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How liposomes pave the way for ocular drug delivery after topical administration

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ABSTRACT

The eye is one of the most specialized organs in the body; one of its flawless functions is vigorously controlling the foreign materials' entrance to the eye. On the other hand, this feature made it challenging to deliver drug molecules to the eye chamber for therapeutic purposes. Other obstacles related to pharmaceuticals' low efficacy are short resistance time on the eye surfaces because of tear and nasolacrimal drainage. The advent of novel drug delivery systems (DDSs), like nanoparticles, was a milestone to overcome these problems, provided they were adeptly designed. In other words, all parameters influencing DDSs must be considered to attain the desired efficacy. This review discusses liposomes' essential characteristics as one of the most favored carriers that can affect the ocular drug bioavailability and efficacy. Here, we discussed the physiology of the eye, the mechanics of medicine distribution, and other factors affecting drug delivery. Then, all of the liposome's features, including composition, physicochemical properties, and drug targeting capability, which may alter the local distribution of the medication to the eye, were reviewed. In this review paper, prior investigations' outcomes are discussed to create appropriate liposomal vesicles for efficient ocular drug delivery.

1. Introduction

The most convenient procedure for ocular diseases is topical administration; it offers the advantages of high patient compliance and little side effects provided certain criteria are met, including the lack of eye burn sensation and blurred vision, as well as good bioavailability. The latter is essential because it can affect the therapeutic efficacy and frequency of the drug administration. Some conventional dosage forms may not be suitable for ocular drug delivery; for example, non-aqueous preparations may cause blurred vision or eye irritation, and suspensions and emulsions can accompany little biocompatibility. On the other hand, solutions have a low resistance time on the eye's surface. Hence, rheology modifiers are frequently used in formulations to improve viscosity and thus retention time. Some other limitations can also hamper the topical drug delivery efficacy. The dose-volume limit, precorneal removal by blinking, nasolacrimal drainage and tear, degradation by enzymes, and presence of efflux transporters are drawbacks, which all reduce the effectiveness of treatment [1]. Furthermore, many medications cannot easily diffuse into ocular tissues, either locally or systemically. In this case, the eye acts as a barrier for drug entering; subsequently, in some cases, the intraocular injection would be the only available option, and formulating a topical preparation would be challenging.

In ocular drug delivery, several attempts have been undertaken and are still being investigated to improve the bioavailability of topically administered drugs. Some progress in the field of novel drug delivery systems (DDSs), like nanoparticles, has addressed obstacles related to topical ocular drug delivery [2–5]. They could generally increase drug surface retention, help overcome ocular barriers, reduce the toxicity or irritation of the drugs, protect the susceptible molecules against degradation, and increase bioavailability.

Liposomes are spherical vesicles made of amphiphilic molecules which encompass one or more aqueous compartments inside. They can carry both lipophilic and hydrophilic drugs. Having beneficial characteristics, they showed promising results in ocular drug delivery [6]. Many criteria must be addressed to achieve a unique and efficient drug formulation; for example, designing an appropriate DDS might present various obstacles. DDS characteristics and their interaction with the

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body are key factors in evaluating a drug's physicochemical qualities, stability, and efficacy. Therefore, a drug's route of administration, prospective bodily destinations, as well as its target properties should all be considered when designing a drug's formulation [7]. As illustrated in Fig. 1, an overview of liposomal formulations is provided to facilitate comprehension of the different ocular drug delivery systems.

In the present review, we aim to have a new look at liposomes and how they can interact with the eye surfaces, triumph ocular barriers, and increase drug penetration into the eye. To do this, we will first review the ocular features, followed by a discussion of the factors affecting absorption. Finally, various issues regarding liposomes, such as their contents, manufacturing method, and physicochemical characteristics, like surface charge and size that influence ocular absorption, will be evaluated. The results could help to design efficient liposomes for ocular drug delivery.

2. Drug diffusion principles

In the case of the liposome, the drug can enter the eye with its carrier, or the liposome serves as a depot on the eye surface from which the drug is released, and the naked drug itself diffuses in the eye. In both cases, the ideal conditions are met when the drug enters the eye at a constant rate (i.e., zero-order) over a relatively prolonged time. Besides, the liposome should provide a quite high drug concentration on the eye's surface, i.e., drug release from the liposome must be high enough during the liposome's resistance time on the eye surface.

The diffusant must penetrate the eye by going through numerous layers to reach the ocular tissues. Because passive diffusion is the predominant route for ocular medication penetration, diffusion rules control diffusant transport. Fick's first law (equation (1)) can describe the parameters associated with the drug diffusion into a membrane, like skin or eye layers if the carrier-mediated drug transport is ignored. According to this law, the rate of transfer of diffusant ($\frac{dM}{dt}$) is proportional to the concentration gradient ($\frac{dC}{dx}$), diffusion coefficient (D), surface area (S), and partition coefficient of the molecule (K). Sometimes, the diffusion coefficient, along with the partition coefficient, is considered the permeability coefficient (P).

$$\frac{dM}{dt} = DKS\frac{\Delta C}{\Delta x} = PS\frac{\Delta C}{\Delta x} \quad \text{(Equation 1)}$$

This equation can also be used for release from a system in which dM/dt or rate of release is the amount of drug released (dM) from the carrier over the time of dt, dC is the concentration difference ($C_1 - C_2$) on both sides of the membrane, for example, the liposome outer shell can be considered as a membrane, and drugs in the core compartment must pass through it to be released, and dx shows the layer thickness, i.e., the distance that the diffusant moves.

The diffusion coefficient determines how easily a molecule can pass through the layer. The diffusion capability can be influenced by the medium density, the drug molecule's and medium's attributes, and their interactions. For example, the drug molecule's size should not exceed a specific cutoff; thus, molecular weight is an essential factor. Any possible interactions between the diffusant and the medium can also slow down the diffusion rate, depending on the molecule's chemical structure and the medium's components. For instance, mediums with negatively charged components can interact with positively charged molecules and prevent their diffusion. From the pharmaceutical point of view, some ingredients are added to formulations for enhancing drug penetration; by changing the media characteristics, these sorption promoters boost the diffusion coefficient and accelerate the drug movement.

The partition coefficient is an index for the similarity of the diffusant and the medium, i.e., if the intended layer is composed of lipophilic components, molecules whit higher log $P_{(octanol/water)}$ have an affinity for it; this can hinder the further movement of the molecule to the next medium. According to Fig. 2, there are three main layers with different characteristics in the cornea, so a drug molecule can have a higher affinity to one of them and be less inclined to enter other layers. Hence, the partitioning of the molecule to the next layer would be hindered. Consequently, all mentioned factors can impact the drug penetration to the cornea after topical administration. If none of the parameters on the right of Equation One change over time, the rate remains constant and the zero-rate rate occurs, which is the most desired kinetics in drug delivery.

For example, if the drug concentration on the eye's surface does not fluctuate over time and the sink condition is fulfilled, the concentration gradient stays constant. This condition may occur when the drug formulation forms a reservoir on the surface of the eye, and the absorbed drug molecules are replenished by newly available drugs from the deposit, keeping the C1 constant.

The rate will not be constant over time if any of the values on the right of equation one (Eq. (1)) change. For these scenarios, certain equations based on Fick's law are proposed. The Nernst–Brunner (eq. (2)) equation is well-known; it mimics Fick's equation, in which the concentration gradient ($\frac{dC}{dx}$) changes with time.

$$\text{"the Nernst} - \text{Brunner "} \text{ equation: } dM/dt = \frac{K\ (C_1 - C_2)}{dx}; \quad \text{(Equation 2)}$$

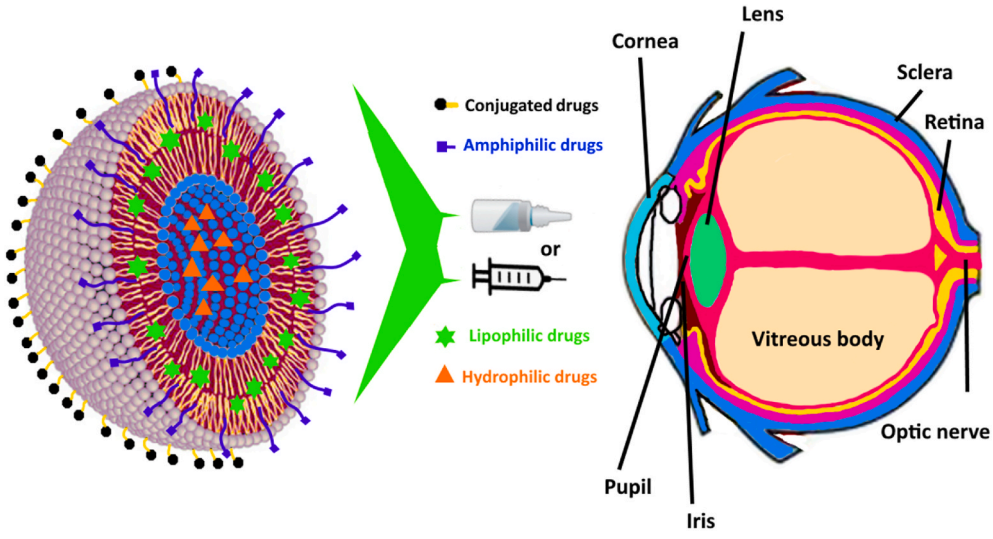

Fig. 1. Illustration of liposomal delivery of the types of drugs into the ocular system.

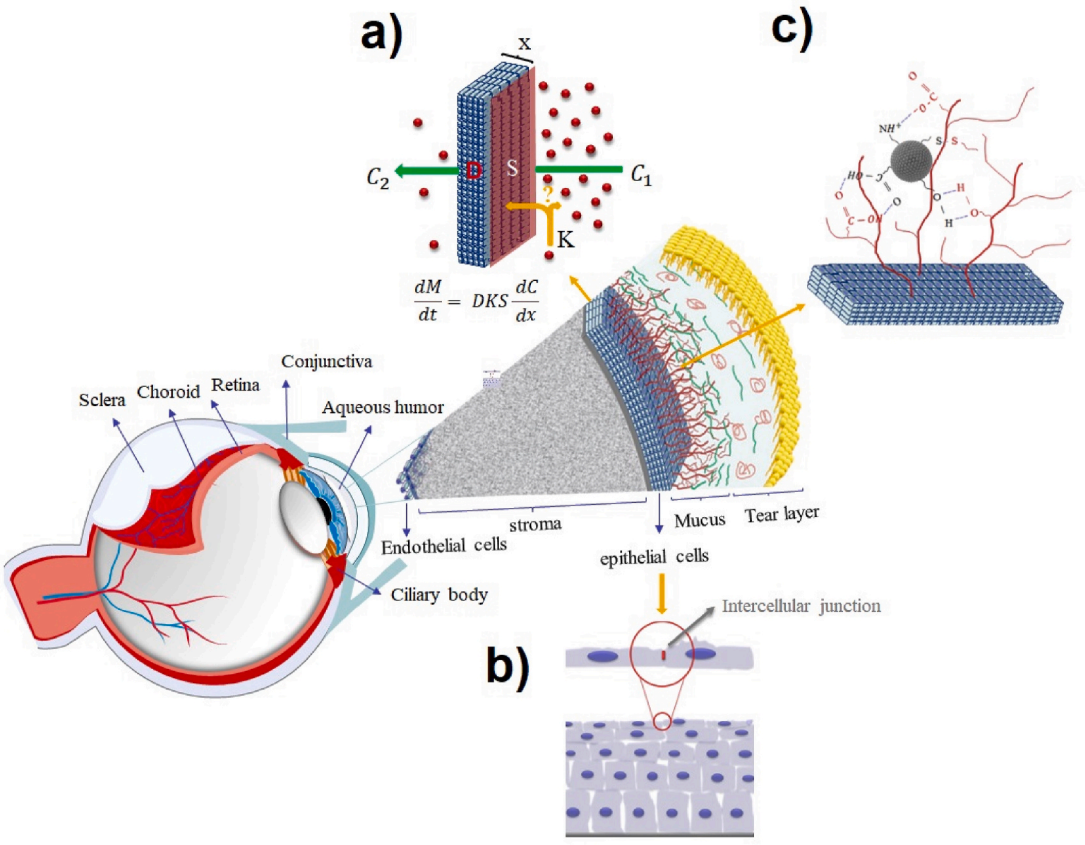

Fig. 2. The cornea is composed of several layers with different characteristics, which are covered with tear film. After topical administration, drug molecules must be able to pass through these layers to enter the eye. a) A depiction of the factors that affect the flux of drug molecules across the cornea layers; according to the first Fick's law, the concentration difference on both sides of a membrane is the driving force for molecule movement. D, k, s, and x represent diffusion coefficient, the partition coefficient of the drug molecule, the surface area that the molecule can pass through, and thickness of the membrane, respectively. b) The tight junction between epithelium cells of the cornea is the main barrier that hinders the molecules' entrance. c) A strategy for increasing the resistance time of drugs on the eye is using drug carriers, like liposomes, with functionalized surfaces. As they interact with the eye's surface, the drug has a greater chance of penetrating the eye. Dashes represent some possible interactions.

where K is a constant, implying that everything on the right side of Fick's equation is constant except C1. According to the Nernst–Brunner equation, if the concentration in the donor compartment varies over time, such as the quantity of drug on the surface of the eye, the drug transport rate will follow First-order kinetics and be dependent on the drug concentration or C1. When there is no drug reservoir, the quantity of drug in the eye diminishes as the drug is transported into the eye [8,9]. However, there are also more sophisticated models that are just not required to pay here.

3. The role of the eye physiology on ocular drug absorption

Given that the drug comes into contact with the eye surfaces in topical administration, it is essential to comprehend the eye's properties. In general, the eye comprises two parts: the anterior portion is filled with fluid, and the posterior area is filled with vitreous. The anterior section of the eye comprises the area between the cornea and the lens, whereas the posterior part extends the distance between the lens and the retina. The cornea is the anterior part's outer layer that encompasses the sclera, choroid, and retina.

After topical administration, drugs could utilize some routes for penetrating the eye, including transcorneal or transscleral. In the transcorneal path, after passing the cornea, the drug enters the aqueous humor from which it can diffuse to intraocular tissues. On the other hand, the transit route could be the conjunctiva, the sclera, the choroid, and the retina in order in a transscleral way. Diffusion is the primary process by which drugs penetrate the eye, although transporters and pinocytosis can be beneficial in some cases [10]. The surface of the eye is covered with tear film and mucus. Tears may readily wash away or dilute medications that have been administered. Mucus is a viscous fluid made up of mostly water, lipids, and mucin. Mucin contains a glycoprotein structure and is responsible for the mucosa's gel-like texture.

There are two forms of mucin at the surface of epithelia, membrane-bound and secretory mucins. Mucin present in the most superficial part of the eye has more turnover than inner parts. Sialic or sulfonic acid moiety on the sugar part of the mucin renders them a negative charge. Once the drugs pass through this layer, they reach the layer of epithelial cells beneath it. Therefore, mucoadhesive formulations could enhance drug resistance on the eye's surface [11,12]. Mucoadhesive also helps the drug's intimate contact with the absorption site, which reduces the mentioned path in Fick's first law. The cornea is a multilayered and avascular tissue; each layer has its characteristics. The outer layer comprises epithelial cells with tight junctions, thus limiting the intercellular passage (paracellular) of drug molecules, especially hydrophilic compounds, so principally lipophilic drugs can pass through this layer via the intracellular r route (transcellular). However, it should be noted that lipophilic drugs on the eye's surface can enter the systemic circulation through the nasolacrimal duct instead of entering the cornea, and some of the drugs may be lost [13].

This layer can be a depo site for lipophilic molecules, as they do not tend to partition to the stroma, a more hydrophilic medium beneath epithelial layers [10]. For providing the concentration gradient and hence the rate of drug penetration, the surface concentration must be

high enough. Enhancing drug solubility can be beneficial, for example, incorporating lipophilic molecules in liposomes. If the carriers can use the paracellular pathway or open up the intercellular space, it can help more to hydrophilic drugs. Using penetration enhancers in the formulation can also be a suitable strategy to overcome this layer. Formulation's pH is also essential; it must be adjusted so that ionizable drugs stay in their unionized form for better permeability. In some situations, to keep the drug soluble in preparations, pH is tuned to enhance the ionized form, but by lowering buffering capacity, the pH can easily change in contact with the eye, and unionized drugs predominate [14].

The cornea's next main layer is the stroma layer, composed of about 80% water. For a drug molecule to diffuse this layer, it requires having enough partition coefficient, i.e., have more tendency to leave the epithelium cells and enter this new hydrophilic medium. So, it is not an environment of interest for lipophilic compounds. By contrast, this layer can serve as a good depot for hydrophilic drugs. Again, here carriers can come to the aid of drugs. For example, highly lipophilic or hydrophilic drugs can be enclosed by carriers with optimum hydrophilicity for acquiring enough partitioning to all these media; for instance, the liposome can accommodate both types of these drugs and by changing its compositions and surface characteristics, the corneal drug transport can be increased.

The innermost layer is the endothelium layer of one layer of cells. This layer can let the lipophilic drug pass; its leaky tight junctions can also permit some hydrophilic molecules to cross over. Putting all these together, from the lipophilicity point of view, a drug with a lipophilicity/hydrophilicity balance could have more chance to pass the cornea and reach the next parts of the eye. They need to have suitable hydrophilicity (aqueous solubility) for providing enough concentration on the corneal surface and hence impart concentration gradient as well as for partitioning to the more hydrophile layer of the cornea. For example, it was shown that the optimum log P(octanol/water) for corneal penetration for a variety of compounds are two to three, which confirmed the intermediate lipophilicity. However, the presence of specific transporters (uptake or efflux transporters) can cause deviation from this range [13]. Besides, ionizable agents that obtain different ionization forms in various environments can also favor ocular drug diffusion. However, the pH in the different layers of the cornea is not much different. So, for topical ocular drug delivery, considering the physicochemical properties of the drug molecule is critical; they can be optimized by some molecular modification [13,15]. Aqueous humor is a viscose fluid filling the eye's anterior compartment; its chemical composition is similar to plasma. It is consistently secreted by the ciliary body and discharged by the Schlemm's canal. Its flow can cause the drug's washout, which gives the drug little chance to penetrate other eye tissues [10].

In the transscleral pathway, the drug molecule first contacts the conjunctiva that covers the sclera. Conjunctiva is a vascularized and thin layer; its pores have more expansive space, about 20 times larger than the cornea, allowing passage of larger molecules. According to Fick's law, it has more surface area than the cornea, boosting the drug diffusion. The conjunctiva gives the green light to hydrophilic agents despite the cornea, which is more permeable to small lipophilic drugs. In this regard, the drug's molecular weight is critical since 20 kDa is the cut-off point for molecular transport. Lipophilic molecules use the transcellular pathway here. Some enzymes, like esterase, efflux transporters, and drug drainage to blood or lymphatic vessels, can hinder drug penetration [1].

A mucopolysaccharide matrix, which contains fibrillar proteins such as collagen and a high amount of water, makes up the sclera, which does not have a vascular network. Drug transport here mainly takes place through passive diffusion. Size, physicochemical attributes, and surface charge of difussant are key factors for passing the sclera. For example, hydrophilic drugs pass through the aqueous pore, but if they bear a positive charge, they can interact with negatively charged components of the sclera's pores and trap there. Conjunctiva and sclera are more permeable than cornea because they are less compact, i.e., looser tight junctions provide much intercellular space. The choroid is a highly vascular structure that lies underneath the sclera. Some drugs, particularly lipophilic molecules, may be eliminated by blood vessels in this region or pass through the vascular endothelium before reaching deeper layers, preventing them from reaching their target [16]. Finally, the retina is the innermost layer at the posterior eye segment containing functional cells; this region targets many drugs intended to treat posterior eye diseases. The retinal pigment epithelium (RPE)'s tight junction composes the outer blood-retinal barrier (BRB), which strongly restricts the entrance of foreign molecules [17,18]. Accordingly, some suggestions for increasing the efficiency of drug delivery are as follows: the formulation must provide enough concentration of the drug on the eye surface to keep the concentration gradient across the layers, i.e., the driving force; this can be achieved by reducing the precorneal clearance of the drug, for example using mucoadhesive systems and by increasing the diffusant dissolution in the formulation. Having a suitable log P (octanol/water) helps the molecule move in different mediums. Size is another parameter for penetration; generally, drugs with molecular weight less than 700 Da can use the paracellular pathway [19]. Some formulations also involve some ingredients to change the biologic membrane structure and enhance the article's transportation by increasing the diffusion coefficient. Moreover, transporter-targeted delivery could be a promising strategy in some situations.

4. Vesicular nanocarrier

Nanocarriers have opened a new avenue for efficient ocular drug delivery. They can enhance the drug half-life on the eye's surface, increase drug solubility, and improve drug transportation across the eye layers by changing the drug molecule or biologic structures' properties [20,21]. Of various nanoparticles used for ocular drug delivery, vesicular carriers have shown promising results. This kind of nanostructure is composed of amphiphilic materials that surround at least one small interior compartment. In addition to the amphiphiles, other components may also be used to render new characteristics to them. For example, cholesterol is usually used to make liposomes more rigid and prevent the drug's premature release. Compounds of a vesicle can be of lipid or non-lipid origin. Lipid nanoparticles, particularly liposomes and niosomes, are the most extensively studied vesicular carriers for ocular drug delivery [22]. The purpose of this review is to focus on the role of liposomes in ocular drug delivery and discuss the therapeutic challenges and advantages.

4.1. Liposomes

Liposomes are formed when amphiphilic molecules aggregate in an aqueous phase to create a spherical shape with at least one hydrophilic compartment. On the other hand, micelles are formed of amphiphilic molecules with an outer hydrophilic shell and an inner lipophilic core. The critical packing parameter (CPP) indicates how amphiphile assembly will be arranged. CPP is defined as the ratio of the molecule's volume to the head group's area (the hydrophilic part) multiplied by the hydrophobic tail length. This ratio shows how the volume of the molecule deviates from a cylinder. For example, when the CCP ratio is between half and one, amphiphiles assume the shape of a short cone and form bilayer liposomes. This is often seen when two lipophilic tails coexist in the same molecule.

On the other hand, if the molecule contains a large tail, its structure shifts to a cone shape and is more prone to make the single layer micellar structure. So, the ratio between tail length and the space that the head group occupied is important for developing the liposomal architecture [23]. Fig. 3 shows the main compositions of the conformational liposome designed as a drug delivery system.

Liposomes are the most typical vesicular system used to deliver drugs to the eye. Among the many benefits, they have the ability to increase

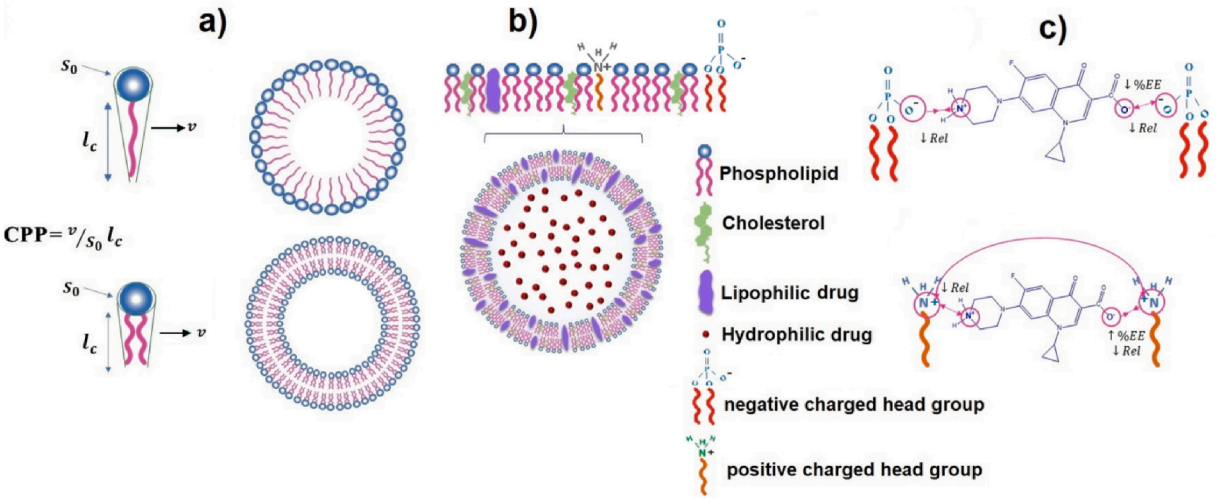

Fig. 3. The influence of carriers' constituents on the vesicular structure. a) Depending on the ratio of amphiphile volume (v) to the head's surface and length, they can assemble in a monolayer, like micelles, or bilayer vesicles, namely liposomes. b) Liposomes are suitable for accommodating both lipophilic and hydrophilic drugs. Incorporating some molecules, like cholesterol or charged ones, can also affect the liposome characteristics and its interaction with the loaded drug, affecting the drug release and % entrapment efficacy; such interactions are shown in c) for ciprofloxacin.

drug concentrations in various ocular tissues by prolonging drug resistance at the eye surface, increasing corneal permeation, and controlling drug release. In addition, they are not toxic or irritating to the eyes.

Liposomes can efficiently load both the hydrophilic and hydrophobic drugs between their lipophilic tail spaces or aqueous core, respectively. But drugs with dual nature, i.e., log $P_{(octanol/water)}$ between 1.7 and 5, cannot be effectively enclosed because they can partition through the layers to the surrounding environment. These drugs may be incorporated into the liposome through cleavable covalent bonds or electrostatic interactions; altering the pH of the interior compartment can also aid to entrap weak basic or acidic drugs by raising the levels of ionized molecules [24,25]. As the cornea is more resistant to hydrophilic drugs, liposomes can efficiently help these molecules' trascorneal movement. In addition, the interior aqueous spaces are sufficient enough to support the loading of these molecules. Fig. 4 manifests the different methods of liposome synthesis along with how to load lipophilic and hydrophilic drugs.

In the following, the effect of liposome components, surface modification, and some other significant properties of liposomes that could affect ocular drug delivery will be reviewed.

4.1.1. The influence of liposome constituents and their features in ocular drug delivery

4.1.1.1. The effect of the amphiphile's head group charge. Phospholipids are widely used as liposome components. They typically comprise a glycerol molecule that puts together two fatty acid molecules (the tails) and a polar derivative of the phosphate group (the head group). The head group properties dictate the liposome interaction with the surrounding, like dealing with confronted cells [26], whereas the tails command the vesicle's flexibility and cargo retention. The surface charge has shown a pivotal influence on liposome resistance time onto the eye, prolonging the drug's physiologic effect. It can also affect drug entrapment efficacy (EE) and release [27].

In ocular drug delivery, stearyl amine (SA) and diacetyl phosphate (DCP) were extensively used as charge-inducing agents to liposomes, which render them a positive or negative charge, respectively [28]. These charged molecules' effect on the percentage of EE and drug release depends on the drug molecule characteristics. Abdelbary G. et al. (2011) studied the EE percentage and release of ciprofloxacin HCl (bearing both positively charged nitrogen and negatively charged hydroxyl groups) in the presence of negative or positive lipids. Incorporating the positive charged SA into the liposome bilayer could reduce the drug's release, as positive charges in the ciprofloxacin and SA repel each other and interferes with the drug diffusion through the bilayer while leaving the liposome. Besides, the negative part of the drug (hydroxyl group) can attract SA. The positively charged lipid could also cause dense pack layers in the liposome. However, the excess amount of the positively charged component would proceed to the bilayer instability, and drug release could happen more effortlessly.

On the other hand, the electrostatic interaction of negatively charged hydroxyl groups of molecule and SA caused the EE percentage to be enhanced compared to the neutral or negative liposomes. The inclusion of DCP (in a concentration of 0.5% or 1%) in the liposome could repel the ciprofloxacin's hydroxyl group and reduce its EE percentage. In addition, DCP (1%) could interact with protonated nitrogen in the ciprofloxacin molecule or repel the negative part of it and hamper its passage through the membrane, reducing its release [29]. The negative charge could not meaningfully benefit the therapeutic effect or its duration. Whereas positively charged liposomes could interact with the negatively charged mucin on the eye's surface, this adherence can reduce their preocular clearance through drainage; the more resistance time, the more chance to permeate to the eye. In another study [30], the acetazolamide (a weak acid, bearing negative charge) EE and release percentages were compared among positive, neutral, and negative liposomes. The results showed that the EE percentage order was positive > neutral > negative, and concerning drug release, it was negative > neutral > positive. They concluded this result is because of the attraction force between the negatively charged drug and positively charged lipid and the repulsion between the drug and DCP. Also, positively charged multilamellar vesicles (MLVs) (PC:CH: SA, 7:4:1 M ratio) could more efficiently reduce the intraocular pressure (IOP) in the rabbit model during 8 h because of the electrostatic attraction between liposomes and negatively charged mucin as well as reduced drainage of the drug by the nasolachrymal flow. However, positively charged MLVs (PC:CH: SA, 7:7:1 M ratio) showed high EE percentage had lower IOP reducing effect because of their tightened structure accompanied by limited drug release.

Other studies using charge-inducing agents followed these results as well [31,32]. According to in vitro trials, acyclovir solution penetrated the cornea faster than its liposomal formulation. However, in vivo experiments have shown that acyclovir in solution may be present in the aqueous humor for a short time after treatment due to its short half-life. Acyclovir was found in aqueous humor for longer times in the case of

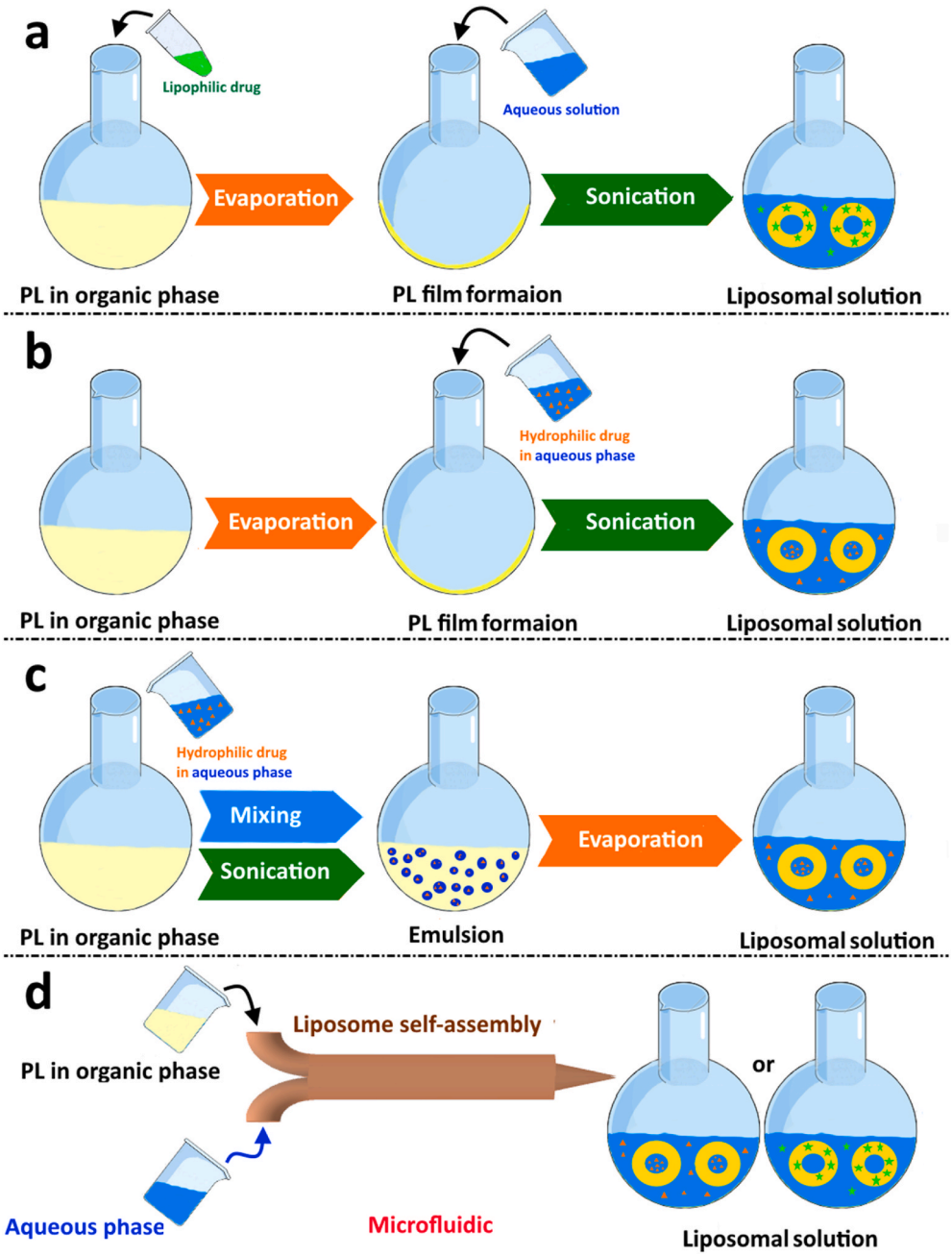

Fig. 4. Schematic Synthesis of liposomes. a) Liposomes for loading of lipophilic drugs by phospholipid film formation method b) Liposomes for loading of hydrophilic drugs by phospholipid film formation method c) Emulsion formation method for the Synthesis of liposomes containing all the types of drugs and d) microfluidic method for liposome synthesis and drug loading.

liposomal formulations, particularly positive ones, due to the prolonged resistance time [33]. These results show that resistance time is a critical factor in efficient ocular drug delivery. A similar trend was also observed in some other studies [34].

It must be noticed that positively charged liposomes can be advantageous if they do not irritate the eyes; for example, it was shown that stearyl amine could irritate the eye. The drug diffusion to the eye's posterior segment after topical instillation can differ from the transcorneal pathway. For example, there was no significant difference in retinal disposition among the positive, neutral, or negative ssLips. All of these carriers could effectively transfer the fluorescent cargo to the retina; this might be because of the affinity of the phospholipid component of the liposome for the conjunctiva cells, which alongside protective property of liposomes' bilayer membrane, the small particle size, and the low rigidity enhance drug permeation [35]. Among these factors, the size has been shown a significant impact, which could be because in the non-corneal pathway, in addition to the transcellular pathway, the intercellular pathway can be used. The incorporation of amine-containing spermine in liposomes also makes positively charged vesicles with mucoadhesive features, which provoke enhanced drug permeation [36].

The effects of incorporating charged lipids in the liposome construct on *trans*-scleral transport were studied in another work. 1, 2-dipalmitoyl-sn-glycerol-3-phosphocholine (DPPC) along with 1, 2-dipalmitoyl-3-trimethylammonium- propane (chloride salt) (DPTAP) or 1, 2-dipalmitoyl-sn-glycerol-3-phospho-(1′-rac-glycerol) (sodium salt) (DPPG) as positive or negative charge inducers, respectively, was utilized. The negatively charged liposome comprising DPPC-DPPG showed the higher

drug (ranibizumab) entrapment efficacy of various formulations. They concluded that electrostatic attraction between the positively charged protein and negatively charged liposome could help this issue. In addition, compared with the DPPC liposome, the negatively charged liposomes showed less and positively charged one displayed more drug release under the in vitro condition. By conducting ex vivo studies, % cumulative drug transport by both negatively and positively charged liposomes was lower than DPPC or DPPC-Chol, which is an indicator of their sustained drug release. They found the DPPC-DPPG liposome is the best carrier for ranibizumab due to its high percentage of EE along with some extent of penetration to the sclera, which acts as a depot there releases drug sustainably [37]. A positively charged liposome could interact with the negatively charged sclera's surface, disrupting its passage through the sclera. The encouraging point is that they can be served as a drug depot, and the released payload passes the sclera. The drug release from this depot would also increase the local concentration of the drug and gradient concentration, which produces more driving forces for drug diffusion. In comparison, negatively charged liposomes themselves facilitate *trans*-scleral drug delivery.

4.1.1.2. The influence of length and saturation degree of the tails. Generally, all parts of the amphiphile molecule, i.e., the polar head group and the exploited fatty acid, can affect the liposome attributes. They can influence the stability and Transition temperature (TT) of the liposome and the encapsulation efficacy, drug release, and tissue distribution [38,39]. For instance, as the tail length increased, the more hydrophobic interaction resulted, and the liposome's structure became more stable and impermeable, leading to sustained release of its cargo. Furthermore, it can enhance drug distribution as it can keep inside the drug more efficiently. A fully saturated acyl group can also intensify the tails' hydrophobic interaction, whereas unsaturation deviates the tail orientation and results in weaker interplay [40]. Transition temperature (TT) of lipids is an index that shows the intensity of the interactions. Above this temperature, the physical state converts from an ordered gel phase to a more disordered state, i.e., chains adopt random directions (liquid crystalline state), and liposome gets further permeable. TT increase as lipids become more interconnected. So, purity and source of phospholipids are also of importance. For example, the phospholipids' degree of saturation in the egg yolk is more than soybean, affecting the drug release and EE percentage [39].

Hironaka et al. (2009) compare the eye distribution of the two submicron-sized liposomes (SSLip) composed of egg phosphatidylcholine (EPC) or L-α-distearoyl phosphatidylcholine (DSPC with fully saturated C18 FAs). According to their results, a more rigid DSPC containing SSLips has reached the retina more than more flexible EPC SSlips. They concluded that the liposomes' distribution in the posterior part of the eye is related to the vesicles' rigidity, and more rigid liposomes have more chances to get there. One reason for this can be the relationship between rigidity and drug entrapment, i.e., the vesicle's stability [41]. Because liposomes may gradually release their cargo over a longer time, the frequency of ocular drug administrations can be reduced by densely packed tails in liposomes. Furthermore, for this purpose, the vesicle must also remain in place for an extended time, such as electrostatic interactions between the surface components and positively charged liposome [42]. In addition, the inclusion of other molecules in the liposome structure can influence the features of the liposomes as well; some of these include cholesterol, various types of surfactants or other edge activators, and penetration enhancers.

4.1.1.3. The role of cholesterol incorporation. Stability during shelf life is the primary concern of liposomes. Cholesterol is one of the most incorporated molecules in the liposomes, modifying the membrane's rheological features and changing its stability. Generally, when cholesterol is used along with unsaturated phosphatidylcholines (PCs), like egg PC, it increases the membrane's rigidity and helps liposome stability and drug retention, especially hydrophilic drugs. On the other hand, cholesterol alongside saturated PC, like DPPC and DSPC, causes more permeability and drug leakage [35,43]. The therapeutic efficacy could be prolonged by reducing drug release. For example, a study on the impact of the cholesterol ratio relative to egg PC has shown that the EE percentage of the drug (acetazolamide) has been improved by raising cholesterol contents, and the in vitro release got to slow down. This happened because cholesterol can limit the tails' movements and alter the membrane's fluidity [30]. But, the behavior in ciprofloxacin-loaded liposomes was somehow different. Liposomes containing ciprofloxacin hydrochloride had a lower EE percentage when cholesterol was added to soya PC. The membrane's linear structure was thought to be disrupted by cholesterol, which enhanced the membrane's hydrophobicity. In vitro studies have also shown that raising cholesterol alters the release of drugs. It was also displayed that increasing cholesterol causes altered drug release in vitro [29].

Another study found that a DPPC based liposomal formulation including a 4:1 M ratio of DPPC to cholesterol increased drug entrapment efficiency, *trans*-scleral transport, and in vitro drug release compared to DPPC alone. As DPPC is a saturated PC, the addition of the cholesterol could alter the membrane's gel state and render the liposome flexible and able to diffuse to the sclera [37]. About retinal delivery of liposomes constructed from DSPC/DCP/Cholesterol, the lipophilic fluorescent dye, coumarin-6, was less detected in the inner plexiform layer (IPL) while cholesterol content increased. The results showed that less rigid liposomes have more retinal delivery efficacy [35]. In addition, cholesterol content can affect the EE percentage of lipophilic drugs, as it can occupy the inter lipid spaces in the membrane. For instance, by altering the lipid to cholesterol ratio, the EE percentage of brinzolamide (Brz) was first increased to an optimum value. Then, adding more cholesterol caused lowered the EE percentage [44].

4.1.1.4. The role of edge activators and penetration enhancers on transmembrane diffusion. Adding extra molecules, such as cholesterol, to the makeup of liposomes could boost their performance. This group includes edge activators as well as penetration enhancers.

4.1.1.4.1. Penetration enhancers. Using penetration enhancers in ocular drug delivery has been widely considered. These agents perform their actions through different mechanisms [45]. For example, compounds like Ethylenediaminetetraacetic acid (EDTA) or its analogs and crown ethers were shown to enhance corneal penetration via sequestering calcium ions and changing corneal resistance well as losing the epithelial's tight junction [46–48]. Evidence shows that cyclodextrin and its derivatives could alter corneal epithelial integrity by taking up the cornea's cholesterol and other lipophilic components. Therefore, they aid naked drug molecules to penetrate the corneal membrane [49]. Amphiphile molecules can interact physically or chemically with the membrane constituents to open the way for drug molecules to pass through [45]. For instance, surfactants can be inserted into the epithelial cell membrane and solubilize the phospholipids or lose the tight junctions [47]. Anionic fatty acids can form ion-pair with cationic drug molecules, and the formed nonionic complex can more readily penetrate the membrane. They can also affect phospholipid bilayer integrity and facilitate drug transport [45]. Cell-penetrating peptides (CPPs) have also been shown to be effective in transcorneal penetration; their mechanisms of action depending on their amino acid sequences [48,50]. Penetration enhancers have also contributed to liposome efficacy [51,52]. For example, surfactants as penetration enhancers can be easily placed in the liposome membrane and promote their penetration, along with rendering flexibility to them [53–55].

The main point about using penetration enhancers is that they must not be irritant or noxious to the eye; as an example, benzalkonium chloride, a cationic surfactant, can enhance drug transport through the cornea but causes corneal damage.

4.1.1.4.2. Edge activators. Adding edge activators to liposomes, i.e.,

transferosomes, makes them more flexible and higher adaptable, which causes liposomes to transport more easily through biological barriers, primarily facilitating the intercellular passage. If the drug passes intercellular instead of the transcellular way, it can also bypass the efflux proteins or intracellular enzymes. Nonionic surfactants, like Labrafil®, Labrazol®, Span®s, and Tween®s [56], bile salts (in terms of bilosomes), and α-tocopherol derivatives are some edge activators that have been used in ocular drug delivery. Generally, edge activator molecules are located between liposomes' membrane components and disrupt their dense packed structure by losing their interactions and making them flexible and fluidized. These deformable liposomes can be squeezed between cells to use the intercellular pathway without disrupting their integrity. The deformability feature makes them more stable under the influence of external stresses and allows them to go through pores as small as one-tenth of their size. The deformability of transferosomes takes place through the demixing of constituents of their membrane under external stress. In this way, surfactants lose their symmetrical dispersion due to external pressure and move to areas of the membrane with more curvature; they can redistribute after removing the stress and reconstruct the vesicle. This unique property can help transferosomes retain their entrapped cargos inside while passing the biological membranes, like cornea, and the drug is released slowly after that. Reduced deformability makes vesicle reconstruction more difficult, which can cause drug loss [57]. It must be considered that the presence of the surfactants can destabilize the membrane and change the vesicle elasticity along with increase the aqueous solubility of the lipophilic drugs hence the % drug entrapment efficacy can be reduced [54,58]. Teransferosomes are much studied in transdermal drug delivery; however, their efficiency will not be the same for both due to differences in the eye and the skin's physiology. For example, regarding skin, the vesicles first face dead cells of the stratum corneum with low water content. The hydration gradient across the skin layers, namely stratum corneum, viable cells of the epidermis, and derm, is the main driving force that causes transferosomes to cross the skin.

Mohsen et al. developed a series of bilosomes that contained various bile salts, namely sodium cholate (SC), sodium deoxycholate (SDC), sodium taurocholate (STC), and sodium tauroglycocholate (STGC), along with Span 60 and cholesterol to modify the drug (acetazolamide) concerns, i.e., its low solubility and ocular penetration. A noisome formulation of Span 60, cholesterol, and acetazolamide was also prepared to compare with the bile salts incorporated. The prepared vesicles had negative zeta potential, ranging from 350 to around 730 nm and a high percentage of EE. They were able to release acetazolamide sustainably because of the drug's affinity to the bilosomes components. Besides, they strengthed and extended the acetazolamide physiological effect, IOP lowering. Using lipophilic surfactant bile salts versus Span 60 can help the enhanced EE percentage of this lipophile drug. Bile salts can be conducive to perturbating the vesicle's bilayer membrane and increasing its flexibility and drug accommodation. However, there is a threshold for bile salts concentration to reach the maximum percentage of EE. The bile salts' molecular weight (Mw) also played a role in the percentage of EE and bilosome size; the higher Mw, the superior percentage of EE and size. Span 60, as a penetration enhancer, along with bile salt, contributed to increased penetration of the vesicles. Although the potential of bile salts' mucolytic property was stated, their tests confirmed the safety of these bilosomes [59].

In a study conducted by Arroyo et al., sodium deoxycholate with or without ethanol (as penetration enhancer) was used to make deformable liposomes (DLs). Incorporating an edge activator could increase curvature radius and vesicle size, especially when ethanol is combined (with the highest elasticity index). This phenomenon is because of the disrupted interaction between dense-packed components of the membrane. However, in vitro studies using artificial membrane revealed that these deformable liposomes had a smaller flux and permeability coefficient than conventional liposome (CL) or drug (timolol) solution. The declared reasons were the more extensive size and lipid components (including cholesterol)' amount of the DLs than the CL, making this comparison complicated. Even though the cumulative amount of drug passed during 24 h and pharmacologic effects were not significantly different among liposomal formulations (CL and DLs) [60].

Another study assessed the effect of bile salts, namely sodium taurocholate, sodium deoxycholate, and sodium glycocholate, on corneal permeability. Liposomes carrying bile salts possessed a negative surface charge, and all liposomes were approximated to be 100 nm in diameter. Ex vivo and in vivo studies showed an increased corneal permeation of liposomes containing bile salts, i.e., more permeability coefficient than liposomes of soy PC and cholesterol, and the DLs transverse the cornea faster than CL. This condition can happen because bile salts can open tight junctions between epithelial cells instead of enhancing transcellular transport since cellular uptake of conventional liposomes was more than these flexible liposomes. However, liposomes with sodium deoxycholate depicted toxicity and irritation to the human corneal epithelial cells and rabbit eye, which must be considered when selecting an edge activator [61].

A comparison of some formulations with almost similar sizes, around 650 nm, including liposome, transferosome containing bile salt, and vesicles comprise labrasol as a penetration enhancing (PEVs) revealed transcorneal penetration rate decreased in the order of transferosomes, liposomes, and PEVs. Again, it is because of the bile salt's effect on the tight junctions and the affinity of two other formulations to the eye's surface. There was no significant difference among all vesicles but was much more than the drug solution attributed to phospholipid presence. Liposome showed a higher drug, but two other formulations had prolonged drug release because of delayed clearance from aqueous humor and more resistance time. In this study, the liposome's drug bioavailability and % EE were higher than the transferosome and PEVs [54]. The purpose of the other study was to design D-alpha-tocopheryl poly (ethylene glycol 1000) succinate (TPGS) modified liposomes for enhancing the transcorneal permeability of drugs. The liposome had a particle size of less than 100 nm. TPGS modification made sustain release vehicles and drug transcorneal permeation improved; the permeation coefficient was increased compared to the conventional liposome or drug suspension; the reason for this delayed-release manner was probably contributed to hydrophilic PEG chains. P-gp efflux pumps in the cornea can inhibit drug penetration, and GTPS could inhibit P-gps and help penetration proceed [44]. Solutol HS-15 (polyoxyethylene esters of 12-hydroxystearic acid) was also considered as an edge activator. The deformable liposome (DL) exerted a greater percentage of EE than the conventional liposome composed of cholesterol, egg PC, and drug solution. Hydrogen bonding between the carboxyl of drug molecules and the edge activators hydroxyl groups is responsible for increased drug solubility in the membrane. They also concluded that the edge activator's addition could reduce the particle size (from 117.5 $\pm$ 1.3 nm in the case of conventional liposomes to 107.7 $\pm$ 2.8 nm for DLs) because of the enhanced flexibility [62].

Surfactants such as twin 20 and sodium deoxycholate (Deo-Na) are used to produce a range of transformers. Various properties, including molecular weight, solubility, CMC and surface charge, differentiate these surfactants from one another. Tween 20 is non-ionized and less bulky than Deo-Na; therefore, it can pack the membrane more, resulting in less flexibility. The results proved that the type of surfactant and lipid to surfactant ratio are the most critical factors influencing the formulation's flexibility. Both Deo-Na and cholesterol contain sterols that can compete for the same interstitial space. However, due to its lipophilicity compared to Deo-Na, cholesterol is predominant. So, they concluded that the Deo-Na to cholesterol ratio is of importance for achieving a flexible vesicle. Despite liposomes, these flexible transferosomes could carry the drug through the membrane and then release the drug sustainably [57].

4.1.2. Modification of liposome by surface coating

The liposomes can boost the drug's contact time with the eye surface;

therefore, they raise the chance of the drug diffusion through the layers of the eye. Given that remaining there, it could not significantly affect the drug's penetration into the eye and only increases the formulation's resistance time and act as a reservoir of the drug on the eye's surface. This condition can be helpful as one of the main drawbacks in ocular drug delivery is the short resistance time. Size can play a role as well; giant liposomes, approximately bigger than 200 nm, mainly retain at the eye's surface, whereas smaller ones can convey the drug molecules and progress their transport. Some surface modifications, like coating liposomes with polymers, can also be beneficial if this condition is intended.

In some cases, due to the increasing size of the carrier and its interaction with the eye's surface, coated liposomes cannot pass through the eye membranes, and this is the drug molecule alone that passes through different layers of the eye after release. Furthermore, the most significant advantages of this kind of coated liposome are enhanced EE percentage, controlled drug release, and higher stability [63]. To do this, the coating must comprise functional groups that could interact with eye surface components, particularly the mucin. Positively charged coats can promote surface adherence and prolong the site's retention by binding to the negatively charged mucins. Negative or neutral liposomes cannot be significantly useful unless they bear functional groups through which they can react with the eye's surface and show the mucoadhesive characteristic. For instance, by having carboxylic groups, carbomers can participate in hydrogen bonding with mucin [40,56].

Polyamidoamine dendrimer (PAMAM G3) has been used for coating the liposome with the aim of posterior eye drug delivery. The resultant liposome had a particle size of around 150 nm with a relatively negative charge. Their amine groups could interact with mucin and show the mucoadhesive property. They also showed enhanced corneal epithelial cell uptake and EE percentage. Moreover, they could penetrate the cornea and reach the deeper layers of the eye and improve drug bioavailability and pharmacologic effects in the rat retina [64].

Poly L-Lysine (PLL) is a polypeptide with a positive charge due to having amine groups. In a study, DCP was used to render a negative charge to liposomes and make lysine coating more efficient. Although the particles remained slightly negative after coating, there were still enough unbound amine groups to bind to the eye's surface. PLL was used with different molecular weights and concentrations, and the results showed that both factors were essential for the efficacy of drug delivery to the retina. PLL-coated liposomes with high molecular weights showed a higher aggregation rate, which led to an increase in particle size and a decrease in ocular absorption. This condition could happen due to the interaction of free PLL's amine groups with other liposomes. The increased pharmacological effect was related to the more preocular resistance time, viz on the conjunctiva, so they have more opportunity to enter the cells via cellular mechanisms like endocytosis and reach the retina [65].

Coating nanocarriers, including liposomes with chitosan, were extensively considered in the field of ocular drug delivery. Chitosan coats the surface of liposomes and renders them a positive charge, enabling them to interact with the eye's surface through electrostatic interaction. Accordingly, it creates a drug depot on the eye's surface, and due to the carrier's close contact with the eye, the drug will travel a short distance on the eye's surface to reach the cornea. In the case of chitosan, some evidence indicates it can also help in the ocular permeability of the drug through some mechanisms like opening corneal epithelial cells tight junctions [29,62,66–68]. Tan G et al. have prepared chitosan-coated liposomes with an average size around 150 nm, which is still under the penetration threshold. The coated liposome could enhance the apparent permeability in comparison with plain liposomes. This condition can be attributed to chitosan's specific characterization, opening the epithelial cells' tight junctions [69]. Furthermore, compared to plain ciprofloxacin drops, the positively charged liposome formulation demonstrated a longer resistance time and higher drug level on the eye's surface after 4 h, coating the liposome with the cationic chitosan polymer prolonged this duration to 8 h. However, this seems as if the chitosan coat enables the drug to be released over a longer period [29].

Exploitation PEG as the coating polymer is also advantageous for drug bioavailability as it can increase solubility, protecting against enzymatic degradation and clearance of the drug [70]. However, there is evidence that PEGylation can hamper ocular permeation as it can prevent interaction between the carrier and corneal surface, which results in limited cellular drug uptake [71].

4.1.3. The contribution of liposome size in the ocular DDSs efficacy

Vesicle size is an essential factor influencing drug-membrane interactions. Generally, the smaller the size, the more contact the particles make with the surface, resulting in more interplay and retention [35]. On the other hand, there are limited accessible spaces between epithelial cells for particles to pass through; besides, the small liposomes can penetrate the mucosal layer on the eye surface more [41]. In some cases, submicron-sized particles have the advantage of using intracellular pathways as well. So, particle size can be a pivotal factor for high yield diffusion through eye layers. It has been proved that, in the case of drug penetration, the size threshold is around 200 nm and 100 nm for the anterior and posterior compartments of the eye, respectively [65]. In liposomes, size can also affect the loading capacity and drug release rate; i.e., more massive particles have a higher volume-to-surface ratio. As the size increases, so does the volume of the interior space that holds the drug [30]. This fact is exceptionally truthful for hydrophilic drugs that are located in the internal compartment of the liposome. Instead, the smaller vesicles have more surface area available for drug release [34]. In one study, liposomes with sizes ranging from 100 to 600 nm were synthesized and their diffusion into the retina was evaluated 30 min after post-installation. The results revealed that penetration into the deeper eye layers of sclera-choroid-RPE was increased as the liposome size decreased. They also compared liposomes with other formulations, such as polystyrene and lipid emulsion, with the same size (100 nm) and zeta potential. It showed that vesicle size influences ocular passage and the ability of vesicles to interact with ocular membranes and their stability are influential [35]. Another study prepared various formulations of transferrin bearing-liposomes and examined the effect of particle size on drug delivery to the posterior part of the eye. They showed that, depending on the size, topically applied liposomes could deliver to the rear compartment utilizing blood circulation. To reach RPE cells, they must be smaller than about 80 nm and not larger than 100 nm, as they could not go through the choroidal pores; choroidal endothelium was the retention site of these more giant liposomes. However, it should be noted that the presence of a targeting agent on the surface of these liposomes led them to the RPE cells after crossing the choroidal barrier [38].

4.1.4. The influence of the preparation method on some critical features affecting the efficiency of liposomes

Numerous methods have been used to make liposomes, including lipid film hydration [72], reverse phase evaporation [73,74], double emulsion [75], ethanol injection (or nanoprecipitation by solvent displacement) [70,72,76], ammonium sulfate gradient [69], calcium acetate gradient, and polyol dilution methods [77]. Using different procedures, these methods attempt to put together the amphiphilic molecules in a bilayer shell to surround an aqueous space. A variety of modifications are applied in the components or techniques of construction of liposomes to achieve liposomes with different physicochemical properties. Extruding giant liposomes through a certain membrane with a specified cutoff reduces their size and polydispersity index (PDI). Furthermore, freezing-melting, ultrasonication or homogenization could reduce particle size and PDI [78].

The pharmacokinetics of liposomal formulations could be influenced by manipulating the features such as their size [77], size polydispersity [72], zeta potential [77], lamellarity [75], entrapment efficacy [77], release rate [79], corneal penetration [77].

Liposomes may be loaded with a variety of drugs using a range of techniques. Among these, ammonium sulfate gradient or calcium acetate loading liposomes was commonly applied. For this, liposomes are first prepared in a solution of ammonium sulfate or calcium acetate by hydrating method, and then the drugs are loaded into them. Since the drug solution is added after the lipid hydration step, less the drug solution is required for the drug loading. In the hydration method, the volume ratio of the aqueous phase containing the drug to the liposome's internal compartment is high, reducing EE percentage. For example, in the calcium acetate gradient method used for acidic diclofenac loading in liposomes, the EE percentage was higher comparing the conventional hydration method. However, liposomes' stability was reduced, which was dealt with by coating the particles using PVA polymers [63].

4.1.5. The influence of targeting agent

Targeting agents benefit the drug to reach the target site in sufficient quantities and, at the same time, reduce the drug's loss due to going to unneeded places. Targeted drug delivery has been extensively considered for systemic drug delivery because blood flow can distribute the drug throughout the body, including the non-target sites. Meanwhile, some organs may have more affinity to the drug, resulting in less medication reaching the target site. Other main reasons for targeting include reducing side effects, using lower doses, and lowering costs. In the case of topical drug delivery to the eye in which the drug formulation is applied directly to its leading site of action, the drug is more likely to reach its target cells, reducing the need for targeting agents. However, particularly in drug delivery to the posterior segment of the eye, targeting agents can be beneficial and increase the effectiveness of drug delivery since a unique cell line may be of interest target. For example, the RPE cells can express transferrin receptors; thus, coupling transferrin with the liposomes can promote nanoparticle uptake by the RPE cells [73]. Attachment of transferrin to the nanoliposomes for active targeting to the RPE cells welcomed some merits. For example, topically administered transferrin conjugated liposomes with the optimized size could reach the RPE cells and produce stronger fluorescence than the pegylated liposomes. Similarly, larger transferrin-decorated liposomes could retain in the choroid's capillaries as they also express few transferrin receptors [38].

Another study used annexin A5 to enhance drug absorption through the cornea to convey Avastin to the retina via topical administration. Annexin A5 can attach anionic phospholipids to the cornea's surface, facilitating medication absorption by epithelial cells through endocytosis. Here annexin A5 can be considered a ligand that interacts with phospholipids to promote transcytosis; however, it is not an agent that directly targets a particular molecule or receptor on the target site [80]. Liposomes modified using Ala-Pro-Arg-Pro-Gly (APRPG) as a vessel-homing peptide were synthesized and loaded with an angiogenesis inhibitor drug to target angiogenic vessels in choroidal neovascularization (CNV). This targeted drug delivery system was administered intravitreally after CNV induction by laser and showed to reduce the retina's CNV lesions [81]. Arginine-glycine-aspartate (RGD) is widely exploited as a targeting agent in ocular drug delivery. This tripeptide has a high affinity for integrin αvβ3 on endothelial cells. iRGD was used for enhancing topical ocular drug delivery efficacy of brinzolamide (Brz) loaded liposome [71]. Their results showed that thanks to iRGD, this modified liposome had improved corneal penetration and conveyed its payload to the posterior part of the eye; the main reason was the receptor-mediated endocytosis.

There are some other studies on ocular drug delivery using RGD; including, modifying dendrimer with a cyclic RGD for targeting integrin αvβ3 on neovessels [79], poly (ethylene glycol)– poly(lactic-co-glycolic acid) polymeric nanoparticle modified with transactivated transcription (TAT), and RGD [82], RGD nano micelles, DSPE-PEG2000-cRGD [83], PEGylated liposomes bearing RGD and encapsulated with VEGF-siRNA for enhancing the RPE cells uptake through receptor-mediated endocytosis [84,85]. The pepT-1 receptor is highly expressed in the cornea and conjunctiva and another molecule is considered active targeting through its ligands. Reacting with PepT-1transporter, its ligands, like divaline, could help nanocarriers reach the retina via transcytosis [86]. Folate receptors were located in the RPE cells' membrane and are crucial for folate transport in the retina [87]. In cancerous conditions, like retinoblastoma, the expression of some receptors on the cell surface changes; for example, the folate receptor is generally overexpressed [88]. Exploitation folate as a homing device can guide the drug-loaded carrier to the cancerous cells, which the carrier entrance then can be through endocytosis [89]. In this regard, there are some attempts in ocular drug delivery. For instance, conjugation of folic acid to nanomicelles of poly (styrene-co-maleic acid) [90], nanoparticles of poly (ethylene glycol)-b-polycaprolactone conjugated with folate for enhancing drug, triamcinolone, uptake by the RPE cells to control neovascularization are examples of targeted ocular drug delivery [91]. Some groups reported passive targeting to angiogenic vessels by cationic liposomes. The cationic liposomes can accumulate in newly formed vessels like CNV lesions and guide the drug to the neovessels after systemic administration [92]. Although cationic liposomes may efficiently attach to active angiogenesis, they are not suitable for IV injection into some organs such as the liver and spleen because they are easily eliminated from blood circulation. Systemic intravenous injection of cationic liposomes loaded with therapeutic drugs for CNV in the rat demonstrated that they are useful for ocular neovascularization treatment, which can be a suitable alternative for intraocular injections [93]. Immunoliposome decorated with HSV glycoprotein D antibody also showed promising results; these vesicles could interact with HSV infected corneal cells more hence producing more drug, acyclovir, concentration there [94]. Aptamers also encouraged selective ocular treatment, although it needs more investigation [95].

5. Conclusions and perspectives

Direct eye contact with an outside environment provides a high degree of protection against exogenous chemicals, making topical drugs the least permeability and bioavailability. Like other routes of drug administration, the physicochemical characteristics of drugs are also important. Furthermore, stricter standards such as sterility and isotonicity must be addressed for ocular drug administration. To avoid irritating or blurring eyesight, it should also have a pH near the eye's pH, a typical adverse effect of oily products. Water-soluble or pH-sensitive drugs might complicate delivery situations into ocular tissues.

These requirements also make the situation more challenging; some drugs have little water solubility or are just soluble in a narrow pH range. It can be stated that ocular injection may be the only choice, especially for posterior ocular diseases, for some drugs, which some adverse effects and discomforts can accompany. Thus a self-administrable system with minimum side effects would be superior.

So far, multiple approaches have been used to overcome the obstacle toward topical ocular drug delivery, although acquiring efficient drug delivery remains a challenge. Meanwhile, the use of different nanoparticles as a carrier was of the most promising strategies in this regard. The present study evaluated the feasibility of liposomes as bioavailability enhancers of topical ophthalmic drugs. These versatile nanoparticles are composed of biocompatible lipids that increase the therapeutic efficacy of lipophilic and hydrophilic agents. They could help both anterior and posterior aye chambers drug delivery; their advantages are controlling drug release, reducing drug toxicity, improving solubility, permeation, surface retention, therapeutic effects, and bioavailability of drugs, with the potential of targeting. All these benefits can be reached by the precise manipulation of liposomes and regarding eye physiology.

This review summarized literature related to liposomal carriers, the role of the liposome components, and their physicochemical properties, all discussed and put together their outcomes for general consent. All the discussed issues can be considered in the further design of liposomes to

have a more successful formulation. It must be noted that most of these findings are mostly based on preclinical evaluations with a long way to clinical usage, but still useful. Besides, in most of these studies, the effect of liposomes alone has been investigated, not in an acceptable formulation for ocular use. In contrast, any substance in the formulation can affect performance. The other issue is that the entrance path to the anterior and posterior parts of the eye, transcorneal vs. transscleral pathway, is somewhat different, in which diverse environments are encountered; thus, these two compartments must be considered separately. All these cases must keep into consideration while designing a drug carrier to validate the formulation.

Despite vase research, there is still a lack of enough studies on ocular drug targeting and posterior drug delivery through topical administration; the role of efflux transporters still needs to be discovered. Accordingly, proposing a precise paradigm is somehow tricky, but combining different strategies, like using some additives in formulation along with the liposomes, like using new penetration enhancers or other technologies, like using composite formulations, and enhancing liposome stability could be helpful. Identification of new targets is also of value. Future work should focus more on liposomes in the final formulation and combine them with other promising agents to seek help from other formulation components to increase efficiency, such as formulating the liposomes in novel vehicles to produce an all-in-one system.

Declaration of competing interest

The authors of the article declare that they have had no conflict of interest in the publication of the article and are fully aware of the details of the article.

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