Review On Liposomal Gel In The Administration Of Ocular Drug Delivery System

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Abstract: Ocular drug delivery is one of the most challenging endeavors among the various available drug delivery systems. Liposomes also proved to enhance drug solubility and controlled distribution, as well as their capacity for surface modifications for targeted, prolonged, and sustained release. The present review is dedicated to highlighting and updating the liposomal carrier for ocular drug delivery. There are different administration routes for ophthalmic drug delivery that are widely used to reach the posterior segment in clinical practice. These drugs administration routes face many challenges to either overcome problems associated with solubility and permeability depending upon the route of drug administration [5]. *Keywords: Ocular drug delivery, approaches to enhance ocular drug delivery, Liposomal gel compositions, Method of preparation, Drug loading, Mechanism of drug release through liposome.

1. Introduction:

1.1 Topical administration

One of the prevalent routes of drug administration is topical usage. In the topical route, conventional formulations e. g. ointments, eye drops, and suspensions are used for good patient compliance. Drug delivery to the targeted ocular tissues is limited by several local barriers. Lacrimation and washing of drugs during lacrimation are the main challenges, and if we decided to use a drug topically, it must absorb sufficiently and rapidly before washing with tear. The other challenge is the corneal epithelium barrier. Drugs must have the capability to penetrate the corneal layers. Interaction of a drug with tear film enzymes or proteins and also with anterior chamber molecules is the other challenge. After each step after the administration of drug formulation via topical route.[5]

There are many approaches for systemic administration of drug delivery into the deeper region of eye and they are as following:

- Subconjunctival injection
- Periocular implant
- Intravitreal injection
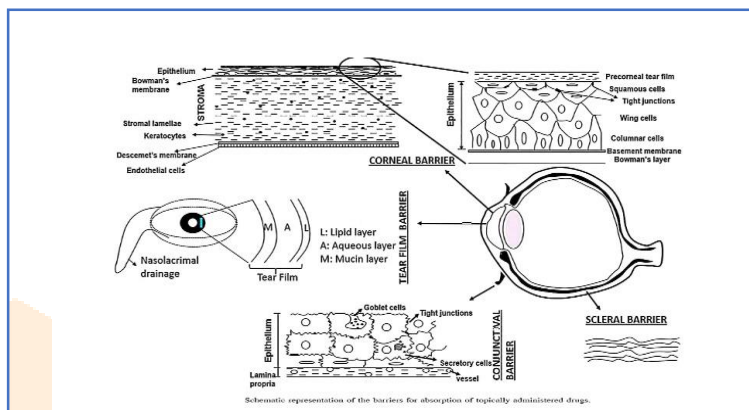- Suprachoroidal injection
- Systemic administration

Fig.1.1: Ocular Barrier for Ophthalmic Drug Delivery.

Considering the challenges in ocular drug delivery, efforts have been made to formulate ophthalmic formulation in a way that can minimize the drug loss and maximize the drugs ocular bioavailability. The characteristics of an ideal topical drug role and clinical significance remains unclear delivery system can be summarized as follows. Although, it has been suggested that transporters in cornea may provide important avenue for enhanced drug delivery.

1. Should be able to resist precorneal clearance and provide prolonged corneal contact time [14].
2. Should be delivered in a dosage form that provides adequate trans-corneal absorption
3. Should be of suitable viscosity that provides good corneal contact time.
4. Should have a suitable pH that Favors the absorbable form of drug molecule and non-irritant to ocular surface.
5. Should cause minimal adverse effects.
6. Should require sufficiently low frequency of administration to ensure patient compliance.

1.2 Transconjunctival-Scleral Absorption

The cells in the superficial layer of conjunctival epithelium have tight junctions (Figure1.l), however, as stated earlier these tight junctions are leaky. Therefore, conjunctival permeability to hydrophilic drugs is higher than that of corneal permeability and molecules up to the size of 20000- 40000 Dalton can pass through the conjunctiva. Conjunctival permeability coefficients for many compounds, like B-blockers and timolol prodrugs are higher than their corneal permeabilities. The ocular availability of peptides through conjunctiva is expected to be limited not only due to large molecular size but also due to degradation by enzymes secreted by conjunctiva. Presence of carrier-mediated mechanisms in the conjunctival epithelium has also been suggested to play an important role in transferring drug molecules to the interior of the eye.

Since conjunctiva is richly supplied with blood vessels and lymphatics and has a large surface area, it is also a site of significant loss of topically applied drugs due to systemic absorption.

Fig Ocular barriers to drug delivery: **(a)** the tear film is consist of the mucin, aqueous, and lipid layers; **(b)** the corneal layer is composed of the endothelium, Descemet's membrane, stroma, Bowman's membrane, and epithelium; **(c)** the conjunctival barrier; **(d)** the blood-aqueous barrier begins at the ciliary body stroma and is formed by the basement membrane, pigmented and non-pigmented cells and is specified with the basement membrane; **(e)** the blood-retinal barrier is composed of Bowman's membrane, RPE, photoreceptors, horizontal cells, bipolar cells, amacrine cells, and the retinal ganglion cell.
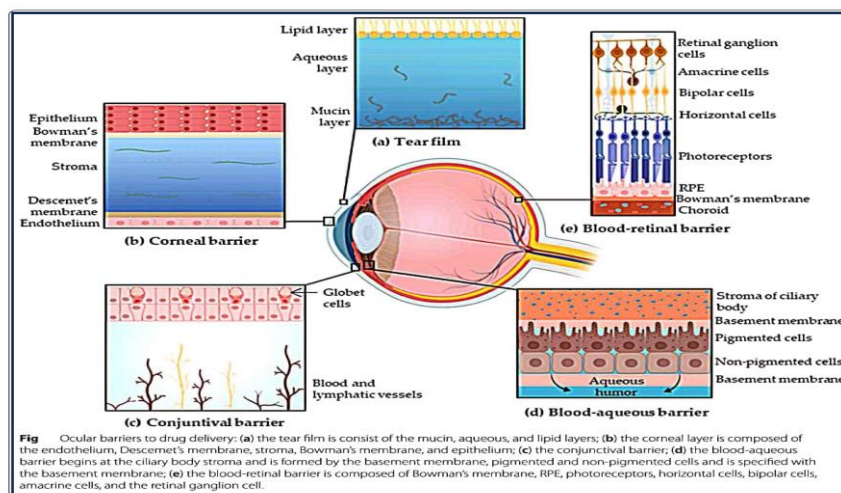
Fig.1.2: Transconjunctival-Scleral Absorption

In order to achieve the above-mentioned characteristics of a topical drug delivery system, several approaches have been adapted. Viscosity enhancing polymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose are added to topical formulation to reduce precorneal drug clearance and enhance the corneal contact time. Penetration enhancers that modify the integrity of corneal epithelium and increase drug permeability have also been used. Some of the examples of penetration enhancers include cetylpyridinium chloride, lasalocid, benzalkonium chloride, parabens, Tween 20, saponins, bile salts and bile acids. These substances have the disadvantage of causing corneal toxicity. A prodrug approach has also been used to achieve suitable polarity of drug molecules that favours transcellular uptake [14].

1.3 Liposomal Gel Compositions

1.3.1 Lipids and phospholipids used for liposomes:

Structurally, liposomes are spherical or multilayered spherical vesicles made by the self-assembly of diacyl-chain phospholipids (lipid bilayer) in aqueous solutions. The bilayer phospholipid membrane has a hydrophobic tail and a hydrophilic head that leads to the formation of an amphiphilic structure. Liposomes can be made from both natural and synthetic phospholipids. Lipid composition strongly affects liposome characteristics that include: particle size, rigidity, fluidity, stability, and electrical charge. For example, liposomes formulated from natural unsaturated, as egg or soybean phosphatidylcholine, provide highly permeable and low stable properties [7]. Though, saturated-phospholipids-based liposomes such as dipalmitoyl phosphatidylcholine led to rigid and almost impermeable bilayer structures. The hydrophilic group in the lipids may be negatively, positively charged, or zwitter ionic.

1.3.2 Solvents

In various methods of liposome preparation involves different solvents but preferentially n-hexane, diethyl ether, isopropyl alcohol, methanol, ethanol dichloromethane in different ratio and proportion are used.

1.3.3 Surfactants

Surfactants were utilized in liposomes formulations to modify the encapsulation and release properties of liposomes through surface tension reduction between different immiscible phases. Commonly utilized surfactants in liposomes formulations are: sodium cholate, Span 60, Span 80, Tween 60, and Tween 80.

1.3.4 Gelling Agents

Gel formulation includes a gelling agent carbomers, hydroxyethyl cellulose, and hydroxypropyl cellulose are the most widely used and solubilizers. Depending on the excipients used, a gel can be transparent (most common), translucent, or opaque. *Transcutol®P* is compatible with all types of gelling agents and can be used at a very high concentration in the gel without altering its structure. Clear gels are obtained. *Labrasol®* is compatible with all types of gelling agents. Depending on the concentration, clear or opaque gels are obtained [13].

2. Methods of preparation

Liposomes can be formulated using different approaches. The process of liposome manufacture and the phospholipids type critically affects the final liposomes characteristics. Liposome's fabrication procedures are as follows:

2.1 Thin film hydration method (Bangham method):

In this method, all lipids and the hydrophobic drug are dissolved in suitable organic solvent using a round-bottom flask. The organic solvent then evaporated gently under reduced pressure to create a thin film layer. The obtained thin film is then hydrated, at above the transition temperature (Tm) of the used lipid, with an aqueous buffer solution. The hydration solution may contain a hydrophilic drug/s to be loaded into the liposomes aqueous core. The rate of hydration determines the efficiency of drug encapsulation, which the slower the rate of hydration, the higher the encapsulation efficiency. Liposomes resizing, lamellarity types and particles distributions may be controlled by either extrusion through a polycarbonate membranes of specific pore sizes or the use of bath or probe sonicator.
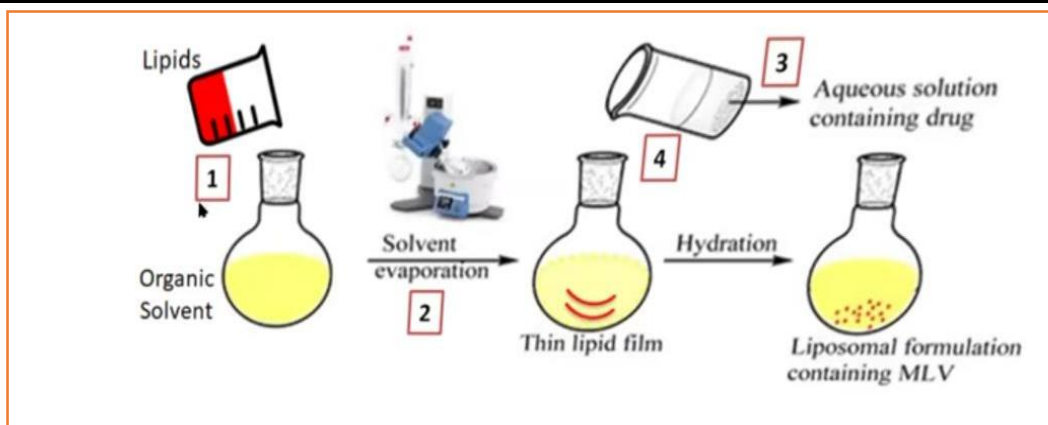
Fig.2.1: Thin film hydration method (Bangham method)

Extrusion method ensures stable liposomes with more encapsulation efficiency over sonication. Sonication usually produce SUVs liposomes and may also degrade or hydrolyse encapsulated drugs and/or lipids. Probe sonication may subject liposomes suspensions to potential metal contamination.[1]

2.2 Solvent injection method:

The injection methods were classified according to the type of organic solvent used. An organic solvent dissolving the lipids and the hydrophobic active agents were rapidly injected into an aqueous phase. Diethyl ether enable direct solvent evaporation during mixing process at a temperature above to the boiling point of the used solvent. Utilizing ethanol for injection required a 10-to-20-fold aqueous solution and ethanol can be evaporated under vacuum using a rotary evaporator, dialysis, or filtering. This method mostly prepared liposomal formulations with higher polydispersity indexes (PDI). In addition, continuous exposure to high temperature and organic solvent might reduce drug and lipids stability.

2.3 Detergent removal method

In this method, lipids and a high critical micelle concentration (CMC) surfactant were dissolved in a suitable organic solvent using a round bottom flask. A thin film was obtained at the bottom of the flask after solvent gentle evaporation. A mixed micelles solution then obtained by hydrating the lipid film in an aqueous solution containing the drug molecules. The surfactant is then removed by dialysis, size-exclusion chromatography, adsorption onto hydrophobic beads or dilution. Finally, a LUVs liposomes vesicle will be formulated after solution concentration. A main drawback of this method is that most hydrophilic drugs are separated from the liposomes during detergent removal step.

2.4 Dehydration-rehydration method

It is an organic solvent free method to produce LUVs using sonication. This method based on direct dispersing of the lipids at low concentrations into an aqueous solution containing the drug molecules followed by sonication. First, the dehydration step to evaporate water under nitrogen to create multilayered film entrapping the drug molecules. Then, a hydration step to form large vesicles encapsulating the drug molecules. This method is simple but with high heterogeneity of the liposomes sizes.

2.5 pH jumping method

Another solvent-free method for liposomes preparation is the pH jumping method. In this method, the aqueous solution of phosphatidic acid and phosphatidylcholine are exposed to almost four-fold increase in pH over a short time to break down MLVs into SUVs. The ratio of phosphatidic acid: phosphatidyl choline determine the percentage of SUVs versus LUVs produced.

2.6 Microfluidic channel method

The microfluidic channel method has been recently proposed as a novel method for liposomes preparation. Microfluidics provides a tool to employ liquids within microscopic channels. In this method, lipids are dissolved in ethanol or isopropanol, and the resultant solution is injected upright or in the opposite direction to the aqueous medium within the micro-channels. This method involves continuous axial mixing of the organic and aqueous solutions leads to liposomes formation. Liposomes are stabilized using surfactants to avoid coagulation and separation. Microfluidic channel methods control the mixing process of organic and aqueous phases to achieve reproducible liposomes with proper average size, polydispersity, morphology, and lamellarity.

2.7 Supercritical fluidic method

This method utilized a supercritical fluid, carbon dioxide (CO_2), to dissolve lipids instead of using organic solvents. A high-performance liquid pump provides a continuous flow of the aqueous phase into a cell that contains the supercritical lipid solution, allowing phase transition of the dissolved phospholipids. Upon abrupt decrease in pressure, liposomes will form after completely removing of CO_2. 5-fold higher encapsulation efficiencies were obtained by this method. This method suffers from high cost, low yield, and special infrastructures even with using the environmentally safe and cheap carbon dioxide.

3. Liposomal drug loading

Passive loading entraps hydrophilic drug in the liposomes aqueous core during lipid bilayer formation, while hydrophobic drugs accumulate in the small-sized hydrophobic lipid bilayer. Passive loading suffers from bilayer destabilization, high drug/lipid ratio, and rapid drug release. Therefore, improving the aqueous solubility of these hydrophobic drugs by cyclodextrin host-guest complexation were successfully applied and permit liposomes aqueous core loading by forming drug-in-cyclodextrins-in-liposomes delivery system[6]. Active or remote loading has been developed to ensure high encapsulation efficiency of precious chemotherapeutic agents. Remote loading can be achieved into preformed liposomes by pH gradient and/or potential ionic differences across liposomal bilayer membranes. The success of intraliposomal remote loading is govern by to main parameters, drug aqueous solubility in presence of an ionizable functional group in drug chemical. Intraliposomal active loading of hydrophobic drugs in response to ionic and/or pH gradients across the liposomes bilayer was developed. This procedure enables hydrophobic drugs to accumulate inside the liposomes core after the vesicles are created. The advantage of this method is that the loading of the drug can be performed independently of liposomes preparation conditions [10].
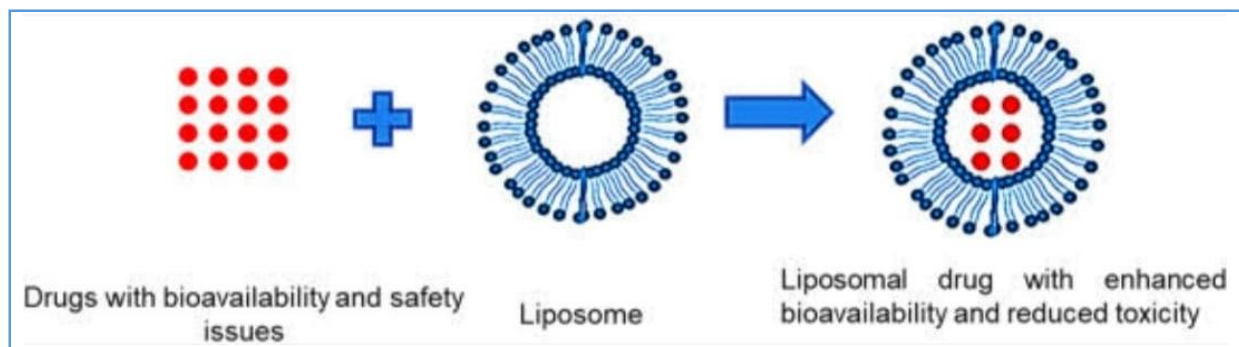
Fig.4: Liposomal Drug Loading

Most potentially active drugs are weak bases possessing primary, secondary, or tertiary amine functional groups that can be loaded in response to pH gradients. Drugs that are not weak bases, or do not have an ionizable functional group, can be converted to weak base prodrugs or encapsulated with amino-modified carriers as cyclodextrins, therefore allowing encapsulation and intraliposomal retention.

4. Formulation of Liposomal Ophthalmic Gel:

The weighed quantities of polymers were kept for swelling overnight in distilled water and dissolved (heated, if necessary) using a magnetic stirrer. The liposomal suspension containing drug was added in to the polymeric solution with continuous stirring. Benzalkonium chloride was added to the resulting. The pH of the formulation was adjusted to 7.4 using 0.1 N NaoH or 0.1 N HCl After the drug loading in the liposome the most important step is formulating the gel consisting the desired viscosity suitable for surface of eye. The gel should have to be prepared in aseptic area in aseptic conditions. After the mixing of liposomal suspension with the gel solution homogenization is done with the help of magnetic stirrer at controlled temperature conditions to achieved the liposomal gel of desired viscosity.

5 Mechanisms of Drug Release Through Liposome on Ocular Surface:

The mechanisms of interaction of liposomes with cell membranes that result into intracellular drug delivery have been studied extensively but are poorly understood. Due to highly complex nature of this interaction, the interpretation of experimental data is often difficult. The initial liposome-cell membrane interaction is the key process that leads to intracellular drug delivery. This liposome-cell membrane interaction may involve different receptors on different cell types or more than one receptor on a particular cell and is greatly affected by the lipid composition of liposomes. Largely, four mechanisms of intracellular drug delivery by liposomes are widely accepted and are as follows:

(1) Adsorption: Adsorption of liposomes to cell membrane is one of the important mechanisms of intracellular drug delivery. The adsorbed liposomes, in the presence of cell surface proteins, become leaky and release their contents in the vicinity of cell membrane. This results in a higher concentration of drug close to cell membrane and facilitates cellular uptake of drug by passive diffusion or transport [2].

(2) Endocytosis: Adsorption of liposomes on the surface of cell membrane is followed by their engulfment and internalization into endosomes. Endosomes transport liposomes to lysosomes. Subsequently, lysosomal enzymes degrade the lipids and release the entrapped drug into the cytoplasm.[10]

(3) Fusion: Fusion of lipid bilayer of liposomes with lipoidal cell membrane by intermixing and lateral diffusion of lipids results in direct delivery of liposomal contents into the cytoplasm.

(4) Lipid exchange: Due to the similarity of liposomal membrane lipids with the cell membrane phospholipids, lipid transfer proteins in the cell membrane recognize liposomes and consequently cause lipid exchange. This results in the destabilization of liposomal mem- branes and intracellular release of drug molecules [9]. An understanding of the mechanisms of intracellular drug delivery by liposomes provides the basis for bringing about manipulations in the characteristics of liposomes to enhance their favourable interaction with cell membranes and hence the drug delivery [12].

6. Conclusion: The ophthalmic gel formulated by using the liposomes as the carrier for achieving sustained released drug delivery. The ophthalmic drug which has low aqueous solubility can successfully delivered by this liposomal gel formulation to the systemic circulation. The liposomal ophthalmic gel can also be used to improve the in vivo drug bioavailability.

7. References:

1) Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: Structure, composition, types, and clinical applications. Heliyon. 2022 May 1.

2) Agarwal R, Iezhitsa I, Agarwal P, Abdul Nasir NA, Razali N, Alyautdin R, Ismail NM. Liposomes in topical ophthalmic drug delivery: an update. Drug delivery. 2016 May 3;23(4):1075-91.

3) Afarid M, Mahmoodi S, Baghban R. Recent achievements in nano-based technologies for ocular disease diagnosis and treatment, review and update. Journal of Nanobiotechnology. 2022 Dec;20(1):1-36.

4) Nakhaei P, Margiana R, Bokov DO, Abdelbasset WK, Jadidi Kouhbanani MA, Varma RS, Marofi F, Jarahian M, Beheshtkhoo N. Liposomes: structure, biomedical applications, and stability parameters with emphasis on cholesterol. Frontiers in bioengineering and biotechnology. 2021 Sep 9; 9:705886.

5) Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: An overview. World journal of pharmacology. 2013;2(2):47.

6) Vakili-Ghartavol R, Rezayat SM, Faridi-Majidi R, Sadri K, Jaafari MR. Optimization of Docetaxel Loading Conditions in Liposomes: Proposing potential products for metastatic breast carcinoma chemotherapy. Scientific reports. 2020 Mar 27;10(1):5569.

7) Large DE, Abdelmessih RG, Fink EA, Auguste DT. Liposome composition in drug delivery design, synthesis, characterization, and clinical application. Advanced drug delivery reviews. 2021 Sep1; 176:113851.

8) Briuglia ML, Rotella C, McFarlane A, Lamprou DA. Influence of cholesterol on liposome stability and on in vitro drug release. Drug delivery and translational research. 2015 Jun; 5:231-42.

9) Anderson M, Omri A. The effect of different lipid components on the in vitro stability and release kinetics of liposome formulations. Drug delivery. 2004 Jan 1;11(1):33-9.

10) Betageri GV, Parsons DL. Drug encapsulation and release from multilamellar and unilamellar liposomes. International journal of pharmaceutics. 1992 Mar 31;81(2-3):235-41.

11) Mishra GP, Bagui M, Tamboli V, Mitra AK. Recent applications of liposomes in ophthalmic drug delivery. Journal of drug delivery. 2011;2011.

12) López-Cano JJ, González-Cela-Casamayor MA, Andrés-Guerrero V, Herrero-Vanrell R, Molina-Martínez IT. Liposomes as vehicles for topical ophthalmic drug delivery and ocular surface protection. Expert opinion on drug delivery. 2021 Jul 3;18(7):819-47.

13) hui-hui Z, qiu-hua L, zhi-jun Y, wei-san P, shu-fang N. Novel ophthalmic timolol meleate liposomal-hydrogel and its improved local glaucomatous therapeutic effect in vivo. Drug Delivery. 2011 Oct 1;18(7):502-10.

14) Nakhaie Nejad M, Ghasemian M, Nabi Maybodi M, Ramezani V. Development of a Liposomal Gel for Prolonged Ophthalmic Soluble Drug Delivery. ChemistrySelect . 2023 Mar 6;8(9): e202204727.

15) Mezei M, Meisner D. Liposomes and nanoparticles as ocular drug delivery systems. In Biopharmaceutics of ocular drug delivery 2019 Aug 15 (pp. 91-104). CRC Press.