International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 15, Issue 5, 2023

Review Article

A COMPREHENSIVE REVIEW ON PRONIOSOMES: A NEW CONCEPT IN OCULAR DRUG DELIVERY

AKHILESH PATEL[1], UJWAL HAVELIKAR[1*], VIPIN SHARMA[2], SUCHITRA YADAV[2], SAKSHI RATHEE[2], BINITA GHOSH[1], KARTIK GILL[1], GAMDHUR SINGH[1], LALIT SHARMA[3], ARINDAM KOLAY[1]

[1]NIMS Institute of Pharmacy, NIMS University Jaipur-303121, Rajasthan, India. [2]DDR College of Pharmacy Gurugram-122504, Haryana, India. [3]SGT University Gurugram-122505, Haryana, India

[*]Corresponding author: Ujwal Havelikar; [*]Email: havelikar.ujwal@nimsuniversity.org

Received: 12 Jun 2023, Revised and Accepted: 01 Aug 2023

ABSTRACT

The concept of novel drug delivery with the comparison of modern and conventional delivery system. The Ocular is the most challenging organ to deliver drugs after the brain and conventional delivery systems currently available in the arsenal have severe limitations thus there is a strong demand for an improved ocular delivery system and a suitable opinion is a novel drug delivery system. Noisome and liposome are dominant vesicular carriers in ocular drug delivery, as both systems improve the bioavailability of drugs and are well tolerated in ocular; however, both delivery systems have critical drawbacks of physicochemical stability during storage, lacking contain in dispersion and fusion of nanoparticles. The gel form is formulated by the coacervation phase's parathion method. The material utilized for the formulation of proniosomes are non-ionic surfactant, cholesterol, carrier and alcohol are well tolerable and nontoxic in the ocular. The benefits offered to ocular drug delivery are prolonged retention time of formulation on the ocular surface, enhance ocular penetration to deliver effective therapeutic dosage, improve bioavailability of hydrophobic, lipophilic and herbal drugs, biocompatible, biodegradable, nontoxic and stable stored in pro-vesicle state. Hereby article will review proniosomes drug delivery from the perspective of ophthalmic delivery, discussing proniosomes as an ocular carrier, materials and methods their effect on ocular drug delivery and depth explanation of recent studies of proniosome in the ocular. Proniosomes are one of the sterile drug delivery systems that have seen a tremendous increase in popularity and are heavily utilized in cancer therapy. Researchers and academicians generally agree that incorporating the medicine into niosomes will improve its ability to target tissues where it is needed. Proniosomes created by academics and researchers. Niosomes that are produced from protostomes are a promising medication delivery system. They are well known for avoiding several issues related to aqueous noisome dispersion as well as issues with physical stability such aggregation, fusion, and leakage. They make transportation, distribution, storage, and dosage even more convenient. Proniosomes not only present a promising medication delivery method but also have the potential to speed up the skin barrier's repair.

Keywords: Ocular drug delivery, Proniosome, Bioavailability, Biocompatible, Lipophilic, Pro-vesicle

DOI: https://dx.doi.org/10.22159/ijcpr.2023v15i5.3048. Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

The human eye is a sophisticated sensory organ with complex Physiology and anatomy, physiologically eye is divided into two segments Anterior and Posterior connect with each other and other sensory organs through a network of nerves, being a sensory organ eye is protected by various structural and functional defensive barriers [1, 2], Despite being fortified by complex defense mechanisms several diseases breach it either by Physical force or by immune-deficiency and systemic disease [3]. For the treatment of ocular disease, a conventional drug delivery system is utilized, and 90% of ophthalmic drug are primarily administered by a topical route, as topical administration of drugs seems to be an ideal route of administration. However, the topical dosage has to overcome the physicochemical barriers include drug lipophilicity, solubility, molecular size, biological barriers include tear film corneal epithelium, systemic absorption from conjunctival capillaries system, blood Aqueous barrier and blood-retina barrier and normal physiological actions like blinking, tear turnover and nasolacrimal drainage [3]. Topical eye drops, eye Solution or Suspension, and eye ointments are the popular dosage forms. Ointments offer an advantage over eye drops such as increased contact time, reduced nasolacrimal drainage, minimization of tear dilution and higher effective concentration at the site of application [4]. The main disadvantage is blurred vision however; the use of water-soluble bases called gels has increased recently due to their advantages such as spreadability, stability and low irritability. There is a wide range of ophthalmic products available in the market out of which 70% of prescriptions include conventional eye drops [5]. The reasons may be due to the ease of bulk scale manufacturing, high patient acceptability, drug product efficacy, stability and cost-effectiveness, however, for efficient ocular drug delivery with an eye drop, high corneal permeation with longer drug cornea contact time is required. This can't be achievable by conventional ocular dosage forms. Peri-ocular and in traversal administration routes are used to overcome the inefficiency of topical dosage forms but they are not very patient-compliant [6] Table 1 discussed the benefits and challenges of conventional ocular dosage forms. Novel drug delivery systems are a suitable alternative to conventional ocular dosage forms [7]. Novel drug delivery systems, mainly vesicular carriers, are predominantly studied in ocular drug delivery; commonly studied are liposomes and noisome. Despite having all unique advantages, the major drawback of liposome is low physicochemical stability and high scale-up cost in manufacturing. Noisome introduced by L'Oreal in 1975 is an on-ionic surfactant formulation developed to overcome the physicochemical instability of liposome a lipid-based vesicle drug carrier; noisome classify chemical instability only however, physical instability like fusion, aggregation and leakage during storage still a concern in Noisome [8]. Pro-vesicular delivery system Proniosomes and Proniosomes have similar properties as a vesicular system but improved physicochemical stability thus effectively dealing with the drawbacks of the conventional vesicular system. Pro-liposome was introduced by Nicholas Payne and colleagues in 1986, which short out only the physical instability; chemical instability is still a concern and a vacuum or nitrogen atmosphere is required during storage to counter phosphatides choline oxidation [9, 10]. Proniosome was inducted by Hu and Rhodes in 1999, is a non-ionic surfactant-based drug carrier that resolves the major drawback of liposome, and niosomes proniosome and emerged as a potential drug delivery system in every aspect [11].

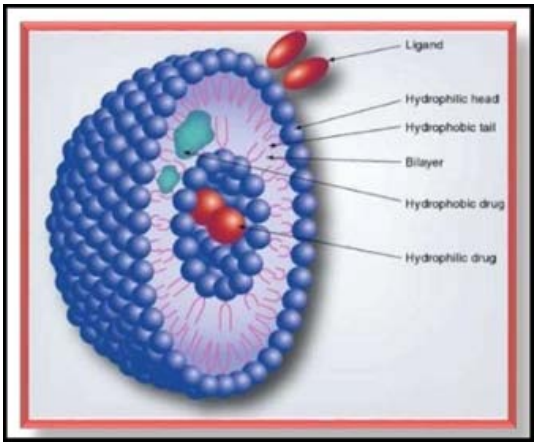

Fig. 1: Proniosome

Proniosomes novel ocular drug delivery system

The main concern with lipid-based vesicle systems is low physicochemical stability and high scale-up cost in manufacturing. In the way of resolving concerns of lipid-based vesicle systems, the Proniosomes delivery system emerged as a suitable and affordable solution [12]. Proniosomes is a new aspect to overcome physicochemical instability and manufacturing concerns; however, inheriting all advantages and properties of conventional lipid vesicle systems. These are controlled release, suitable for both hydrophobic and hydrophilic drugs, improved and enhanced bioavailability, enhanced efficacy and therapeutic index of a drug, site specification of the drug, biodegradable, biocompatible and non-toxic [13]. Proniosomes are pro-vesicle systems upon hydration with suitable solution give improve noisome, formed by the self-assembly property of non-ionic surfactant. Proniosomes are the modified form of noisome, clarifying the physical instability of noisomes, such as aggregation, leakage, and fusion during storage. In the beginning, Proniosomes are predominantly researched in oral, topical and transdermal exploring the potential of Proniosomes as a drug delivery system, in recent 2014 first time Proniosomes is explored as an ocular carrier since then Proniosomes has been a potential ocular drug delivery system [14]. Proniosomes are classified as dry Proniosomes and proniosome-based gel. Dry proniosome was inducted by Hu and Rhodes 1999, as a dried free-flowing powder that upon hydration with suitable solvent, provides no isoform that are superior to conventional noisome as dry proniosome is stored in powder dosage form and dry proniosome can be converted to various dosage form like Beads, Tablets and can be filled in capsules. Proniosome-based gel was developed and inducted by *Vore et al.* as a formulation that has a semi-solid gel-like consistency that can be applied either as gel directly on the site of action or hydrated in a suitable solvent to provide noisome [15]. Both types of proniosome have been established as promising drug carriers and hold immense potential in the future.

Advantages of proniosome delivery system [16-18]

- Proniosome is a Pro-vesicular which can be stored in inactive pro form and converted into a vesicle carrier of a drug when needed, thus avoiding degradation of the drug during storage.
- It uses Surfactant instead of Phospholipid, which is the prime ingredient in lipid-based based delivery systems and is physiochemical unstable; thus, proniosome is more stable than lipid-based delivery.
- Noisome is basically an on-surfactant-based vesicle aqueous dispersion which, with time, under leakage of drug, fusion and sedimentation in dispersion, on the other hand, proniosome avoids the separation problems.
- It avoids the use of large amounts of organic solvent as used in Transfarosome and liposomes.
- It can encapsulate both hydrophilic and hydrophobic drugs.
- It improves ocular retention and enhances ocular penetration. Proniosome is a simple, affordable and easy to scale up formulation.

Proniosomes method of preparation

- Proniosome is a pro-vesicle system, either a dried free-flow powder or a liquid crystalline. Methods used for the preparation of dry proniosome are a slurry method and spray coating method, while proteasome-based gel gelis prepared by the coacervation phase separation method detailed in the methods below.

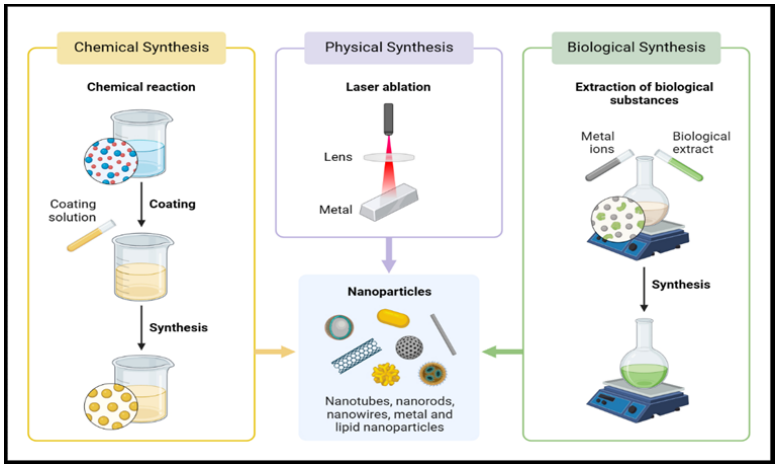

Fig. 2: Methods of preparations of nanoparticles (Proniosomes)

Slurry method

Surry method is a less noisome and more productive method. Carefully weighted surfactant, cholesterol and drug are added in a solvent and mixed by heating into the round bottom flask; the mouth is covered to prevent evaporation of the solvent. Add carrier to the above solution, disperse carrier completely, and additional solvent can be added to form a slurry. After that, the flask is attached to the rotary evaporator. Rotated with heating to obtain dry film on the wall of the rotating flask, sometimes lyophilized to completely remove the solvent [19]. Scrapped the film to obtain dry, free flow proniosome. Store the dry proniosome for evaluation in a tight container [19]. Table 2 consists of the proniosome prepared by the slurry method. The slurry method has a few disadvantages as the slurry method is predominantly used in oral and pulmonary drug delivery, the procedure is time-consuming and sometimes the

mixture adheres flask and is difficult to remove also, a high amount of alcohol is required and special equipment is required to remove organic material which is again is time-consuming thus not an ideal method for ocular formulation of proniosome [20, 21].

Table 1: Slurry method with different drugs and its merits

Drug	BCS class	Method	Merit	Reference
Doxycycline HCL, Metronidazole	BCS class Ⅰ Hydrophilic	Slurry method	Improve Niosomes, high EE% Drug proniosome have good flow and improve physical stability.	*Heba A Gad* (2013)[19]
Vinpocetine	BCS class Ⅱ Hydrophobic	Slurry method	High EE%, Homogenous Particle size.	*Song S* (2013) [20]
Candesartan Cilexetil	BCS class Ⅱ Hydrophobic	Slurry method	Improve noisome, enhance drug loading efficiency	*Yuksel N* (2014) [21]
Acemetacin	BCS class Ⅱ Hydrophobic	Slurry method	Multi-lamellar noisome	*Shehata MT* (2014)[22]
Pioglitazone	BCS class Ⅱ Hydrophobic	Slurry method	Sustained release, high EE%, Dry proniosome suitable for either tablets or capsule	*Shukr HM* (2015)[23]
Betaxolol HLC	BCS class Ⅱ	Slurry method	Unilamellar vesicle, improve stability and enhance ocular bioavailability	*V. viswanath* (2020) [24]

Spray coating method [23, 24]

The spray coating method was introduced by hu and Rhodes *et al.* 1999 formulated dry, free-flow proniosome. Proniosome is prepared by mixing surfactant: cholesterol in the required ratio, dissolved in a solvent. Take carrier in a round bottom flask attached to rotary evaporator apparatus. Solutions of surfactant cholesterol are introduced by spraying on the carrier in a round bottom flask in a controlled manner avoid Surry formation. Followed by rotation and heating of the round bottom flask to evaporator solvent, which leads to dry film on the flask wall; repeat again and again until the surfactant cholesterol solution is devoid; evaporator until dry powder is formulated. Dry proniosome is stored in a vacuum at room temperature [25, 26]. Table 3 consists of the proniosome prepared by the Spray coating method. The method is complex and requires complex equipment, the scale-up of the formulation is difficult, and the time-consuming procedure is a few known disadvantages of the spray coating method.

Table 2: Spray coating method with different drugs and their merit [25, 28]

Drug	BCS class	Method	Merit	Reference
Cromolyn Sodium	BCS class Ⅱ Hydrophobic	Spray method	High EE%, provide appropriates (2 µm), controlled release.	*Elbary-Abd. A* (2007)[25]
Celecoxib	BCS class Ⅱ Hydrophobic	Spray method	Dry proniosome in capsule enhances bioavailability.	*Nasr Mohamed* (2009)[26]
Ketoprofen	BCS class Ⅱ Hydrophobic	Spray method	High EE%, improves physical Stability and provide control drug release.	*Marwa Abdallah. H*(2011)[27]
Fiurbiprofen	BCS class Ⅱ Hydrophobic	Spray method	Sustained drug release, high EE% improve biocompatibility, prolong systemic drug.	*Verma Preeti* (2016)[28]

Coacervation phase method [26, 27]

Proniosome-based gel, a liquid crystalline structure consisting of a lamellar micellar model, has double layers of aligned molecules with water present between surfactant layers as shown in fig. 1. In 1997, Vora *et al.* introduced the coacervation phase method and formulated a proniosome gel of levonorgestrel. For the preparation of proniosome gel, take the non-ionic surfactant main ingredient of proniosome (the bilayer of the vesicle is formed by the surfactant alkyl chain during hydration). cholesterol and/or lecithin act as a membrane stabilizer, in a wide mouth glass vial (2 cm mouth 5 cm length), add alcohol and dissolved by heating in a water bath with continuous stirring at 60-70 ℃ Until lipid is completely dissolved Cover the mouth to prevent solvent lose. In a vial, the solution is formed at 60 ℃, and a small amount of alcohol prevents micelles formation. After that, distilled water is added to the vial, and stirred in a water bath at 60 ℃ until a clear or translucent solution is obtained. Kept the solution to cool down slowly at room temperature to form a gel; during the cooling phase, due to the small amount of solvent, the chemistry between lipid (surfactant, cholesterol) and the solvent is reduced, resulting in a decreased solubility of lipid (surfactant, cholesterol) in solvent [27]. Table 4 consists of the proniosome prepared by the Coacervation phase method. The coacervation phase separation method simple and effective for the formation of gel and ocular gel is the most preferable topical ocular drug delivery system.

Materials of proniosome [28, 29]

Non-ionic surfactant

Surfactants are also known as Surface acting agents; the surfactant is the main ingredient of noisome and Proniosome [30]; the surfactant is classified by charge present on the polar head group, namely as non-ionic, anionic, cationic and amphoteric has extensive studies in various noble drug delivery system [39]. In ocular delivery, non-ionic surfactants are commonly used, as they show the least toxicity in ocular, are biocompatibility and biodegradability with/in ocular tissue e.g. sorbitan esters, Polysorbates, polyoxyethylene lauryl ether [31]. In proteosome for ocular drug delivery, Non-ionic Surfactant implements numerous tasks such as Gelling agent, in 2016, *Khalil M. Rawai et al*. [32, 33], span 60 as Co-Surfactant in Lomefloxacin HLC proniosome based gel for ocular delivery act as a gelling agent, as span 60 have high Transition temperature (Tc) thus provide highly ordered gel Structure to formulated proniosome based gel. As a Stabilizer [34], non-ionic surfactants consisting of free Hydroxyl group provide adequate Zeta Potential to Proniosome formulations thus preventing aggregation during the storage period [35]. Penetration Enhance property of surfactant is well known; surfactant act by modifying the protective mechanism of the cornea, thus providing adequate penetration enhancement through the topical route, Brimonidine tartrate loaded proniosome studies revealed that *in vivo* release of proniosome formulation is double that of marketed formulation thus span 60 a non-ionic surfactant act as a penetration enhancer and finally surfactant act as a solubilizing agent for both hydrophilic and hydrophobic drug in proniosome based formulation, Dorzolamide HCL is a hydrophilic drug formulated into proniosome based gel for ocular delivery utilized non-ionic surfactant span 40 a hydrophilic surfactant intensified solubility of Dorzolamide in the lipid phase of formulation during preparation. Properties required in surfactant for the formulation of a stable proniosome and their effects on the overall performance of formulation are described below [36, 37].

Table 3: Common non-ionic surfactant used in ocular delivery [38, 39]

Surfactant series	Common name	Chemical name	HLB value
Span	Span20	Sorbitan Monolaurate Sorbitan Monopalmitate Sorbitan Stearate	8.2
	Span40	Sorbitan Tristearate Sorbitan monooleate	6.4
	Span60		4.7
	Span65		2.1
	Span80		4.3
Tween	Tween20	Polyoxyethylene 20 Sorbitan Monolaurate Polyoxyethylene 20	16.7
	Tween40	Sorbitan Monopalmitate Polyoxyethylene 20 Sorbitan Monostearate	15.6
	Tween60	Polyoxyethylene 20 Sorbitan Monooleate	14.9
	Tween80		15
Brij	Brij35	Polyoxyethylene(23) Lauryl ether Polyoxyethylene (2) Acetyl ether	16.9
	Brij52	Polyoxyethylene (2) stearyl ether Polyoxyethylene (2) Oleyl ether	5.3
	Brij72	Polyoxyethylene(20)Oleyl ether	4.9
	Brij92		5
	Brij98		15
Pluronic	Pluronic F68 PluronicL121	Polyoxyethylene block Copolymer Poly (ethylene glycol)-block-Poly (Propylene Glycol) block Poly (ethylene glycol)	0.5 25
Poloxamer	Poloxamer188	2-(2-propoxypropoxy) ethanol	29
Cremophor	Cremophore RH40	Polyoxyethylene glycerol 35 Hydrogenated castor oil	14-16
	Cremophore EL35	Polyoxyethylene glycerol 40 Hydrogenated Castor oil	13.5

HLB value hydrophilic-lipophilic balance is a classification parameter of surfactants dividing surfactants into two groups' lipophilic surfactant HLB value (3-6) and hydrophilic surfactant HLB value (6-16). The lipophilic group of surfactants is highly soluble in lipid and organic solvents; meanwhile, hydrophilic surfactants are readily solubilized in an aqueous medium [40-42]. In proniosome for ocular and general HLB value of surfactant effect the Entrapment efficiency, release, vesicle size and even formulation of proniosome. In general Low HLB, value surfactant gives high Entrapment Efficiency while high surfactants give low Entrapment Efficiency, proniosomal gel of ketoconazole reveal span 60, and span 65 have low HLB value and offer high Entrapment Efficiency as compared to Span 20, and span 80 have high HLB value give low Entrapment Efficiency. A similar result is observed in Dorzolamide HLC proniosomal gel at low HLB value surfactants yield high Entrapment Efficiency as low HLB value of surfactant means high hydrophobicity of vesicle bilayer results in entrapment of a large amount of drug molecule [43], another study by *Khalil M. Rawai et al.* reveal that designed HLB can be achieved by mixing two surfactants [44]. The HLB value of surfactant also has a significant effect on the vesicle size of proniosomal derived niosomes dispersion, Dorzolamide proniosomal gel for ocular delivery revealed that low HLB value surfactant gives small vesicle as compared to high HLB value as low HLB surfactant limit the uptake of the aqueous medium in core of vesicle. *In vitro* release of low HLB value surfactant is slow than High HLB value surfactant as hydrophilic surfactant dissolves hydrophobic solute more rapidly than lipophilic surfactant in an aqueous medium [45]. The length of the Alkyl chain of surfactants has a crucial effect on the Entrapment Efficiency of proniosomal formulation; each surfactant has a different lipophilic alkyl chain. Surfactants with long saturated chains provide high Entrapment Efficiency as compared to short alkyl chains and unsaturated alkyl chains. In proteosome-loaded Brimonidine tartrate, span 60 (C18) give high Entrapment Efficiency of Brimonidine tartrate as compared to Brij 52 (C14) and unsaturated alkyl chain tween 80 (C18) consisting of a double bond leading to the formation of leaky bilayer thus low encapsulation of Brimonidine also alkyl chain effect the release of the drug, span 60 provide sustain and slow release of Brimonidine [46]. Transition Temperature (Tc) of non-ionic surfactant is a major property to be considered, for the formulation of stable proniosomal gel and proniosome derived noisome, High Tc of surfactant provide high order gel and rigid bilayer thus formulated proniosome have high Entrapment Efficiency and sustained release [47]. Above we discuss about effect properties of surfactant on proniosome formulation for ocular delivery, Another factor to be considered is concentration of surfactant in proniosome formulation, In proniosome derived noisome dispersion of Dorzolamide studied the effect of concentration of span 40, increasing span 40 concentration from 180 to 630 mg exhibit increase in Entrapment Efficiency of Dorzolamide due to numerical rise in formulation noisome dispersion, effect of increase concentration of span 40 on particle size is Negative as increase concentration lead to larger Particle size as more Dorzolamide entrapped in core of vesicle, Another study conducted on proniosome gel of Brimonidine tartrate for ocular delivery reveal that formulation prepared with high concentration surfactants show enhancement in Entrapment Efficiency of drug in bilayer of vesicle, effect of concentration of surfactant on release shows that high surfactant based formulation restrict release of drug due to viscous noisome dispersion [48]. The surfactant to be utilized in the formulation of proniosome for ocular delivery should have an HLB value between 4-9, have a saturated long alkyl chain and have a high Transition temperature. Some common nonionic surfactants used in preparation are shown in table 5.

Cholesterol

Cholesterol in proteosome-derived noisome and conventional niosomes is a primary additive, providing rigidity to the bilayer of the vesicle thus decreasing the leakage of loaded drug from the vesicle and also increasing the entrapment efficiency of the vesicle [48, 49]. The effect of the number of cholesterols with surfactant in the formulation of noisome and proniosome is widely studied, concluded that with an increase in the amount of cholesterol entrapment efficiency increase but after a certain concentration shape decrease in entrapment efficiency is reported as cholesterol competes with drug for the shape in surfactant bilayer and increase the hydrophobicity [50]. In proniosome-loaded Dorzolamide for ocular delivery studied the effect of Cholesterol on entrapment efficiency and release of Dorzolamide, concluded that cholesterol beyond a certain amount in the proniosome lead to disruption of vesicle bilayer thus causes low entrapment efficiency, as cholesterol increase rigidity of bilayer as limiting the release of hydrophilic drug Dorzolamide form vesicle core. Another important ability of cholesterol is to abolish gel to the sol phase transition of the vesicle. The release is also affected by cholesterol, the noisome prepared with cholesterol show slow release thus lowering the permeability of the bilayer. Membrane stability is also a reported function of cholesterol with or without Lecithin. Lecithin in the proniosome is used as a membrane stabilizer and penetration enhancer. Thus, from the above studies, optimized cholesterol in vesicle play a significant role.

Carrier material

They are the additive of dry Proniosome with surfactant and cholesterol providing increased surface area and enhanced entrapment efficiency. The parameter for a carrier to be used in proniosome is carrier should be non-toxic, poorly soluble in the solvent used in the formulation and highly water soluble. Commonly used carriers are Maltodextrin, Sorbitol and Mannitol and to a lesser extent are magnesium aluminum silicate, Spray dried lactose and Sucrose Stearates [49]. Used Maltodextrin as a carrier for Oral drug

delivery for Condesarten cilextile. *Verma et al. 2012* use Sorbitol as a carrier for the parenteral drug delivery of Flurbiprefer [50]. *Abd-Elbary et al. 2008* used Sucrose stearate as a carrier for pulmonary drug delivery of Cromolyn sodium. *Supriya Verma, Singh Bhupinder et al. 2018* utilized Maltodextrin as a carrier for ocular delivery and provides stable dry proteosome-loaded Aceclofenac. Formulated Betaxolol-loaded proniosome utilized Maltodextrin as a carrier for ocular delivery [50].

Table 4: Ocular route of administration with benefits and challenges [1, 22, 49]

Route	Benefits	Challenges
Topical	Highly patient compliance, self-administrable and non-invasive.	Cornea acts as barrier, tear dilution and turn overrate, nasolacrimal drainage.
Oral/systemic	Noninvasive, direct drug delivery tapestried or segment and sustains release.	Blood retinal barrier, Blood aqueous barrier, cataract, and endophthalmitis.
Intracameral	Drug delivery to anterior segment, Reduce corneal and systemic side effects.	Toxic anterior segment syndrome and Thyroid eye disease.
Sub conjunctival	Delivery to anterior and posterior segment, site for depot formulation.	Conjunctival and choroidal circulation.
Retro bulbar	Administer high local doses of anesthetics, more effective and minimal influence on IOP.	Hemorrhage, globe perforation And respiratory arrest.

Recent development in proniosome for ocular delivery

Tacrolimus

The primary function of an eye is vision if vision is distorted by means like damage to the cornea, or any secondary disease in an ageing person, restoring vision by Medication is not possible thus corneal allograft is recommended but the common disadvantage of graft is rejection by the body. Tacrolimus is an immunosuppressive agent that acts by suppressing the immune response by the body after corneal allograft. It was recently, 2014 first proniosome gel-derived niosomes for ocular delivery was formulated by *Qi li et al.* to treat ocular anti-allograft rejection. Tacrolimus drug is highly hydrophobic and has 822.5D molecular weight thus intraocular release by conventional means is limited. Conventional noisome have physical instability issues explained above. Proniosome of tacrolimus prepared by coacervation phase method, proniosomal gel obtained was reconstituted by normal saline into noisome for *in vitro and in vivo* characterization immediately before application thus circumventing stability issue of noisome. Transmission electron microscopy revealed a spherical nano-particle having 1 µm diameter, polydispersity index 0.21±0.03 and 8mv zeta potential. The surface tension of the formulation explains the spreading of formulation on the applied surface, surface tension was found low at 72.13±0.06 dynes/cm. Entrapment efficiency (EE %) of the derived noisome by hydration in normal saline is high at 95.34±0.02%. The stability of Tacrolimus loaded proniosome is studied for 3 mo at various temperatures (4℃, 25℃ 40℃, and no tothe minus reduction in EE% is reported. *In vitro* Tacrolimus release by isolated rabbit corneal is studied, compared with the suspension of Tacrolimus shows derived noisome have high and significant release due to the 1.33 µm particle size, surfactant and lecithin act as the permeation enhancement. Ocular irritation studies show no irritation. Histological inspection studies of 21 d on ocular tissue show that noisome is corneal biocompatibility, thus safe for ocular. *In vivo* studies were conducted on rat cornea, post-operation 8 d to prevent immune-mediated rejection. Proniosome-derived noisome of Tacrolimus successfully treats the allograft rejection.

Levofloxacin

Conventional Levofloxacin Ophthalmic drops are utilized for the treatment of Topical ocular bacterial infections, but Conventions Ophthalmic drops of Levofloxacin have low bioavailability, thus required frequent dosing, in 2014, *dhanger K. R et al.* prepared proniosome loaded Levofloxacin for ocular delivery, method exercised is coacervation phase. Formulated proniosomal gel is scanned for vesicle size, insoluble drug crystals and any physical instability by a light microscope. Photographs unveil a unilamellar spherical vesicle accompanied by no aggregation observed. According to Entrapment efficiency (EE%), observation span 40 shows high EE% than span 60 may be due to the HLB value of span 40 being high. Morphology of Levofloxacin loaded proniosome by scanning electron microscopy illustrated smooth surface. Conducted *in vitro* release study of formulations on Franz-diffusion cell for 24 hr., apprised linear release and 90% released. Ocular irritancy studies on albino rabbits illustrated no ocular irritancy [51].

Lomefloxacin HLC

Bacterial Conjunctivitis is commonly known as Pink eye, caused by Bacteria that breach the Ocular conjunctiva and inject into the eye. Lomefloxacin HLC is an Anti-bacterial agent that acts by inhibiting the replication of bacterial DNA, available as the conventional ophthalmic drop. *Khalil et al.*, in 2016 prepared proniosome-loaded Lomefloxacin HLC for ocular delivery to increase drug retention and sustained release in the ocular cornea. The method exercised to formulate proniosome gel is coacervation phase separation, different types of non-ionic surfactant are used (span 60, 40, 20, tween 20, 40, 60, 80 and Brij) but the study revealed that span 60 (HLB 4.7, Tc 53 °C) solely formed gel individually; other surfactant required a mixture of span 60 in different ratio to form a stable gel. Entrapment efficiency (EE %) studies disclose that the length of the alkyl chain of surfactant is an important factor for high EE% value. Span 60 and tween 60 mixtures have high EE%. The vesicle size study illustrated that a low HLB provides a small vesicle size as compared to a high HLB value. However, all the formulations have a nano-size range. *In vitro* release study exhibit release is surfactant dependent, short alkyl chain length, and release from the formulation range from 33.56±0.69%-83.95±0.3%. Span 60: Tween 90 ratios have suitable release. Morphology after hydration is seen by Transmission electron microscopy (TME) relieved vesicles are spherical, smooth and nano-sized. 3 mo of stability studies at various temperatures divulge no or negligible change in EE% and vesicle size. An ocular irritancy test was conducted to evaluate redness, inflammation or tear production after the application of proniosome formulation, but no such active observed. This formulation is safe and proniosome can be an alternative to eye drops, and prolong corneal retention and penetration; thus, proniosomal gel is a promising ocular delivery system.

Ketoconazole

Fungal infection of the ocular also called Ophthalmic Mycoses, the incidence of fungal infection has increased due to a large number of patients' extended use of Immunosuppression agents, long-term use of broad-spectrum antibiotics and patients with Immunosuppressive disorder are highly vulnerable to fungal infections. Fungal Keratitis is a serious corneal disease that may result in loss of vision; incidents of fungal keratitis are emerging on a global scale with the highest number of cases in India, Nepal, China and other developing and underdeveloped countries. Fungal Keratitis is an inflammation of layers of the cornea, adaptive immune-mediated inflammation results in tissue necrosis of the surrounding area [52]. As fungi penetrate the stroma layer of the cornea, it leads to further tissue damage, scarring, and opacification of the cornea. Fungal keratitis is historically associated with trauma with organic or vegetative

matter or objects contaminated with soil, Abrasions caused by contaminated contact lenses, pre-existing systemic conditions and ocular surface problems. Most commonly associated Filamentous fungi are Fusarium and Aspergillus, and yeast-like fungi, such as *Candida*, Calvaria and other phaeo hyphomycosis, Scedosporium apiospermum and Paecilomyces [53]. Ketoconazole is an anti-fungal agent belonging to the imidazole's family that acts by inhibiting Ergosterol synthesis and thus show fungicidal action; ophthalmic Ketoconazole have major limitations, such as ketoconazole is lipophilic thus low solubility in water and having high molecular weight hinder penetration in the cornea, ophthalmic formulation of Ketoconazole required multiple dosing and provide poor bioavailability. In 2017, *Abdelbary et al.* prepared a proniosomal gel of ketoconazole (KET) for ocular delivery, having the objective to evaluate the preformation of KET proniosomal gel in the ocular. The method employed was the coacervation-phase method using different non-ionic surfactants of different HLB and Tc, with and without lecithin having constant cholesterol constant. Formulation of proniosomal gel hydrated with Sorensen's phosphate buffer pH 7.4 to yield noisome. EE% of prepared formulations range form (37.50±1.15 to 93.00±1.10), span series due to low HLB and high Tc with and without lecithin permit high EE%, increased cholesterol cause increased drug loading capacity, but sharp decreases have been reported when a high amount of cholesterol is incorporated. Because cholesterol may complete with the drug in the bilayer. Particle size range from nano to micron after hydration of proniosomal gel to niosomes, increasing surfactant/lipid ratio leads to increase particle size, increase cholesterol increased hydrophilicity of vesicle decreased vesicle size due to decrease or limited water intake. *In vitro* release and biphasic release were reported. The rapid release was reported in the initial phase due to an unentrapped drug; after a few hours' slow releases were observed, *and ex vivo* reports steady-state flux and high permeability coefficient. *In vivo* comparison between proniosomal gel and KET suspension in albino rabbits, reveal the concentration of KET in the aqueous humor is 73 times high than proniosomal gel as compared to KET suspension. The ocular irritancy tests reports no redness, inflammation or tear production.

Dorzolamide HCL

In 2018, *Faudo H. N et al.* prepared proniosomal gel of Dorzolamide HCL, is a water-soluble anti-glaucoma drug. The method utilized is coacervation phase separation, formulated proniosomal gel hydrated by phosphate buffer saline (PBS) 7.4pH to provide noisome. The entrapment efficiency (EE%) study reveals that a high amount of cholesterol with a low concentration of surfactant will decrease the EE% due to disruption of the noisome linear structure, low concentration surfactant cannot stabilize vesicular membrane. At high concentration of surfactant EE% increase with an increasing amount of cholesterol but to a certain limit because of the increased hydrophobicity and decrease entrapment of hydrophilic drug. Particle size study reveals an increase in cholesterol decreased particle size due to cholesterol molecular cemented between surfactant alkyl chains. *In vitro* release study shows biphasic release, rapid release followed by sustained release for 8 h, report claim increase in cholesterol amount decreased release as the rigidity of vesicle increased and quash of gel to sol conversion of vesicle, well spherical proniosome derived noisome confirm by Transmission electron microscopy. *In vivo* study observation no ocular irritation proniosome derived noisome increase the bioavailability of hydrophilic drug Dorzolamide HLC due to prolong interaction with the cornea and sustained release of the drug [49].

Brimonidine tartrate

Brimonidine Tartrate is a α2 adrenergic agonist used in glaucoma treatment; glaucoma is indicated by high IOP leading to blindness and server nerve pain, and Brimonidine Tartrate acts by reducing IOP and reducing pressure on the optical nerve. Brimonidine Tartrate ophthalmic drops have bioavailability limitations and thus requested frequent dosing. In 2019, *Eldesb emadalac et al.* prepared proniosome gel derived noisome for ocular delivery of Brimonidine tartrate, an anti-glaucoma hydrophilic drug. The method to apply was coacervation phase separation; formulated proniosome gel is hydration to give noisome. Hydrated proniosome were evaluated for EE%, *in vitro* and *in vivo.* EE% study of formulation reveals an increase in EE% with an increase in surfactant concentration, due to increase hydrophobicity. The particle size of the reconstituted noisome has a size less than 5 µm suitable for ocular preparation. *In vitro* release shows sustained release. After gamma sterilization, no significant reduction or change was reported. Draize test of optimized formulation reveals no ocular irritation in the corneal, iris and conjunctiva. *In vivo* studies reveal prolong retention time and improve bio-availability by sustaining release from proniosomal gel derive niosomes [48].

Dorzolamide hydrochloride

Dorzolamide Hydrochloride a water-soluble drug. This is used for the treatment of interocular pressure due to glaucoma by suppressing the carbonic anhydrase in the glaucoma eye. Dorzolamide Hydrochloride drops are available in the market for the treatment of glaucoma but have poor ocular Bioavailability due to the per-ocular barrier and thus required frequent doses. In 2020, *Sayed S, Abdelmotelab M* studies Dorzolamide Proniosome based gel for effective ocular delivery to treat Glaucoma, the method employed to formulate is the Coacervation Phase method. Non-ionic surfactants employed are Span (20, 60), Tween (20, 60), Pluronic L121, Pluronic F68, Cremophore EL and Cremophore RH 40. Formulated proniosomal gel is studied for various parameters to ensure Dorzolamide Hydrochloride Proniosomal gel is effective for Ocular delivery. Entrapment efficiency (EE%) of Dorzolamide-loaded proniosomal gel determine after hydrating gel in 7.4 pH Phosphate Buffer Saline, high EE% is observed with a surfactant having a long length of alkyl chain and low HLB also indicates high EE%. Particle size and Polydispersity Index is an important parameter for ocular delivery, all formed vesicles are nano-sized with homogenous PDI. The size of the vesicle is related to the HLB valve, the lower the HBL smaller the size of the vesicle. Biphasic release observed in *in vitro* release. DSC review reflects that drugs and excipients are completely compatible. TMS exhibit well-identified shape and spherical morphology. Ex vivo permeation of optimized formulation consists of Surfactant Span 60 exhibits low permeation and better retention in the ocular surface. 3 mo of storage show no significant change in EE% and particle size. *In vivo* studies reveal a decrease in IOP up to 12h [47].

Aceclofenac

Aceclofenac is a non-steroidal anti-inflammatory agent used in the treatment of inflammation by acting on COX-2 inhibitor, generally administrated by oral route thus limiting Aceclofenac efficiency and efficacy on the site of action, *Verma S, Singh B et al.* In 2018 prepared proniosome based gel of Aceclofenac for ocular delivery for treatment of ocular inflammation by utilizing the Slurry method, weighted amount of span 60 surfactants, cholesterol and methanol in the round bottom flask are mixed with heating finally add Maltodextrin to form slurry followed by removing of organic solvent under reduced pressure (70-80 rpm) till dry white film found on the wall of Round Bottom Flask. The dry powder obtained is further dried in a vacuum oven to obtain a free-flowing powered Aceclofenac Proniosome, formulated Aceclofenac proniosome powder is evaluated on various parameters for calculating Aceclofenac proniosome efficiency in ocular delivery. After incorporation of proniosomal derived niosomes in Carbapol revealed enhanced trans-corneal penetration and prolonged retention time of Aceclofenac, rheological studies provided data showing non-Newtonian behavior. Stability studies data exhibit that Aceclofenac proniosome based gel is suitable for ocular delivery. Calculation of all Parameters points that Aceclofenac Proniosome gel is effective in the treatment of Ocular inflammation [50].

Betaxolol hydrochloric acid

Betaxolol HCL is an Anti-Hypertensive drug and is also used for the treatment of open-angle glaucoma common ocular disease that leads to increased ocular pressure if left untreated causing blindness. Conventional Betaxolol HCL eye drop has specific limitations such as low bioavailability and therapeutic ineffectiveness. In 2020, *V. Viswanath P. Tulasi* prepared Betaxolol HCL proniosome using 32 factorial designs independent variables are cholesterol and span 60

surfactants and the dependent variable are Entrapment efficiency, Drug Content and drug release. The method utilized for the formulation is the slurry method producing free-flowing dry proniosome loaded Betaxolol HCL, prepared Betaxolol HCL proniosome are subjected to various evaluation parameters for ocular delivery. Entrapment efficiency and drug Content studies of proniosome-loaded Betaxolol HCL reveal that a high concentration of surfactant has a positive effect on Entrapment efficiency meanwhile concentrations above 50 mg show a shape decline in Entrapment Efficiency. *In vitro* drug release studies exhibit linear release, the effect of dependent variables on release show high surfactant concentration provides enhance drug release while cholesterol concentration shows restriction in release when incorporated in the high amount due to enhance rigidity of bilayer and hindering penetration of Betaxolol HCL form bilayer. The pH of the formulations is between 6.1-6.7 which is non-irritant in the ocular. Vesicle size of Proniosome loaded Betaxolol HCL are unilamellar of size 3.1-3.6 nm.

Curcumin

Curcumin is an FDA-approved herbal drug that has many therapeutic from anti-inflammatory to anti-cancer without adverse effects. Curcumin is also used in ocular as an anti-inflammatory agent and occurs as a defensive phenomenon, being a natural herbal medicine, solubility, limited bioavailability and absorption are known drawbacks of herbal drugs. In 2020, Aboali A, Fatma*et al.* prepared curcumin-loaded proniosomal gel for ocular delivery for the treatment of ocular inflammation. The method utilized for the formulation of Curcumin loaded proniosome gel is the Coacervation phase method, surfactant employed is span 60, tween 80 and Cremophor Rh with an equal ratio of lecithin and 10% of cholesterol, prepared curcumin-loaded proniosome gel is subjected to evaluation parameters such as vesicle size, Entrapment Efficiency, release study, stability study and ocular irritation. After the successful formulation of Curcumin proniosomal gel is hydrated to produce noisome dispersion is evaluated for Size determination, found out that dispersion is in nano size (192.5±0.2-768.6±0.4) according to the studies particle size depends on HLB value. High HLB causes a decrease in hydrophobicity thus vesicles obtained are larger vesicles, another factor that affects the particle size of produced proniosome diverted noisome dispersion is the concentration of surfactant, with increased concentration of surfactant (Fcr250, Fcr300 and Fcr350) reduction in vesicle size observed as highamount enhancer vesicle formation. PDI is less than>1 (0.36-0.68). Zeta potential causes great electro repulsion between vesicles thus low aggregation in noisome dispersion. All Curcumin loaded proniosomal gel derived noisome how negative high Zeta potential due to the presence of a free hydroxyl group in surfactant and lipids. Low Zeta Potential value of Cremophore (F_{cr250}, F_{cr300} and F_{cr350}) with an increase in amount indicates in stability, thus formulation should best or edin proniosomal gel form to avoid in stability issue of noisome dispersion of Curcumin. Noisome may form *in vivo* with tears. Entrapment Efficiency studies of all curcumin loaded proniosomal gel revealed that encapsulation of curcumin depends on surfactant and amount of surfactant. A non-ionic surfactant having a Low HLB value, long alkyl chain and transition temperature (Tc) yield high Entrapment Efficiency, in span 60 utilized formulation Entrapment Efficiency is 98.1±1 % due to the fact that span 60 has a low (4.7) HLB, long alkyl hydrocarbon and high Tc(54 ℃) providing highly ordered bilayer, thus F_{sp} have high Entrapment Efficiency, while Tween 80 utilized formulation, on the other hand, have leaky bilayer due to high HLB value (15) and presence of double bond in alkyl chain resulting in a bend in bilayer lead to the loose membrane. Cremophore used formulation show low Entrapment Efficiency (72.4 %±0.1) due to the fact that Cremophore is liquid at room temperature have high HLB (14-16) contributed to leaky bilayer although an increase in the concentration of Cremophore (250,300,350) significant enhancement in entrapment of curcumin due to numerical multiplication of vesicle formulation. Finally, cholesterol and lecithin act as membrane stabilizers and are kept constant. *In vitro* release of Curcumin forms all formulations exhibit sustained release up to 24 h, and the biphasic pattern is observed, Factors governing the release of curcumin from proniosomal gel are surfactant types and amount of surfactant. Span 60 based formulations show the slowest release followed by Tween 80 and then Cremophore. Span 60-based proniosome gel has a rigid highly or de red bilayer thus slowing the Curcumin release from the compact bilayer however Curcumin release by Tween 80 and Cremophore is high due to the leaky bilayer. Cremophore based formulations reveal with increasing concentration there will be a significant enhancement in the release of curcumin as hydrophilic surfactants dissolve hydrophobic salute in an aqueous medium better than hydrophobic surfactants. Membrane stabilizer cholesterol and lecithin reduce leakage and stabilized the bilayer kept constant. Selected formulationF_{cr300} subjected to lyophilization shows a negative effect with a reduction in Entrapment Efficiency and an increase in particle size due to rupture and fusion of vesicle dispersion during lyophilization. TEM and SEM of selected formulation before and after lyophilization show nano-sized spherical Multi-lamellar noisome with a smooth and non-pores surface, after lyophilization noisome, confirms spherical shape with aggregation and rough surface. The Trans corneal study of this elected formulation shows 3.22-fold permeability compared to the lyophilized formulation and curcumin dispersion due to the presence of non-ionic surfactant enhanced corneal permeability. Corneal hydration level is normal for selection proniosomal gel formulation (75.4±2.5) thus confirming safe for the eye. *In vivo* studies were performed on the rabbit to observe the action and reaction of both proniosome gels loaded curcumin and the eye, no ocular irritation was observed in the rabbit eye, thus selected formulation is safe for the ocular. A stability study reveals that proniosomal gel is more stable than lyophilized formulation during the storage period no significant change is observed thus curcumin loaded proniosomal gel is stable and suitable for ocular delivery [40].

CONCLUSION

Proniosomes are one of the sterile drug delivery systems that have seen a tremendous increase in popularity and are heavily utilized in cancer therapy. Researchers and academicians generally agree that incorporating the medicine into niosomes will improve its ability to target tissues where it is needed. Proniosomes created by academics and researchers. Niosomes that are produced from protostomes are a promising medication delivery system. They are well known for avoiding several issues related to aqueous noisome dispersion as well as issues with physical stability such aggregation, fusion, and leakage. They make transportation, distribution, storage, and dosage even more convenient. Proniosomes not only present a promising medication delivery method but also have the potential to speed up the skin barrier's repair.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Gaudana R, Anathula HK, Parenky A, Mitra AK. Ocular drug delivery. American Association of Pharmaceutical Scientists. 2010 Sep;12(3):348-60.
2. Bachu RD, Chowdhury P, Al-Saedi ZHF, Karla PK, Boddu SHS. Ocular drug delivery barriers-role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceutics. 2018 Feb 27;10(1):28. doi: 10.3390/pharmaceutics10010028, PMID 29495528.
3. Shell JW. Ophthalmic drug delivery systems. Surv Ophthalmol. 1984 Sep 1;29(2):117-28. doi: 10.1016/0039-6257(84)90168-1, PMID 6505951.
4. Yellepeddi VK, Palakurthi S. Recent advances in topical ocular drug delivery. J Ocul Pharmacol Ther. 2016 Mar 1;32(2):67-82. doi: 10.1089/jop.2015.0047, PMID 26666398.
5. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmacol. 2013;2(2):47-64. doi: 10.5497/wjp.v2.i2.47, PMID 25590022.

6. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharm Res. 2009 May;26(5):1197-216. doi: 10.1007/s11095-008-9694-0, PMID 18758924.
7. Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discov Today. 2008 Feb 1;13(3-4):144-51. doi: 10.1016/j.drudis.2007.10.021, PMID 18275912.
8. Ahmad MZ, Mohammed AA, Mokhtar Ibrahim M. Technology overview and drug delivery application of proniosome. Pharm Dev Technol. 2017 Apr 3;22(3):302-11. doi: 10.3109/10837450.2015.1135344, PMID 26794727.
9. Bayindir ZS, Yuksel N. Provesicles as novel drug delivery systems. Curr Pharm Biotechnol. 2015;16(4):344-64. doi: 10.2174/1389201016666150206101443, PMID 25658383.
10. Bachhav AA. Proniosome: a novel nonionic provesicules as potential drug carrier. Asian J Pharm (AJP) Free Full Text Artic Asian J Pharm. 2016 Sep 10;10(03).
11. Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. Int J Pharm. 1999 Aug 5;185(1):23-35. doi: 10.1016/s0378-5173(99)00122-2, PMID 10425362.
12. Hofland HEJ, Bouwstra JA, Ponec M, Bodde HE, Spies F, Verhoef JC. Interactions of non-ionic surfactant vesicles with cultured keratinocytes and human skin *in vitro*: a survey of toxicological aspects and ultrastructural changes in stratum corneum. J Control Release. 1991 Jun 1;16(1-2):155-67. doi: 10.1016/0168-3659(91)90039-G.
13. Sadiq M, Nirosha K. Review on proniosome-a novel approach to vesicular system. Int J Novel Trends Pharm Sci. 2014 Sep 10;4(5):97-100.
14. Li Q, Li Z, Zeng W, Ge S, Lu H, Wu C. Proniosome-derived niosomes for tacrolimus topical ocular delivery: *in vitro* cornea permeation, ocular irritation, and *in vivo* anti-allograft rejection. Eur J Pharm Sci. 2014 Oct 1;62:115-23. doi: 10.1016/j.ejps.2014.05.020, PMID 24905830.
15. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release. 1998 Jul 31;54(2):149-65. doi: 10.1016/s0168-3659(97)00100-4, PMID 9724902.
16. Khatoon M, Shah KU, Din FU, Shah SU, Rehman AU, Dilawar N. Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug Deliv. 2017 Nov 1;24(2);Suppl1:56-69. doi: 10.1080/10717544.2017.1384520, PMID 29130758.
17. Proniosome UTA. A novel approach to vesicular drug delivery. Int J Pharm Pharm Sci Res. 2013;3(1):1-6.
18. Rajkumar J. Gv R, Burada S. Recent update on proniosomal gel as topical drug delivery system. Asian J Pharm Clin Res. 2019 Jan 7;12(1):54-61.
19. Gad HA, Kamel AO, Sammour OA, El Dessouky HF. Vesicular powder as carrier for doxycycline hydrochloride and metronidazole combination therapy. Pharm Dev Technol. 2014 Sep 1;19(6):755-68. doi: 10.3109/10837450.2013.829098, PMID 23981239.
20. Song S, Tian B, Chen F, Zhang W, Pan Y, Zhang Q. Potentials of proniosomes for improving the oral bioavailability of poorly water-soluble drugs. Drug Dev Ind Pharm. 2015 Jan 2;41(1):51-62. doi: 10.3109/03639045.2013.845841, PMID 24111828.
21. Yuksel N, Bayindir ZS, Aksakal E, Ozcelikay AT. In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: *in vitro* and *in vivo* evaluations. Int J Biol Macromol. 2016 Jan 1;82:453-63. doi: 10.1016/j.ijbiomac.2015.10.019, PMID 26455402.
22. Shehata TM, Abdallah MH, Ibrahim MM. Proniosomal oral tablets for controlled delivery and enhanced pharmacokinetic properties of acemetacin. AAPS PharmSciTech. 2015 Apr;16(2):375-83. doi: 10.1208/s12249-014-0233-5, PMID 25319057.
23. Shukr MH, Eltablawy NA. Development and optimization of novel controlled-release pioglitazone provesicular powders using 3^2 factorial design. Drug Deliv Transl Res. 2015 Feb 1;5(1):51-62. doi: 10.1007/s13346-014-0215-x, PMID 25787339.
24. Viswanath V, Tulasi P. Formulation, optimization and characterization of betaxolol hydrochloride proniosomes using 3-2 factorial design. Int J Res Pharm Sci Tech. 2020 Feb 18;1(3):89-97. doi: 10.33974/ijrpst.v1i3.161.
25. Abd-Elbary A, El-Laithy HM, Tadros MI. Sucrose stearate-based proteosome-derived niosomes for the nebulisable delivery of cromolyn sodium. Int J Pharm. 2008 Jun 5;357(1-2):189-98. doi: 10.1016/j.ijpharm.2008.01.056, PMID 18339494.
26. Nasr M. *In vitro* and *in vivo* evaluation of proniosomes containing celecoxib for oral administration. AAPS PharmSciTech. 2010 Mar;11(1):85-9. doi: 10.1208/s12249-009-9364-5, PMID 20058106.
27. Marwa HA, Omaima AS, Hanaa AE, Hanan ME. Optimizing proniosomes for controlled release of ketoprofen using box-behnken experimental design. Int J Pharm Sci Res. 2011 Aug 1;2(8):2195.
28. Verma P, Prajapati SK, Yadav R, Senyschyn D, Shea PR, Trevaskis NL. Single intravenous dose of novel flurbiprofen-loaded proniosome formulations provides prolonged systemic exposure and anti-inflammatory effect. Mol Pharm. 2016 Nov 7;13(11):3688-99. doi: 10.1021/acs.molpharmaceut.6b00504, PMID 27632682.
29. Li Y, Dong C, Cun D, Liu J, Xiang R, Fang L. Lamellar liquid crystal improves the skin retention of 3-O-ethyl-ascorbic acid and potassium 4-methoxysalicylate *in vitro* and *in vivo* for topical preparation. AAPS PharmSciTech. 2016 Jun;17(3):767-77. doi: 10.1208/s12249-015-0353-6, PMID 26349686.
30. Bai Y, Abbott NL. Recent advances in colloidal and interfacial phenomena involving liquid crystals. Langmuir. 2011 May 17;27(10):5719-38. doi: 10.1021/la103301d, PMID 21090596.
31. Mehta M, Dureja H, Garg M. Development and optimization of boswellic acid-loaded proniosomal gel. Drug Deliv. 2016 Oct 12;23(8):3072-81. doi: 10.3109/10717544.2016.1149744, PMID 26953869.
32. Rajabalaya R, Leen G, Chellian J, Chakravarthi S, David SR. Tolterodine tartrate proniosomal gel transdermal delivery for overactive bladder. Pharmaceutics. 2016 Sep;8(3):27. doi: 10.3390/pharmaceutics8030027, PMID 27589789.
33. Abdelbary GA, Aburahma MH. Oro-dental mucoadhesive proniosomal gel formulation loaded with lornoxicam for management of dental pain. J Liposome Res. 2015 Apr 3;25(2):107-21. doi: 10.3109/08982104.2014.941861, PMID 25058447.
34. M Abdou E, M Ahmed N. Terconazole proniosomal gels: effect of different formulation factors, physicochemical and microbiological evaluation. J Pharm Drug Deliv Res 2016;5:1. doi: 10.4172/2325-9604.1000144.
35. Abdelbary GA, Amin MM, Zakaria MY. Ocular ketoconazole-loaded proniosomal gels: formulation, ex vivo corneal permeation and *in vivo* studies. Drug Deliv. 2017 Jan 1;24(1):309-19. doi: 10.1080/10717544.2016.1247928, PMID 28165809.
36. Khalil RM, Abdelbary GA, Basha M, Awad GE, El-Hashemy HA. Design and evaluation of proniosomes as a carrier for ocular delivery of lomefloxacin HCl. J Liposome Res. 2017 Apr 3;27(2):118-29. doi: 10.3109/08982104.2016.1167737, PMID 27079800.
37. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): fabrication, characterization, pharmaceutical and cosmetic applications. Eur J Pharm Biopharm. 2019 Nov 1;144:18-39. doi: 10.1016/j.ejpb.2019.08.015, PMID 31446046.
38. Sahoo RK, Biswas N, Guha A, Sahoo N, Kuotsu K. Nonionic surfactant vesicles in ocular delivery: innovative approaches and perspectives. BioMed Res Int. 2014 Jan 1;2014:263604. doi: 10.1155/2014/263604, PMID 24995280.
39. Ibrahim SS. The role of surface active agents in ophthalmic drug delivery: a comprehensive review. J Pharm Sci. 2019 Jun 1;108(6):1923-33. doi: 10.1016/j.xphs.2019.01.016, PMID 30684539.
40. Aboali FA, Habib DA, Elbediawy HM, Farid RM. Curcumin-loaded proniosomal gel as a bio friendly alternative for treatment of ocular inflammation: *in vitro* and *in vivo* assessment. Int J Pharm. 2020 Nov 15;589(3):119835.
41. Emad Eldeeb A, Salah S, Ghorab M. Proniosomal gel-derived niosomes: an approach to sustain and improve the ocular delivery of brimonidine tartrate; formulation, *in vitro* characterization, and *in vivo* pharmacodynamic study. Drug

Deliv. 2019 Jan 1;26(1):509-21. doi: 10.1080/10717544.2019.1609622, PMID 31090464.

42. Fouda NH, Abdelrehim RT, Hegazy DA, Habib BA. Sustained ocular delivery of Dorzolamide-HCl via proniosomal gel formulation: *in vitro* characterization, statistical optimization, and *in vivo* pharmacodynamic evaluation in rabbits. Drug Deliv. 2018 Jan 1;25(1):1340-9. doi: 10.1080/10717544.2018.1477861, PMID 29869516.
43. Abreu CR. On the relationship between the hydrophilic-lipophilic balance and the nano architecture of nonionic surfactant systems. J Surfactants Deterg. 2019 Jan;22(5):1001-10.
44. Sayed S, Abdelmotelab M, Amin MM, Khowessah OM. Effect of formulation variables and gamma sterilization on trans corneal permeation and stability of proniosomal gels as ocular platforms for antiglaucomal drug. AAPS PharmSciTech. 2020 Apr;21(3):1-3.
45. Somjid S, Krongsuk S, Johns JR. Cholesterol concentration effect on the bilayer properties and phase formation of niosome bilayers: a molecular dynamics simulation study. J Mol Liq. 2018 Apr 15;256:591-8. doi: 10.1016/j.molliq.2018.02.077.
46. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. J Control Release. 2014 Jul 10;185:22-36. doi: 10.1016/j.jconrel.2014.04.015, PMID 24747765.
47. Uchegbu IF, Florence AT. Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. Adv Colloid Interface Sci. 1995 Jun 27;58(1):1-55. doi: 10.1016/0001-8686(95)00242-I.
48. Hsieh CJ, Chen YW, Hwang DW. Effects of cholesterol on membrane molecular dynamics studied by fast field cycling NMR relaxometry. Phys Chem Chem Phys. 2013;15(39):16634-40. doi: 10.1039/c3cp51739j, PMID 23965762.
49. Akhilesh D, Faishal G, Kamath JV. Comparative study of carriers used in proniosomes. Int J Pharm Chem Sci. 2012;3:6-12.
50. Verma S, Singh B, Katare OP. Proniosomal gel based delivery system of aceclofenac for ocular delivery with improved safety and efficacy. Acute Med Research. 2018;1(1):1-7.
51. Dhangar R, Bhowmick M, Parihar SS, Upmanyu N, Dubey B. Design and evaluation of proniosomes as drug carrier for ocular delivery of levofloxacin. J Drug Deliv Ther. 2014 Sep 14;4(5):182-9.
52. Keay LJ, Gower Ew, lovieno A, Oechsler RA, AlfonsobEc, Matoba A, Cavanagh D, Lee SM, Irvine J, Stulting RD, Mauger TF, Schein OD. Clinical and microbiological characteristics of fungal keratitis in the United States, 2001-2007: a multicenter study. Ophthalmology. 2011 May;118(5):920-6.
53. Satpathy G, Ahmed NH, Nayak N, Tandon R, Sharma N, Agarwal T. Spectrum of mycotic keratitis in north India: sixteen years study from a tertiary care ophthalmic centre. J Infect Public Health. 2019 May-Jun;12(3):367-71. doi: 10.1016/j.jiph.2018.12.005, PMID 30600158.