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APPLICATIONS OF NOVEL VESICULAR DRUG DELIVERY SYSTEM AS OCULAR DRUG VEHICLES: A REVIEW

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ABSTRACT

The eye is the most easily reachable organ available for topical drug delivery of local as well as interiorly acting drugs. Ideal drug delivery system aims to provide loading and maintenance dose of drug while being within therapeutic limits at the desired site of action for the desired period of time. In the treatment of ocular disease, the site of action is very narrow and undesired side effects may cause serious injuries to eye tissues. Thus, ideal ocular drug delivery should be site specific, controlled release and non-irritating. Many drugs (more than 85%) belong to BCS class IV exhibiting poor solubility and permeability. Moreover; the precorneal losses like tear secretion, naso-lachrymal drainage and less permeability of corneal tissue causes only 1% absorption of instilled dose. These limitations lead to increased loading dose and dosing frequency to maintain minimum therapeutic level for action which ultimately causes over exposure of drug to eye and leads to serious side effects. Due to these hurdles of conventional drug delivery system, the vesicular drug delivery system is gaining more popularity day by day as they offer improved permeability and altered bioavailability of drug. These formulations mainly include liposome and niosome made up of phospholipids and non-ionic surfactants respectively. They are non-antigenic, biodegradable and non-irritating. The present article reveals the key-work done on vesicular drug delivery system as potential ocular drug delivery system and justifies the need for further research on vesicular drug delivery system as ocular vehicles.

INTRODUCTION: Eye is the most easily accessible organ for topical drug delivery for local as well as interiorly acting drugs. The eye has major two segments;

1. Anterior segment
2. Posterior segment.

Anterior structure is in front having various optical structures like cornea, pupil, aqueous humor, iris, lens and ciliary body.

Posterior segment of eye includes sclera, choroids, retina, vitreous humor, macula and optical nerve. The cornea has relatively less permeability and hence drug penetration has always remained a critical problem.

It is made up of three distinct layers, i.e. epithelium, stroma and endothelium layers, where each layer exhibits different polarity and a potential rate-limiting structure for drug permeation [1].

The ocular drug delivery has been remained highlighted issue due to its dosing problems and patient compliance. To maintain the minimum therapeutic concentration at the site of action with non-irritating characteristics is always a challenging issue in ocular drug delivery system. The uncommon barriers like tear secretion and blinking of eye causes noticeable loss of instilled dose [2].

The most common routes of drug administration for ocular disease treatment are topical, periocular and intravitreal. Among all these routes, topical route is more preferred due to its non-invasive nature and ease of administration. When drug is delivered through topical route, the absorption of drug takes place either through corneal route or non-corneal route. The corneal route involves cornea, aqueous humor and intraocular tissues where as non-corneal route involves conjunctiva, sclera and choroids.

Approximately only 5% of instilled dose reaches the intraocular tissues due to various responsible factors like pre-corneal drainage and less permeability of corneal epithelium cells. The systemic route can by pass these hurdles but the problems related this route are blood-aqueous barrier and blood-retinal barrier which lead to high loading dose to reach the target site. The high dose and dosing frequency causes unavoidable systemic side effects like stomach upset and disturbed GI motility. The endothelium cells of iris and ciliary blood vessels and non-pigmented ciliary epithelium cells exhibits tight junctional cell complex which acts as blood-aqueous barrier. This barrier plays major role in preventing entry of drugs into the aqueous humor.

Blood retinal barrier is composed of retinal capillary endothelial cells and retinal pigment epithelium (RPE) cells, which prevents the entry of drug into the retina. Frequent intravitreal dosing is required which may cause vitreous hemorrhage, retinal detachment and endophthalmitis. Another serious issue regarding loss of topically instilled drugs in conventional dosage form is from the nasal cavity. Nasal cavity exhibits large surface area and higher permeability of the nasal mucosal membrane compared to that of the cornea. Standard dropper of conventional ocular dosage form delivers around 50-75 µl per drop but large portion of this drop drains out quickly until the eye regains its normal resident volume i.e. 7 µl [3-4]. Due to this limitation, very large loss of instilled medicament occurs and hence very small fraction of dose becomes available at the site of action[5]. Thus, to overcome this issue, development of non-invasive, controlled release targeted drug delivery system is required which can provide drug delivery for prolonged period of time.

Ideal properties of controlled ocular delivery system [6]:

- To provide controlled drug release at the targeted site.
- Reasonable corneal penetration.
- To overcome the zigzag fluctuation caused by conventional ocular drug delivery system.
- Reduced dosing frequency.
- To increase the corneal contact time by providing effective adhesion to corneal surface and corneal retention time, so that the released drug effectively reaches the target site.
- To bypass the anatomical and physiological protective barriers like tear secretion, naso-lacrymal drainage and loss of instilled dose due to blinking of eye.
- To provide comfort and compliance to the patient without blurring the vision.

In novel drug delivery system, the vesicular drug delivery system (VDDS) has gained lot of attention due to its distinct benefits in improving bioavailability and dose frequency reduction. The VDDS has been found valuable for other research areas like immunology, membrane biology, diagnostic techniques and genetic engineering [7]. VDDS plays major role in improving movement of drug to site of action and also provides prolonged and controlled action at the corneal surface by prevention the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface.

VDDS tends to localize and maintain drug concentration at its site of action. The rate of drug penetration depends on the physicochemical properties of the drug like, solubility, particle size, polymorphic form etc. The VDDS has ability to entrap the drugs in vesicles and cross the permeability rate

limiting barriers and hence, VDDS is considered as potential drug carriers. The vesicles act as drug reservoir as well as the drug release rate and the affinity for the site of action can be altered by optimizing the formulation. VDDS generally includes liposomes and niosomes as most preferred ocular drug delivery system.

Vesicles as Ocular Drug Delivery System (ODDS): Liposomes were first introduced as the drug carriers in 1965 [8]. Liposomes are made up of phospholipid bilayers surrounding an aqueous core which may or may not contain drug. It is usually of 10 nm to 10 µm or greater in diameter. They are classified as unilamellar vesicles and multilamellar vesicles (MLVs). The unilamellar vesicles are further classified into small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs) and giant unilamellar vesicles (GUVs) [9-10].

Unilamellar vesicles are composed of single bilayer of phospholipids encapsulating aqueous core whereas, the multilamellar vesicles is composed of multiple phospholipids bilayers. Liposomes can entrap both hydrophilic and lipophilic drugs by partitioning them into hydrophobic domains [11-12]. **Figure 1** represents the basic structure of MLV and ULV.

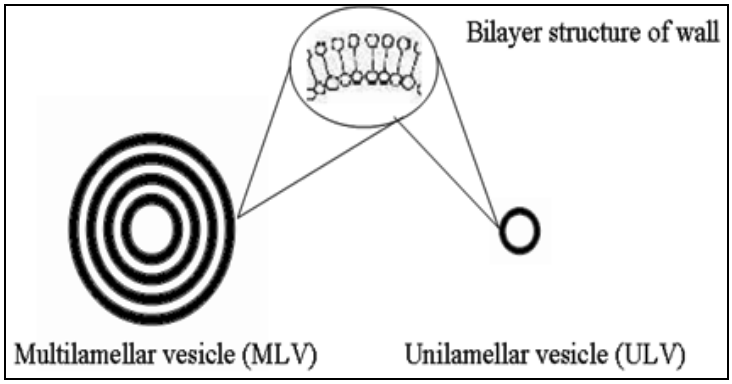

FIGURE 1: BASIC STRUCTURE OF MLV AND ULV

TABLE 1: SIZE OF DIFFERENT TYPES OF LIPOSOMES

Vesicle type	Vesicle size (Geometric mean diameter)
Small unilamellar vesicle (SUV)	20 – 200 nm
Large unilamellar vesicle (LUV)	200 nm – 1.0 µm
Giant unilamellar vesicle (GUV)	> 1.0 µm

Liposomes are made up of various grades of phospholipids and some other ingredients like cholesterol and lipid-conjugated hydrophilic polymers. The cholesterol acts as vesicle stabilizer by improving the firmness of bilayer membrane.

Vesicle morphology liposome depends on the various properties like surface charge, size, surface hydration and fluidity of lipid bilayers. The use of charge inducers is also well known due to their distinct applications. The cornea generally carries negative charge and hence the positively charged liposomes display better corneal permeation. Moreover, the charged liposomes exhibit less aggregation tendency as compared to neutral liposomes.

The only drawback of charged liposome is their higher uptake and rapid clearance by Reticulo-endothelial system (RES) because of their higher interaction with serum proteins. The RES clearance is also vesicle size dependent as the vesicle size below 100 nm are more prone to opsonization and hence they show more circulation time in blood [13].

The liposomes show these many of novel benefits although it has some negative points which require further improvements and optimization. The most common problem of liposome manufacturing is the susceptibility of phospholipids to oxidative degradation in air [14].

Thus, the handling and storage of liposome becomes very critical issue. Many of the researchers have enlisted requirement of nitrogen gas (N_2) in ideal storage facility of phospholipids to avoid oxidative degradation. The purity tests of phospholipids shall be described properly to avoid any unwanted degradation product in finished dosage form. As the phospholipids are natural or semi-synthetic, their cost of production and purity tests makes cost factor a noticeable issue [15].

The niosome vesicles are obtained upon hydration of nonionic surfactant such as monoalkyl or dialkyl polyoxyethylene ether and cholesterol. Just like liposomes, the niosomes are also unilamellar to multilamellar vesicles and can entrap hydrophilic and lipophilic drugs. Niosomes were first introduced in seventies and gradually being developed as potential novel drug delivery system. They exhibit more stability and fewer disadvantages associated with liposomes like, higher cost and degradation problems of phospholipids. Cholesterol is used in combination with various nonionic surfactant for providing vesicle stability same as in liposomes [16-17].

Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti-neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. In addition, handling and storage of niosomes requires no special conditions. In mice, the distribution of drugs incorporated in niosome vesicles has proved to be similar to that obtained after administration of drug encapsulated in liposomes.

Work done in Liposomal Dosage Forms as ODDS: The liposomes were first studied as ocular drug delivery system in 1981 by Smolin *et al*. Authors have described preparation of Idoxuridine liposomes and have compared their therapeutic efficacy with Idoxuridine topical solution for the treatment of herpetic keratitis in the rabbit eye [18].

Schaeffer and Krohn have investigated the role of charged vesicles and size of vesicles in transcorneal permeation in rabiit eye. Authors practically demonstrated approximately four times higher corneal flux of penicillin-G loaded liposomes [19].

Singh and Mezzei have investigated role of Triamcinolone acetonide liposomes in increasing the concentration of drug at the target site. They demonstrated to achieve twice concentration of Triamcinolone acetonide when delivered in liposomal dosage form as compared to conventional drug solution.

However, liposomal formulations of Dihydrostreptomycin sulfate did not aid the corneal permeation. The justification was made that liposomes are less effective to entrap the hydrophilic drugs [20].

Fitzgerald *et al.,* have explored the effects on clearance rate of liposomes by gamma scintigraphy upon topical administration in the rabbit model. They reported that the positively charged SUVs are more effectively retained at cornea site. They justified that positively charged liposomes were being retained due to negative charge present on the corneal cells [21].

Chitosan is well known for its mucoadhesive properties and the same approach was used in liposome formulation by various researchers to improve the residence time in eye at the site of action. Chitosan is biodegradable and its byproducts are also non-toxic, thus the use of chitosan in ODDS is considered safe. Mehanna *et al*., have prepared chitosan coated mucoadhesive liposomes of Ciprofloxacin by reverse phase evaporation method. The prepared liposomes were further coated with chitosan of different molecular weights (chitosomes). They concluded that the liposomes coated with chitosan if high molecular weight were relatively smaller in size, which acted as a barrier to inhibit aggregation.

In vitro release studies showed chitosan coated liposomes released drug delivery slower than uncoated liposomes due to presence of physical barrier at the outer side. *Ex vivo* studies demonstrated that the chitosan coated liposomes shows almost twice permeability as the chitosan aided the diffusion across the cornea cells [22].

Li *et al*., have determined the role of low molecular weight chitosan coated liposomes in ocular drug delivery. Low molecular weight chitosan coated liposomes showed good influence in vivo activity. Authors claimed to achieve higher ex vivo corneal penetration across excised rabbit cornea using low molecular weight coated liposomes. The *in vitro* release was found to be much slower due to presence of physical barrier chitosan. The precorneal loss time was also drastically reduced due to mucoadhesive nature of chitosan. They also reported that there were no signs of adverse effects during study [23].

Zhang *et al*., utilized N-trimethyl chitosan chloride (TMC), a quaternary derivatives of chitosan for coating of coenzyme Q10-loaded liposomes. They reported better stability and less leakiness due to coating. They measured and reported approximately 5 times higher precorneal residence time after topical administration using gamma scintigraphy.

Authors performed draize test and histological analysis to prove biocompatibility of TMC with ocular tissues. The high molecular weight TMC showed better anti-cataract activity in Sprague Dawley rats [24-26].

Habib *et al*., prepared and evaluated Fluconazole loaded liposomes on candidal keratitis model in rabbits. Authors aimed to enhance the antifungal action by prolonging the contact time at the site of action. They carried out comparative efficacy study of the Fluconazole solution and Fluconazole loaded liposomes. They reported to get 1.7 times faster healing with liposomal drug delivery no noticeable side effects [27].

Budai et al. prepared negatively charged ciprofloxacin loaded liposomal hydrogel for the treatment of chronic ocular infectious diseases like conjunctivitis, bacterial keratitis, which requires high drug concentration at the site of infection.

Lecithin and alpha-L-dipalmitoylphosphatidycholine (DPPC) were used as to prepare multilamellar vesicles of liposomes. Hydrogel was prepared by using Poly vinyl alcohol (PVA) and polymethacrylic acid (PMA) derivatives. The gel was evaluated for viscosity, rheological property, in vitro release and ex vivo studies. The Ciprofloxacin loaded liposomes showed better entrapment efficiency due to electrostatic charge properties and showed five time enhancement in transcorneal permeation in rabbit model [28, 29].

Felt *et al*., developed and evaluated oflaxacin-loaded liposomal thermo-sensitive hydrogel for transcorneal permeation of Oflaxacin. Authors reported the difference in vesicle size is arising due to difference in method of preparation. Authors used chitosan/ beta-glycerophosphate thermo-sensitive hydrogel system for fabrication of liposomes in thermo-sensitive gels and observed reduced required energy for gelation step. They also performed transcorneal permeation study using rabbit cornea and reported that Oflaxacin permeates seven times higher from the liposomal formulation compared to Oflaxacin aqueous solution due to mucoadhesive nature of the hydrogel. Researchers reported that the ocular retention time was three times higher due to mucoadhesive properties of hydrogel without any significant adverse effects [30].

Hathout *et al*., carried out encapsulation of Acetazolamide in liposomes by reverse phase evaporation technique (REV) for the treatment of glaucoma with topical administration. Measurement of intraocular pressure (IOP) lowering was carried out and compared with effects produced by Acetazolamide solution. Liposomes prepared by different compositions were evaluated for entrapment efficiency, stability *in vitro* release and IOP lowering efficacy in rabbit model. Authors reported highest entrapment efficiency with positively charged liposomes due to ionic interaction between drug and lipid [31].

Danion *et al*., prepared MLV liposome loaded contact lenses for the site specific delivery of Levofloxacin in treatment of bacterial keratitis. They reported first order release kinetics up to six days. The contact lens as carrier helped to improve the retention time and continuous drug delivery [32, 33].

Mahmoud *et al*., prepared Chloramphenicol (CP) loaded liposomes using dimyristoylphosphatidycholine (DMPC) as lipid part by three different methods like partitioning of CP in the vesicle bilayers, entrapment of CP by normal hydration method and adsorption of CP on the vesicle surface. Those formulations were evaluated for interaction of the drug and phospholipid bilayers and for effectiveness against S. aureus. They concluded that CP located in interfacial region within the hydrophobic core of the liposomes shows better anti-bacterial activity against S. aureus up to 5 hrs [34].

Law *et al*., prepared Acyclovir (ACV) loaded liposomes for topical administration and carried out in vitro corneal penetration and in vivo corneal absorption on male rabbits. They concluded that surface charge of liposomes play key role in corneal penetration and ACV absorption. They stressed on positively charged liposomes to exhibit higher drug entrapment efficiency and better drug release compared to negatively charged liposomes.

They reported the prolonged penetration across the cornea with positively charged liposomes. They reported that penetration rate for positively charged liposomes was approximately 3.6 times higher than ACV solution and approximately two times higher that negatively charged liposomes. They concluded that surface charge on liposomes also play important role in corneal retention time [35].

Kawakami *et al*., prepared liposomes of O-palmitoyl prodrug of Tilisolol to enhance the retention time of Tilisolol in the precorneal area. The administration of liposioome was carried out by topical route as well as intravitreal route in rabbit eye. Upon intravitreal application, they found higher concentration of Tilisolol as compared to free Tilisolol. By topical administration, they reported very low retention of O-palmitioyl Tilisolol in the tear fluid. Thus, to further improve this, they used 2% of sodium carmellose. Sodium carmellose acted as a reservoir for liposomes and thus retention was improved relatively [36].

Barza *et al.,* studied the effects of liposomes size and pathological state of eye upon intravitreal elimination kinetics of carriers. They concluded that the rate of clearance of SUVs was higher than LUVs. They also observed that intraocular inflammation increases the rate of intravitreal clearance [37].

Zhang *et al*., prepared Tacrolimus-loaded liposomes by reverse phase evaporation method for the treatment of uveoretinitis. They further evaluated it for safety and efficacy upon intravitreal injection in rats. No retinal dysfunction was observed in the liposome-treated rats. Histo-pathological examination revealed inflammatory response in comparison to free drug. They claimed to achieve 50ng/mL up to two weeks after single administration of Tacrolimus loaded liposomes. They consluded that Tacrolimus loaded liposomes were more efficacious than the free drug [38].

Cheng *et al*., prepared liposomal prodrug of ganciclovir (GCV) i.e. 1-O-hexadecylpropanediol-3-phospho-Ganciclovir and further injected intravitreally in rabbits. They studied its effects for antiviral treatment against herpes simplex virus type 1 (HSV-1) and human cytomegalovirus (HCMV). They concluded that intravitreal injection of 0.20 nM intravitreal concentrations was most effective without causing any side effects [39].

Fukushima *et al*., formulated Clodronate liposomes used to inhibit infiltration of macrophages in the conjuctiva in treatment of blepharo conjunctivitis developed in Brown Norway rats. Authors stated that Clodronate liposomes very much effective in decreasing the number of ED2-positive macrophages in the conjunctivas. Authors suggested investigating further using liposomes larger than 550 nm to explore thorough research regarding subconjunctival clearance [40].

Work done on niosomal dosage forms as ODDS: Handjani-vila *et al*., first demonstrated the advantages obtained by use of vesicular systems on the skin and specifically the use of non-ionic surfactants in aqueous dispersion. They carried out a comparative toxicity study with classical formulation such as emulsions and concluded that novel vesicular system exhibits low toxicity and better permeation of actives through stratum corneum [41].

Green and Downs studied the ocular penetration of Pilocarpine using radio labeled Pilocarpine in different vehicles. They also reported that an ocular bioavailability of water soluble drug, entrapped in niosomes is due to the role of surfactant. The surfactant decreases the surface tension and hence also acts as penetration enhancers by removing the mucus layer and break functional complexes [42].

Azmin *et al*., prepared vesicles of Methotrexate from a nonionic surfactant, cholesterol and dicetyl phosphate and dosed to mice. They reported that intravenous dose prolonged the release of methotrexate in the blood and also improved its uptake in liver and brain. They concluded the metabolic profile of drug was also altered by the niosomes which decreses the rapid formation of 7-hydroxy methotrexate [43].

Okahata *et al*., prepared bilayer structure using alkyl chain length C_{12}, C_{14}, C_{16} and C_{18}. They reported that vesicles were lamellae and amphiphilic in nature. They concluded that the aggregates were being formed only above the phase transition temperature of surfactant [44].

Baille *et al*., prepared vesicles by hydration of a mixture of a single or double alkyl-chain, non-ionic surfactant with cholesterol. They stated that niosomal vesicles are osmotically active and relatively more stable than liposomes. The vesicles have been characterized by photon correlation spectroscopy, freeze fracture electron micrography, measurement of solute entrapment efficiency, and solute release rates. Vesicular forms of the single chain surfactant which could be formed under certain condition in the absence of cholesterol are also described [15].

Lasic prepared bilayer vesicles by involving some physical agitation and heat. They obtained an assembly in which the hydrophobic parts of the molecule are covered by aqueous solvent and the hydrophilic head groups gets maximum contact with hydrophobic parts. He concluded that requirement of some energy is must for preparation of bilayer vesicles [45].

Saettone *et al*., reported non-ionic vesicles as carriers of Cyclopentolate for ocular drug delivery. They prepared vesicles by sonication polysorbate 20 and cholesterol in various concentrations. They concluded that the vesicles buffered at pH 5.5 increases the transcorneal permeation of Cyclopentolate as compared to a standard buffer solution. They also reported that vesicles remarkably increase the bioavailability Cyclopentolate at ocular site as compared to standard buffer solutions [46].

Aggarwal *et al*., prepared the mucoadhesive niosomes of Cyclopentolate as compared to a standard buffer solution. for ocular drug delivery system improved. Authors used chitosan and carbopol to coat niosomes of Timolol maleate prepared by reverse phase evaporation (REV) method. They carried out comparative *in-vitro* release study with Timolol solution and IOP lowering effect as pharmacodynamic study. They concluded that chitosan coating can significantly extend the release profile of Timolol maleate [47].

Aggarwal *et al*., also prepared Acetazolemide loaded niosomes by reverse phase evaporation and coated them with carbopol to enhance the bio-adhesive nature. Authors reported that sustained action was obtained for 6 hours with 33% more decrease in intraocular pressure.

The bioavailability of Acetazolemide was enhanced almost twice when dosed in niosomal dosage form as compared to free drug solution. They applied microdialysis technique to improve the regional sampling of the tissues [48].

Abdlbary and El-gendy used non ionic surfactant vesicles as carriers for the controlled ocular delivery of Gentamicin sulphate. They prepared and evaluated various nisomal formulations using different surfactants like Tween 60, Tween 80 and Brij 35 in different molar ratios and by thin film hydration technique. They carried out photomicroscopy, transmission electron microscopy and particle size analysis for evaluation of vesicles. They reported that niosomal Gentamicin sulphate shows a high retention as compared to the free drug solution *in-vitro* release study. Authors also carried out ocular irritancy study and concluded that there were no signs of irritation[49].

CONCLUSION: The vesicular drug delivery has its distinctive advantages due to its novel structure. The strategic role of bilayer vesicles has been investigated by many researchers over the time. The critical structure of human eye and its anatomical as well as physiological barriers can be more conveniently overcome by vesicular drug delivery system. The bio-adhesive nature of phospholipids and non-irritating nature of non-ionic surfactants have laid detailed research on vesicles as ocular drug delivery system. The potential action of vesicles drug delivery system will lead to drastically reduced therapy time and excellent patient compliance.

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