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

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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 niosome 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

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 Prioniosomes 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 cut 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 proniosme and emerged as a potential drug delivery system in every aspect [11].
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 isofom 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.

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 protasome-based gel gels prepared by the coacervation phase separation method detailed in the methods below.

Advantages of proniosome delivery system [16-18]
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>BCS class</th>
<th>Method</th>
<th>Merit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline HCL</td>
<td>BCS class I</td>
<td>Hydrophilic</td>
<td>Improve Keratolytic, high EE%, Drug proniosome exhibits better keratolytic activity</td>
<td>[22]</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>BCS class I</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[23]</td>
</tr>
<tr>
<td>Vincocetine</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[24]</td>
</tr>
<tr>
<td>Candesartan Cilexetil</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[25]</td>
</tr>
<tr>
<td>Acemetacin</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[26]</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[27]</td>
</tr>
<tr>
<td>Betaxolol HCL</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Drug proniosome exhibits better keratolytic activity</td>
<td>[28]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>BCS class</th>
<th>Method</th>
<th>Merit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cromolyn</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Dry proniosome increases in capsule enhances bioavailability</td>
<td>[29]</td>
</tr>
<tr>
<td>Sodium</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Dry proniosome increases in capsule enhances bioavailability</td>
<td>[30]</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Dry proniosome increases in capsule enhances bioavailability</td>
<td>[31]</td>
</tr>
<tr>
<td>Ketoqrenin</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Dry proniosome increases in capsule enhances bioavailability</td>
<td>[32]</td>
</tr>
<tr>
<td>Fluibipronin</td>
<td>BCS class II</td>
<td>Hydrophilic</td>
<td>Dry proniosome increases in capsule enhances bioavailability</td>
<td>[33]</td>
</tr>
</tbody>
</table>

### Spray coating method [23, 24]

The spray coating method was introduced by Hu and Rhodes et al. in 1999. It involves the use of a dry, free-flow proniosome. The spray coating method involves mixing surfactant: cholesterol in the required ratio and dissolving in a solvent. The carrier is taken in a round bottom flask attached to a rotary evaporator apparatus. The solution is then sprayed on the carrier in a controlled manner to form a gel. The spray method is simple, requires less equipment, and is a cost-effective method for ocular drug delivery.

### Coacervation phase method [26, 27]

Proniosome-based gel, a liquid crystalline structure consisting of a lamellar micellar model, with 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 at 60-70 °C until lipid is completely dissolved. Cover the mouth to prevent solvent loss. In a vial, the solution is formed at 60 °C, 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 °C until a clear or translucent solution is obtained. The solution is then cooled 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 niosome and Proniosome [30]; the surfactant is classified by charge present on the polar head group, namely as non-ionic, anionic, cationic and amphoteric. 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 proniosome 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 Lomeloxacin HCl 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 Hydroxy 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].
A. Patel et al.


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

<table>
<thead>
<tr>
<th>Surfactant series</th>
<th>Common name</th>
<th>Chemical name</th>
<th>HLB value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Span</td>
<td>Span20</td>
<td>Sorbitan Monolaurate</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Span40</td>
<td>Sorbitan Monopalmitate</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Span60</td>
<td>Sorbitan Stearate</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Span65</td>
<td>Sorbitan Monostearate</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Span80</td>
<td>Sorbitan Monostearate</td>
<td>4.3</td>
</tr>
<tr>
<td>Tween</td>
<td>Tween20</td>
<td>Polyoxylethylene 20</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Tween40</td>
<td>Sorbitan Monopalmitate</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>Tween60</td>
<td>Polyoxylethylene 20</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Tween80</td>
<td>Sorbitan Monostearate</td>
<td>15</td>
</tr>
<tr>
<td>Brij</td>
<td>Brij35</td>
<td>Polyoxylethylene(23)</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>Brij52</td>
<td>Polyoxylethylene(2)</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Brij72</td>
<td>Polyoxylethylene(2)</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Brij92</td>
<td>Polyoxylethylene(2)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Brij98</td>
<td>Polyoxylethylene(2)</td>
<td>15</td>
</tr>
<tr>
<td>Poloxamer</td>
<td>Poloxamer 188</td>
<td>Propylene Glycol</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Poloxamer 188</td>
<td>Polyoxylethylene(2)</td>
<td>29</td>
</tr>
<tr>
<td>Cremophor</td>
<td>Cremophor RH40</td>
<td>Hydrogenated castor oil</td>
<td>14-16</td>
</tr>
<tr>
<td></td>
<td>Cremophor EL35</td>
<td>Hydrogenated castor oil</td>
<td>13.5</td>
</tr>
</tbody>
</table>

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 High Entrapment Efficiency while high surfactants give low Entrapment Efficiency. Some common nonionic surfactants used in proniosome are shown in Table 5.

## Cholesterol

Cholesterol in proniosome-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 cholesterol 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 Brimonidine 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 cilexte. Verma et al. 2012 use Sorbitol as a
carrier for the parenteral drug delivery of Flurbiprofen [50]. Abd-
Elbar 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>
<thead>
<tr>
<th>Route</th>
<th>Benefits</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>Highly patient compliance, self-administrable and non-invasive.</td>
<td>Cornea acts as barrier, tear dilution and turn overrate, nasolacrimal drainage.</td>
</tr>
<tr>
<td>Intracameral</td>
<td>Drug delivery to anterior segment, Reduce corneal and systemic side effects.</td>
<td>Toxic anterior segment syndrome and Thyroid eye disease.</td>
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<tr>
<td>Sub conjunctival</td>
<td>Delivery to anterior and posterior segment, site for depot formulation.</td>
<td>Conjunctival and choroidal circulation.</td>
</tr>
<tr>
<td>Retro bulbar</td>
<td>Administer high local doses of anesthetics, more effective and minimal influence on IOP.</td>
<td>Hemorrhage, globe perforation And respiratory arrest.</td>
</tr>
</tbody>
</table>

### 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 noisome for ocular delivery was formulated by Qi li et al. to
treat ocular anti-allograft rejection. Tacrolimus drug is highly
hydrophobic and has 82.25 MD 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 0.2±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 7.21±0.06 dynes/cm. Entrapment efficiency (EE %) of the derived
noisome by hydration in normal saline is high at 95.3±0±02%. The
stability of Tacrolimus loaded proniosome is studied for 3 mo at
various temperatures (4℃, 25℃, 40℃), and no to
90 ratios have suitable release. Morphology after hydration is seen
in Table 4: Ocular route of administration with benefits and challenges [1, 22, 49]

<table>
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<td>Administer high local doses of anesthetics, more effective and minimal influence on IOP.</td>
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</tr>
</tbody>
</table>

**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 the 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
Bioavailability. In 2017, Ketoconazole required multiple dosing and provided poor weight, hindering penetration in the cornea. Ophthalmic formulation of lipophilic drugs is low solubility in water and having high molecular weight. A method employed was the coacervation-phase method using surfactants to evaluate the preformation of KET proniosomal gel in the ocular model. 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 from 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 completely dissolve in the bilayer. Particle size range from nano to micron after hydration of proniosomal gel to noisomes, increasing surfactant/lipid ratio leads to increase particle size, increased cholesterol increased hydrophobicity of particle has increased size due to decreased solubility of 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 release 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, Fauzo H. N et al prepared proniosomal gel of Dorzolamide HCL, 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 qasch 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 HCL 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 blood 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 increased 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 redness or change was reported. Drazee 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 noisomes [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, Abdelmolotab 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), Phorunic L121, Phorunic 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 alkylic 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 value, 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. PPS exhibit well-identified shape and morphological properties. Ex vivo permeation of optimized formulation consists of Surtanactant 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 administered 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 Shurry method. Weighted amount of span 60 surfactants, cholesterol and methanol in the round bottom flask are mixed with heating finally add Maltodestrin 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 noisomes in Carbopol 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 hydrochloride

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 proniosomal gel. Betaxolol HCL, prepared Betaxolol HCL proniosome are subjected to various evaluation parameters for ocular delivery. Entrapment efficiency and drug release while 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 enhanced 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 and occurs as a defensive phenomenon, being a natural herbal medicine, solubility, limited bioavailability and absorption are known drawbacks of herbal drugs. In 2020, Abuali 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 method. The method 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, it is hydrated; produced noisome dispersion is evaluated for Size determination, found out that dispersion is in nano size (192.5±0.2-76.6±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 than1 (0.36-0.68). Zeta potential causes great electro repulsion between vesicles thus low aggregation in noisome dispersion. All Curcumin loaded proniosomal gel showed noisome how negative high Zeta potential due to the presence of a free hydroxyl group in surfactant and liquids. Low Zeta Potential value of Cremophore (Fcr250, Fcr300 and Fcr350) with an increase in amount indicates in stability, thus formulation should best or edn 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 °C) providing highly ordered bilayer, thus Fcr 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 leaky membrane. Cremophore used formulation show less 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 formation. 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 release curcumin with increasing concentration there will be a significant enhancement in the release of curcumin as hydrophilic surfactants dissolve hydrophobic salure in an aqueous medium better than hydrophobic surfactants. Membrane stabilizer cholesterol and lecithin reduce leakage and stabilized the bilayer kept constant. Selected formulation Fcr350 subjected to lyophilization showed 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±5.25) 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 noisomes will improve its ability to target tissues where it is needed. Proniosomes created by academics and researchers. Niosomes that are produced from protostomes are niosomes 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 niosomes 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 niosomes 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 niosomes 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 niosomes 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

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