These are the water-filled colloidal particles and their wall consists of amphiphilic molecules in a bilayer conformation where hydrophilic drugs are enclosed within the aqueous environment and lipophilic drugs are entrapped in the vesicle bilayer. Most commonly, these vesicles are composed of phospholipids or non-ionic surfactants (Akhtar 2012). Vesicular drug delivery tends to localize and maintain drug concentration at its desired site of action. The rate of drug penetration depends on the physicochemical properties of the drug like, solubility, particle size, polymorphic form etc. VDDS generally includes liposomes and niosomes as most preferred ocular drug delivery system (Modi KA et al., 2012). The concept of targeted drug delivery is designed to achieve the drug concentration at the desired site of action (Lohumi et al., 2012).

**Ideal properties of controlled ocular drug delivery system**

Ideal properties of controlled ocular drug delivery system include controlled drug delivery at the desired targeted site, appropriate corneal penetration. Reduced dosing frequency, increased corneal contact and retention time. It bypasses various anatomical and physiological barriers such as tear secretion, nasolacrimal drainage, enhanced patient compliance etc (Modi and Shelat, 2012).

**Advantages of Ocular Drug Delivery Systems**

Various advantages of ocular drug delivery system are as such ease of convenience, self medication, improved patient compliances, and enhanced penetration of hydrophilic and low molecular weight drugs. Rapid absorption and fast onset of action, it avoids hepatic first pass metabolism.

**Disadvantages of Ocular Drug Delivery Systems**

Various disadvantages associated with ocular drug delivery system are as follows: Limited permeability across the cornea, drainage of the administered dose into the lachrymal duct, leads to systemic side effects and short term therapeutic effect due to eye blinking results in frequent dosage regimen (Kumar et al., 2011).

**VESISULAR OCULAR DRUG DELIVERY**

In the past few years, development of vesicles as a recently formulated novel carrier in the drug delivery has gained lot of attention among the scientists working for the development of novel drug delivery system. A novel drug delivery system should accomplish two purposes i.e. it must deliver the drug at a predetermined
rate and should release the drug at the specific site of action in therapeutically active concentration (Rajera et al., 2011). Drug delivery via vesicles provides prolonged as well as controlled drug delivery at the targeted corneal surface. Thus, a vesicle acts as a prominent carrier system for ophthalmic drug delivery (Kute et al., 2010). Drug entrapped within the vesicular membrane can be easily administered in the form of eye drops. Vesicular drug delivery systems entrap the drug molecule within the lipid bilayer or surfactant vesicles. Thereby, increasing the drug concentration at the site of action with sustained drug delivery, resulting in enhanced bioavailability (Prabhu et al., 2010). In the new era of research, vesicles are considered as a recently developed carrier in ocular drug delivery. Vesicles in spite of providing prolonged and controlled action at the corneal surface of an eye also prevent the metabolism of the drug by the enzymes that are present at the tear/corneal epithelial surface. Therefore, vesicles represent a prominent carrier for an ophthalmic delivery of variety of drugs used in the treatment of ocular diseases (Paul et al., 2010).

Vesicles used in ophthalmic include liposome and niosomes specifically. Liposome act as carrier system for the delivery of variety of drug molecules, proteins, nucleotides, enclosing them with a great potential for their application in ophthalmic (Kute et al., 2010).

Liposomes have been studied by various authors to be efficient in delivering the drug (Table No. 1) through the intravitreal route to the posterior region of the eye (Bejjani et al., 2003). For example, Gaudana et al had formulated ganciclovir loaded liposome and performed in vivo pharmacokinetic study in rabbits, concluding that liposome results in enhanced transcorneal permeation and higher ocular tissue distribution (Gaudana et al., 2009). Thus, the significant advantage of liposome is their ability to come in an intimate contact with the corneal and conjunctival surfaces, thereby, increasing the probability of ocular drug absorption. It is proposed that they increase the residence time as well as drug absorption (Kute et al., 2010). The major disadvantages associated with liposome are chemical instability, oxidative degradation of phospholipids to overcome these limitations of liposome; niosomes are being developed (Patel 2011). They possess various advantages over liposomes such as higher chemical stability, enhanced skin penetration and lower cost as compared to liposome (Prabhu et al., 2010).

**NIOSMES A NOVEL ELASTIC OCULAR VESICULAR CARRIER**

Niosomes are the bilayered vesicular carriers consisting of non-ionic surfactants. They can entrap both lipophilic and hydrophilic drugs within the vesicular membrane (Saini 2012). This type of non-ionic vesicles was first introduced by Handjani (Tangri 2011). They are formed by the hydration of non-ionic surfactant molecules (Rajera et al., 2011). It acts by reducing the systemic drainage and improving the residence time, which further enhances the ocular bioavailability of drug (Saini 2012). These may be multilamellar or unilamellar, composed of an aqueous region enclosed by the bilayer of surfactant molecules. It is composed of two major components i.e. non-ionic surfactants and the additives (cholesterol and charged molecules). The presence of cholesterol provides the rigidity to the bilayer and is an important constituent of the cell membrane. Its presence in niosomes affects fluidity and permeability across the bilayer (Verma 2011) (Fig.1). The main objective behind the development of niosomes is to control the drug release, modify its distribution pattern as well as targeting the drug delivery to the desired site. It is now being studied as an alternative to liposome (Verma 2011). Niosomes represents itself as a prominent drug carrier and has found to be effective enough to reduce the adverse effects of the drug and thus improve the therapeutic effectiveness of a drug in the treatment of various diseases (Gopalakrishnan 2012). It has been employed in delivering drugs via various routes such as intramuscular, intravenous, topical, transdermal and nasal etc (Tarekegn et al., 2010) (Table No. 2).

**Method of Preparation**

Niosomal vesicles were prepared by various methods such as ether-injection method, hand shaking method, sonication, reverse phase evaporation, micro fluidization and emulsion method.

**Advantages of Niosomes**

As a drug delivery system niosomes possess various advantages such as better patient compliance, better therapeutic effect as compared to conventional formulations. It can deliver wide variety of drugs, as it can entrap both hydrophilic and lipophilic drugs. Controlled and sustained drug delivery of drugs, improved bioavailability as compared to conventional dosage forms. Niosomes can be used specifically in targeted drug delivery. More stable than liposomes. Enhanced permeability across the skin (Verma 2011). Niosomes acts in similar ways to Liposome by prolonging the release of entrapped drug and changing the organ distribution and its metabolic stability. Entrapment of various antineoplastic agents in these vesicles has been reported in the literature to reduce the drug related toxic side effects, and on the other hand increasing the anti-tumour efficacy. They can be used in targeting the drug delivery as well as to control its release (Akhilesh et al., 2012).

**Evaluation of Niosomes**

Niosomes were evaluated by various parameters such as percent entrapment efficiency, shape and
morphological study (TEM), in vitro release study, tissue distribution/ in vivo study, ocular irritation test, stability study, membrane rigidity and vesicular surface charge (Verma 2011).

PRECLINICAL AND CLINICAL ASPECTS OF DRUGS DELIVERED VIA NIOSOMAL CARRIERS

To determine the clinical efficacy and safety of the ethosomal carriers loaded with drug, various authors have performed preclinical and clinical studies on this. Given below is a view of various drugs such as anti-glaucomatous, antibacterial, antiviral and anti-inflammatory drugs delivered through niosomal vesicular carriers focusing mainly on preclinical and clinical studies.

BRIMONIDINE TARTRATE

Prabhu et al formulated and evaluated Brimonidine tartrate loaded niosomes for in vitro and in vivo intra ocular pressure lowering activity. In vivo intra ocular pressure lowering activity of the selected niosomal preparations were conducted on male albino rabbits. For this, three rabbits were divided into three groups, each group containing one rabbit. To observe this activity, acute glaucoma was firstly induced in the rabbits by infusing 5% dextrose solution through the marginal ear vein and then the basal intraocular pressure was measured by tonometer. The formulation containing drug (20 µl, drug equivalent to pure drug solution 0.2%) were administered to rabbits in three different levels. In Level 1: Selected formulation was administered 30 min. before administering dextrose solution. Level 2 contains administering formulation as well as dextrose solution together whereas level 3 involves the administration of niosomal formulation containing drug 30 min. after the dextrose solution was infused. Change in Intraocular pressure was measured by tonometer after every 30 min. till the difference in pressure between both controlled and treated eye read zero. All the observations were done in triplicate and mean was then taken. After every treatment washout period of 3 days was given to each rabbit. Ocular hypotensive activity was calculated as the intraocular pressure difference between treated and controlled eye of the same rabbit. Niosomes showed better reduction in intraocular pressure due to the better partitioning of drug between vesicle and eye corneal surface. However, it was observed that delivery of drug via niosomes enhance the local drug concentration at the corneal surface. Prolonged contact time at the desired site of action also improves the bioavailability of the drug. Thus, ocular drug delivery via niosomes modifies the rate as well as extent of absorption, which ultimately results in reducing the intraocular pressure. Thereby, exhibiting the controlled ocular drug delivery (Prabhu et al., 2010).

Sathyavathi et al had formulated niosomal in situ gel incorporating Brimonidine Tartrate for ocular drug delivery and evaluated for entrapment efficiency, vesicle shape, size, in vitro release studies, in vivo activity and stability studies. The present study was investigated for the effective treatment of the ocular disease called ‘glaucoma’. Niosomes were designed by the authors by taking various ratios of span series and cholesterol. In vivo intra ocular pressure lowering activity was conducted in male albino rabbits under this study, four groups were designed, each containing 3 rabbits. The drug formulation was instilled into the rabbit’s eye and the changed in ocular pressure were measured by tonometer before, after 30 min. of the administration and then after every hour in the period of 8 hr. Until the pressure difference between controlled and treated eye reached zero. Selected formulations were then instilled into the corneal surface of the one eye and the contra lateral eye was denoted as a “control”. The ocular hypotensive activity was then measured. It was revealed by the authors that niosomal gel showed better anti-glaucoma activity as compared to niosomal and marketed drops. Thus, it was concluded that niosomal represented itself to a better system as compared to conventional eye drops with improved bioavailability and increased precorneal residence ability (Sathyavathi et al., 2012).

Maiti et al had formulated nanovesicular formulation of brimonidine tartrate for the treatment of glaucoma and evaluated them for in vivo efficacy and eye irritation test. The intraocular pressure measurement study was conducted by the authors on normotensive albino rabbits (2-3 kg). The animals were divided into two groups, containing six rabbits in each group. Group 1st were treated with vesicles whereas Group 2nd was treated with the marketed formulation. The intraocular pressure was measured at different intervals with a standardized tonometer. 50-µl single dose of 0.1% brimonidine preparation was instilled into the left eye of the corneal surface of each rabbit, first after 30 min. and then after every 1 h interval. The intraocular pressure was measured up to 7.5 h. The right eye was used as a control in all the experimental animals. Marketed formulation showed a difference of 16.55 ± 0.69 mmHg intraocular pressure, whereas optimized vesicular formulation showed a lower value 2.85 ± 0.67 mmHg at 3.5 h. Thus it was observed that the tested niosomal formulation demonstrated intraocular pressure-lowering activity more significantly for a prolonged period of time in comparison to a marketed formulation. It was revealed by the authors that the vesicles increased the absorption of drug by altering the corneal permeability of drug. To evaluate the ocular irritancy effects of optimized niosomal formulations, Eye Irritation Test was conducted by the authors on three healthy albino rabbits. Niosomal formulation (single dose, 100-µl) was instilled into the conjunctival sac of left eye of each animal and the untreated eye served as a control. Each animal was observed for any ocular reactions (corneal ulceration,
conjunctival redness, and conjunctival edema), visually by using slit lamp at various time intervals upto 72 hrs. Selected formulations did not showed any sign of irritant effect. Further, a confirmatory test was also conducted on another two animals. It was further examined that animals did not showed any ocular lesion in 3 days of study. Thus, it was concluded by the authors that the optimized niosomal formulation were non-irritant and safe for the ocular delivery (Maiti et al., 2011).

OFLOXACIN

Ofloxacin encapsulated niosomes were designed and characterized for improved ocular delivery by Gupta et al. Niosomes were prepared by taking non-ionic surfactant, Span 60, in various proportions and evaluated for various parameters such as morphological characters, entrapment efficiency, in vitro release studies, stability study determination minimum inhibitory concentration (MIC), ocular irritation test and in vivo study. Preclinical evaluation was done by performing ocular irritation test as well as in vivo study. The optimized formulation was tested on six rabbits, by incorporating it in the cul-de-sac of the left eye. No sign of irritation, inflammation or abnormal discharge were observed in the rabbits. Niosomes (F3) were found to be free from any undesirable irritant effect on cornea, iris and conjunctiva up to 24 hrs. after its application as reported by the author. Thus, it is considered to be an appropriate system for ophthalmic drug delivery. In vivo study was also conducted by the authors in male rabbits (Orytolagus cuniculus) to evaluate the ocular bioavailability of the drug released from the niosomes (F3). Retention time of the standard drug solution was compared with the sample extracted from the aqueous humour. It was revealed by the authors that increase in retention time in aqueous humour was observed with the samples due to the increased contact time of the formulations in the cornea as well due to improved permeability of the drug caused by the niosomes. Thus, the authors concluded that, the niosomal systems represent a system that is capable enough in delivering ofloxacin in a controlled manner efficiently, with improved corneal penetration and bioavailability (Gupta et al., 2010).

DICLOFENAC SODIUM

Diclofenac sodium loaded niosomes were developed by Karthikeyan and characterized for in vivo drug release and ocular irritation test. Male albino rabbits were used by the authors to evaluate in vivo activity. Niosomal preparations were compared with the control formulation. It was reported by the authors that the concentration of diclofenac delivered via niosomes were higher in aqueous humour as compared to the eye drop solution. Niosomal preparations showed Cmax 4.731 µg/ml, Tmax 200 min. and AUC value 513.46 as compared to control which showed Cmax, Tmax, AUC 3.155 µg/ml, 80 min., 351.74 respectively. The ocular irritancy test was done in rabbits to evaluate the preparations for any irritation, redness or inflammation. So, it was observed that the niosomal suspensions did not possess any sign or irritation or redness as compared to the control preparation. Thus, it was revealed by the authors that the niosomes were considered to be a safe vesicular system for the effective ocular drug delivery (Karthikeyan 2009).

NALTREXONE

Nanosized niosomal vesicles encapsulating naltrexone have been developed and optimized by Abdelkader et al with the objective to evaluate the conjunctival as well as corneal tolerance ability of naltrexone and its ingredients. To accomplish this objective, niosomal vesicle of naltrexone hydrochloride was designed by taking the combination of different surfactants or lipids at various concentrations. Specifically for the treatment of diabetic keratopathy. To test the conjunctival and corneal toxicity, hen’s egg test-chorioallantoic membrane (HET-CAM), bovine corneal opacity and permeability (BCOP) test as well as corneal histopathological test were combined. Four selected niosomal formulations subjected to 10 days old HET-CAMs were found to be not showing any irritant effect. Whereas sodium cholate (an ingredient) showed some irritation, which have been observed to be eliminated by incorporating it in niosomes. Thus, it was concluded by the authors that, niosomes possessed better ocular tolerability and less ocular irritation. Thereby, ought to be an effective system for safe and effective drug delivery across the cornea (Abdelkader et al., 2012).

FLUCONAZOLE

Kaur et al had formulated and evaluated elastic surfactant based niosomal vesicular carriers loaded with fluconazole for effective ocular delivery. Niosomes of fluconazole were designed by the authors to prolong the drug release as well as to enhance its effect. These vesicles were prepared by using sorbitan (spans) with an edge activator by ether injection method and characterized for vesicular size, shape, and entrapment efficiency, ex vivo corneal permeability and safety test. It was observed by the authors that niosomal formulation showed improved permeability as compared to the marketed formulation. The prepared vesicles were also found to be more stable under stability study of two months. Safety studies were reported as genotoxicity (Ames test), cytotoxicity (MTT assay), and eye irritation revealed that the niosomes loaded with fluconazole were safe. Thus, exhibiting itself an effective carrier for the ocular drug delivery (Kaur et al., 2004).

FLUPIRTINE MALEATE

Patidar had developed niosomes enclosing flupirtine maleate to enhance the permeability of the drug
across the cornea and characterized them for morphological characters, entrapment efficiency, \textit{in vitro} drug release, stability study and ocular irritation test. Ocular irritation test was performed by the authors and pupil size, redness as well as irritancy was observed with respect to time. This test was done on rabbit’s eyes, by instilling the niosomal suspension drops in right eye. Comparison has been made between right and left eye. It was revealed from this study that niosomal preparations showed no sign of redness or any other inflammation. \textit{In vivo} trigeminal neuralgia test (Nociceptive test)/eye wiping test was done to evaluate the drug release. In this test, seven groups of animals were taken, each containing six rats. Control group and standard group were compared for the results. Where control group animals were supplied with the 5 M NaCl and number of wipes was counted, followed by the wipes showed by the pre-treated groups in which standard solution and the prepared formulations were instilled. Pre-treated groups were then compared with that of the control and standard group. It was reported by the authors that the dose-response relationships between control and standard groups with the pre-treated group were significant as measured by applying one-way ANOVA. Thus, it was concluded that niosomes loaded with flupirtine maleate, can significantly deliver the drug with reduced dosing frequency as well as side effect. Thereby, representing itself a prominent safe and effective vesicular carrier for ocular delivery (Patidar 2012).

**GENTAMICIN**

Niosomes encapsulating gentamicin were reported by Abdelbary for controlled ophthalmic drug delivery. These vesicles were prepared by using different surfactants by thin film hydration method and then evaluated for entrapment efficiency, photo microscopy, particle size analysis, \textit{in vitro} drug release and ocular irritancy test. Formulation F$_4$, F$_6$, F$_{12}$ were subjected to ocular irritancy test, to check either for any redness, inflammation or increased tear production, by instilling the selected preparations (50 $\mu$l) in the eyes of albino rabbits. In all, nine- albino rabbits were used and each formulation was incorporated in the conjunctival sac of the eyes of three rabbits. Contra lateral eye was used as a control. The study was done for 48 hrs. It was reported that, no sign of redness or inflammation was observed with any of the three niosomal formulations. Thus, it was signified by that niosomes constitute themselves as an effective ophthalmic vesicular carrier for the application of gentamicin sulphate (Abdelbary 2008).

**CHLORAMPHENICOL**

Yasin \textit{et al} had designed niosomes of chloramphenicol and compared it with the chloramphenicol eye drop, for the effective treatment of conjunctivitis. Niosomes were prepared by ether injection method and evaluated for particle size, zeta potential, viscosity, entrapment efficiency, and stability study, \textit{in vitro} and \textit{in vivo} studies. \textit{In vivo} study was conducted on twelve rabbits divided into two groups, each containing six rabbits. Ist group was treated with ophthalmic drops of chloramphenicol and second group with niosomal suspensions loaded chloramphenicol. Sample (aqueous humour) was drawn periodically up to 8 hrs and analyzed by HPLC (High performance liquid chromatography) and the study was done in duplicate. For the comparative study, 12 rabbits were used, after conjunctivitis was developed in the, treatment was commenced. 6 rabbits were treated chloramphenicol drops whereas remaining 6 with niosomal suspension. Drops were given in the form of 2 drops in every 2 hrs in Ist two days and then every 2 drops in every 4 hrs. for 3 days, based on the data obtained from \textit{in vivo} study. Niosomal suspensions were then administrated every 6 hrs in Ist two days and then 2 drops in every 12 hrs. for further 3 days. Result was then recorded by visualizing the sign of conjunctivitis and the recovery of the rabbits. It was observed from both the studies that, each group of rabbits showed similar recovery pattern from conjunctivitis. But, niosomal suspensions exhibited better treatment efficacy with less toxic effect as compared to commercial drops. Thereby, improving the patient compliance. No sign of irritation or redness was observed with the Niosomes containing chloramphenicol. Thus, it is concluded that Niosomes were appropriate as a carrier for the treatment of conjunctivitis for ophthalmic sustained release (Yasin \textit{et al}., 2012).

**ACETAZOLAMIDE**

Acetazolamide encapsulated niosomes as ophthalmic carriers were prepared Guinedi \textit{et al} and evaluated for entrapment efficiency, size, shape and in vitro drug release, stability study and ocular irritancy test. It was reported by the authors that niosomal formulations niosomal lowered the intraocular pressure (IOP) in rabbits as compared to free drug solution. Whereas under ocular irritation test carried out for 40 days, the histopathological examination of the corneal tissues of rabbits instilled with niosomal formulations showed slight reversible irritation in the substantia propria of the eye and no other major modification in tissues were observed. Thus, it was concluded that, Niosomes loaded with acetazolamide exhibited an effective and safe delivery system for the ocular drug delivery (Guinedi \textit{et al}., 2005).

Aggarwal \textit{et al} had formulated Niosomes of acetazolamide, with the objective to enhance the topical bioavailability as well as the corneal permeability of acetazolamide. Niosomes encapsulating acetazolamide were prepared by reverse phase evaporation method, coated with carbopol. \textit{In vivo} pharmacodynamic studies performed in male albino rabbits, reported reduction in
intraocular pressure by 33%. The selected niosomal formulation exhibited four times higher concentration as compared to the dorzolamide (Dorzox, a topical marketed product). In this study, authors had compared the aqueous humor disposition of the drug from the selected bioadhesive coated niosomal formulation with the aqueous suspension of the 1% w/v drug. The concentration of acetazolamide absorbed in the aqueous humor from both control and selected niosomal formulation was determined by microdialysis. The peak concentration of amount of drug absorbed in the aqueous humor via niosomal formulation was reported to be twice of that obtained via control suspension, after 20 min. of instillation. Thus, depicting the fact that enhanced penetration was achieved with niosomal formulation. Therefore, it was revealed that Niosomes were effective in enhancing the bioavailability of acetazolamide, effective in the treatment of glaucoma (Aggarwal et al., 2007).

LEVOFLOXACIN
Raghuwanshi et al had formulated Niosomes encapsulated with Levofoxacin for Ophthalmic Controlled Delivery and evaluated them for microscopy, percent entrapment efficiency, in vitro release study, ocular irritation test. The irritation or damaging effect of the selected niosomal formulations were tested on six rabbits by instilling the formulations in the lower cul-de-sac of the left eye of the rabbits, to observe for any redness or inflammation produced by the preparations. From this study, it was reported that none of the selected preparations showed any sign of redness or inflammation. Thus, it was demonstrated by the authors that Niosomes were efficient in prolonging the drug release with reduced side effects, representing itself as a prominent efficient carrier in ocular drug delivery (Raghuwanshi et al., 2012).

CYCLOPENTOLATE
Saettone et al had performed preliminary studies on niosomal vesicles enclosed with cyclopentolate. In vitro absorption study was conducted on rabbit using its cornea and in vivo mydriatic activity was also performed by the authors. It was reported by the authors that in in vitro study, the vesicles buffered at pH 5.5 showed an increased permeation of drug across as compared to a reference buffer solution. In the pharmacodynamic study, Niosomes possessed enhanced bioavailability than the reference solution. Thus, from these two studies, it was concluded by the authors that non-ionic surfactant vesicles (niosomes) enhanced the absorption of the cyclopentolate by altering the permeability across conjunctiva and sclera (Saettone et al., 1996).

TIMOLOL MALEATE
Kaur et al had developed bioadhesive niosomes enclosing timolol maleate and evaluated their pharmacokinetic and pharmacodynamic activity for ocular drug delivery. Male albino rabbits were used for the study to evaluate the timolol maleate concentration in aqueous humor. After instillation of one drop of both timolol maleate solution (TMS) as well as drug loaded bioadhesive niosomes, the drug concentration was measured by microdialysis method. It was observed by the authors that peak concentration of drug in aqueous humor from bioadhesive niosomal formulation was almost 1.7 times of that control drug solution. Thus, from the study it was confirmed that niosomal vesicles exhibited sustained controlled ocular drug delivery (Kaur et al., 2010).

Table No. 1
Ocular delivery of variety of drugs via Liposomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic category</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idoxuridine</td>
<td>Anti-viral</td>
<td>Improved therapeutic efficacy, effective in the treatment of Herpetic Keratitis</td>
<td>Smolin et al. (1981)</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Anti-viral</td>
<td>Improved efficacy with no side effects</td>
<td>Cheng et al. (2000)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Anti-viral</td>
<td>Enhanced penetration and better drug release</td>
<td>Law et al. (2000)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Antibacterial</td>
<td>Improved residence time</td>
<td>Danion et al. (2007)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antibacterial</td>
<td>Higher drug concentration</td>
<td>Budai et al. (2007)</td>
</tr>
<tr>
<td>Acetazolamine</td>
<td>Anti-glaucomatic</td>
<td>Improved efficacy in glaucoma treatment</td>
<td>Hathout et al. (2007)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Antibacterial</td>
<td>Enhanced antibacterial activity</td>
<td>Mahmoud et al. (2008)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Antifungal</td>
<td>Enhanced antifungal activity</td>
<td>Habib et al. (2010)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Immuno suppressant</td>
<td>More effective and safer as compared to free drug.</td>
<td>Zhang et al. (2010)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antibacterial</td>
<td>Reduced toxicity of ciprofloxacin for safe delivery.</td>
<td>Jain and Shastri (2011)</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>Anti-glaucomatic</td>
<td>Sustained delivery with enhanced intraocular pressure lowering effect.</td>
<td>Natarajan et al. (2012)</td>
</tr>
</tbody>
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Table No. 2
Delivery of drugs via Niosomes with their reported preclinical and clinical studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of delivery</th>
<th>Preclinical and clinical study</th>
<th>Inference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Oral</td>
<td>In vivo absorption study</td>
<td>Enhanced absorption</td>
<td>Azmin et al. (1985)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Topical</td>
<td>In vivo CLSM</td>
<td>Enhanced penetration</td>
<td>Jayaraman et al. (1996)</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>Topical</td>
<td>In vitro permeation study</td>
<td>Enhanced permeation</td>
<td>Fang et al. (2001)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Vaginal</td>
<td>In vivo Hypoglycaemic activity</td>
<td>Insulin became active and therapeutically effective for vaginal delivery.</td>
<td>Ning et al. (2005)</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Topical</td>
<td>In vitro drug release</td>
<td>Controlled drug delivery from Niosomes</td>
<td>Suwakul et al. (2008)</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Topical</td>
<td>in vitro skin penetration and permeation study</td>
<td>Increased drug absorption and bioavailability as compared to commercial formulation</td>
<td>Balakrishnan et al. (2009)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Topical</td>
<td>In vitro permeation study</td>
<td>Prolonged drug release with improved permeation.</td>
<td>Das and Palei (2011)</td>
</tr>
<tr>
<td>Clobetasol Propionate</td>
<td>Topical</td>
<td>In vivo pharmacodynamic study (anti-inflammatory activity).</td>
<td>Enhancement in the % reduction in paw oedema exhibited by niosomal gel.</td>
<td>Lingan et al. (2011)</td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>Transdermal</td>
<td>In vitro permeation &amp; in vivo inflammatory activity.</td>
<td>Enhanced permeation and better anti-inflammatory activity as compared to solution of drug.</td>
<td>Singla et al. (2012)</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Hepatic</td>
<td>In vivo hepatoprotective activity &amp; histopathological study.</td>
<td>Improved hepatoprotective efficiency &amp; was found to be safe.</td>
<td>El-Ridy et al. (2012)</td>
</tr>
</tbody>
</table>

Fig. 1. Diagrammatic view of Niosomal vesicular carrier.
CONCLUSION
Niosomes have been considered safe and effective as a recently advanced vesicular carrier for ocular delivery of variety of therapeutically active drugs. The preclinical and clinical studies conducted on niosomes, confirmed the fact that they are capable in enhancing the corneal permeability as well as lowering the intraocular pressure required for the treatment of various ocular disease. The clinical evaluation studies on niosomes are still in progress for targeted drug delivery.

Encapsulation of drug in niosomal vesicles provides a novel approach towards drug delivery system and new attempts have also been in action to enhance the drug delivery potential of niosomes can by using novel concepts like proniosomes, disomes and aquasome, to further explore its widespread utility in the new era of research.

CONFLICT OF INTERESTS
The author declared no conflict of interest.

REFERENCES