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LIPID-BASED EYE DROP FORMULATIONS FOR THE MANAGEMENT OF EVAPORATIVE DRY EYES

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ABSTRACT

Dry eye is a common and ongoing condition where the eyes don't produce enough tears, i.e., the quantity and/or quality of tears produced is insufficient. This leads to discomfort, irritation, and sometimes blurry vision. Over time, it can become a persistent problem that is harder to manage if it is left untreated. The primary cause of evaporative dry eyes is abnormal lipid production, which may occur because of meibomian gland dysfunction. This paper focuses on the treatment alternatives that utilize lipids for the treatment of evaporative dry eyes. The main idea behind developing these lipid-containing eye drops is that they aim to mimic the natural lipid layer of the eye. These lipid-containing eyedrops, can help to reduce the symptoms and manage the discomfort caused by evaporative dry eyes more effectively. Tear-film-oriented diagnosis (TFOD) is a method that is used to identify the specific cause of tear film instability. In TFOD the fluorescein breaks-up pattern of tear film plays a crucial role, by analysing how and where the tear film breaks on the eye surface. The lipids commonly used in the commercial formulation of evaporative dry eye treatment include various ionizable cationic lipids, mineral oil, cholesterol, and, PEGylated lipids. This literature suggests that eye drops containing lipids can help to reduce the symptoms of evaporative dry eyes and improve the comfort and quality of life for people who are suffering from this condition.

KEYWORDS: Evaporative dry eye, Lipid containing eye drops, Meibomian gland dysfunction, Lipid layer, Tear film instability.

1. INTRODUCTION

1.1 Evaporative Dry Eyes

Dry eye is a complex disease that arises because of inadequate tear quantity, inadequate blinking**,** decreased wettability of the ocular surface, incomplete eyelid closure, and instability of tear film. Which may result in the degradation of the tear film, damage/inflammation of the ocular surface and hyperosmolarity of the tear film. The signs and symptoms of evaporative dry eyes include burning, redness, ocular dryness, the feeling of roughness in the eyes, and photophobia.

Dry eye disease can be divided into 2 types i.e. aqueous tear deficient dry eye & evaporative dry eye. Aqueous tear deficient arises because of either Sjogren's syndrome (which is an autoimmune disorder, in this disorder, the body's immune system attacks its healthy cells which are responsible for the production of tears and saliva) or it can be caused because of lacrimal gland insufficiency (reduction in tear volume). Evaporative dry eyes occur because of various factors which include reduced blinking, vitamin A deficiency, exposure to air pollution, use of contact lenses, etc. The primary cause of evaporative dry eyes is abnormal lipid production which occurs because of meibomian gland dysfunction. When the lipid layer is inadequate or thin, it cannot create a smooth & uniform tear film. Which causes the tears to evaporate rapidly and decreases the stability of the tear film.[1]

1.2. Eye Barriers

The eye is a highly complex and unique organ in the body. This complex system is divided into 2 types according to their anatomical site i.e. anterior segment & posterior segment. These segments act as barriers, which make the eye an immune-privileged site, which positively suppresses certain inflammatory and immune responses and also creates a challenge for the penetration of drugs. Anterior segment barrier consists of tear film, cornea, conjunctiva & sclera. The posterior segment barrier consists of a blood-aqueous barrier, choroid & blood-retinal barrier.

In general, drugs easily reach's the anterior segment of eyes after non-invasive topical administration such as eye drops and ointments, but drug have difficulty to reach posterior segment of eye. In the anterior segment of eye, the tear film act as first defensive mechanism to protect the eye against foreign substances which also include topical ophthalmic preparation such as eye drops and eye ointments.

The tear film is composed of 3 layers. The first layer is the outer lipid layer, lipids are secreted from the meibomian gland, these lipids are responsible for preventing the evaporation of water and also maintain the stability of the tear film. The 2nd layer is an aqueous layer. The 3rd layer is the inner layer which is known as glycocalyx. 3rd layer consists of goblet cells, which are responsible for the production of mucin secretion. Mucin are large glycoprotein of high molecular weight which are negatively charged. The gel which is formed by mucin limits the permeability of large molecules because of its pore size (550±50 nm).[2]

1.21 Tear Film Lipid Layer (TFLL)

TFLL consists of 2 lipid layers i.e. outer non-polar lipid layer and the inner polar lipid layer. These lipids are secreted by meibomian glands, secretion of this gland is controlled by neuronal, hormonal & vascular factors.

The outer non-polar lipid layer consists of non-polar lipid molecules like cholesterol esters, wax esters, monoglycerides, diglycerides, triglycerides, diesters, free sterols, and free fatty acids. The inner polar lipid layer consists of polar lipid molecules like omega-hydroxy fatty acids and phospholipids. This polar layer creates an interface with the aqueous layer, which in turn reduces the surface tension of the tear, increases tear viscoelasticity, and further optimizes the arrangement of the tear molecules to control its surface-wetting properties.

TFLL act as a protective barrier any change in its thickness, composition or spreading can lead to increase in the rate of tear evaporation. Tear film instability, evaporation, thinning and break-up are strongly influenced by the tear film lipid layer.[3,4]

1.3. Meibomian Gland /Meibomian Gland Dysfunction

Meibomian glands are the exocrine glands which are found in the upper and lower eyelids. These glands release they product called meibum. Lipids which are present within the meibum shows multiple protective effects at the ocular surface i.e. forming a smooth optical surface for the cornea & reduces the surface tension of tear film.

The function of the meibomian gland is to maintain homeostasis at the ocular surface. Meibomian gland dysfunction is a common disorder. In MGD, meibomian glands are either blocked or the quantity and quality of the lipid produced is altered. Blockage or inflammation of the meibomian gland causes meibum statis, bacterial proliferation, and increased

production of lipase and esterase, which result in lipid degradation, secretion of lipid decreases, and the ability to stabilize the tear film are also reduced. Basic treatment of MGD involves the improvement in daily habits such as maintenance of lid hygiene i.e. application of hot compression and modification of dietary habits.[5]

1.4. Diagnosis And Advance Treatment for Evaporative Dry Eyes

1.4.1 Diagnosis of Evaporative Dry Eye

1. *Tear film stability analysis system*

Tear film stability analysis system involves the evaluation of tear film stability through fluorescein break up time. This test is most widely used test which can performed in any ophthalmic facility. Tear film stability can be assessed by taking corneal topography images immediately after and 10s after eye opening, after this TSAS (tear stability analysis system) enables the evaluation of continuous images of corneal tomography.

2. *Measurement of tear volume at the tear meniscus*

Strip meniscometry is a device which is used to measure the amount of tears, by using a special water absorbing material. Strip meniscometry tube has a tear absorbent which consists of non-woven fabric sandwiched between 2 sheets of polyethylene. Testing should be done from the lateral side to avoid irritation to cornea. Amount of tear fluid which is retained in the tear meniscus can be measured in about 5 seconds.

3. *Fluorescein break-up time*

Instil fluorescein dye and measure the time until tear film break-up. If the tear film break-up in less than 10 sec then it indicates the instability of tear film.

1.4.2. Advanced Treatment Of Evaporative Dry Eye

1. *Aqueous layer treatment*

- Artificial tears: Artificial tear eye drops contain thickening agents such as methylcellulose and/or hyaluronic acid which improves the retention of water on the surface of the eye. Artificial tears are also used in combination with aqueous secretagogue diquafosol sodium.
- Aqueous secretagogues: Diquafosol sodium is an aqueous secretagogue which act on p2y2 receptors which are present in the cornea and conjunctiva, function of this is to promote the secretion of water through increase in the intracellular calcium concentration.

2. Ocular *surface mucin treatment*

- Mucin secretagogues: Diquafosol ophthalmic solution is a p2y2 receptor agonist. The p2y2 receptor is present in various tissues across the body. p2y2 receptors are present in goblet cells, kerato-conjuctival epithelial cells, and meibomian glands on the surface of the eye. Diquafosol induces the secretion of water from the cornea and conjunctival epithelium and also acts upon goblet cells which promote the secretion of secretory mucin.

3. *anti-inflammatory treatment*

Cyclosporine: Cyclosporine is prescribed as an eye drop. Cyclosporin A (CsA) decreases the t-cell activation through interleukin-2. The side effect which is reported by the use of cyclosporin (CsA) instillation is a burning sensation, this side effect can be reduced by combined use of steroid eye drops.[6]

2. LIPID BASED EYE DROP FORMULATION

2.1. Ionizable Cationic Lipids

Ionizable lipids typically consist of 3 primary compounds hydrophilic amine (head group), hydrophobic lipid (tail), and an intermediate linker region that joins these different components. Hydrophilic amine (head group), mainly consists of amines i.e. 1^0 amines, 2^0 amines, 3^0 amines, heterocyclic groups, and guanidine. Depending upon the number of amines groups present in the head group cationic lipids are categorized as mono-amino lipids (or) poly-amino lipids. The size and charge density of the hydrophilic head group affect the acid dissociation constant (PKA), stabilization, and interaction with the cell membrane and increase the lipid nanoparticle output. DLin- MC3-DMA (MC3), ALC-0315, SM-102, ionizable cationic lipids, which have mono-amino lipids in the head region. These lipids are approved by the US. Food and Drug Administration (FDA) for RNA transport. None of these 3 ionizable cationic lipids are biodegradable, which accumulates in the body and leads to cytotoxicity. Ionizable polyamine cationic lipids ionize more strongly than mono-amino groups. Several known lipids have been developed, which include 3060i10, CKK-E12, C12-200, and TTT3.[7]

The Linker fragment connects the hydrophilic head group to the hydrophobic tail chain. Common linkage bonds that connect the head & tail include esters, ethers, carbamates, hydrazines, hydroxyl amines, thioesters, ethanolamines, and amides. These linker fragments influence the stability, biodegradability, and transfection efficiency of lipid nanoparticles

(LNPs). Biodegradable binding fragments are selected because of their rapid in-vivo elimination, which facilitates multiple administration of drugs, and lowers the occurrence of side effects.

The hydrophobic nature of the tail region shows an effect on the pKa, lipophilicity, membrane mobility, and fusion characteristics, which further impacts the nucleation and functional efficacy of lipid-based nanoparticle formulation. Cholesterol, alkane chains, and tocopherol derivatives, which vary in their saturation levels, function as hydrophobic entities. Insertion of hydrophobic cholesterol in the tail chain results in effective quenching. The empirical pka values, which represent the acid dissociation constant of lipid molecules influence the efficacy of the nanoparticle delivery mechanism and the associated transport functionality. The nature of various ionizable cationic lipid components influences the whole formulation and biological properties of lipid nanoparticles (LNPs).[8]

2.2. Mineral Oil

The formulations that contain mineral oil and many other excipients are designed to spread on the ocular surface and reform the muco-aqueous layer. Mineral oil can be formulated as mono-emulsion by using anionic phosphatidylglycerol (Systane ®complete eye drops) and it says that this phospholipid will migrate within the tear film and renew the lipid layer during normal blinking which stabilizes the tear film up to 8 hours. Mineral oil nanoemulsion reduces the friction effects of the cells and shows long-lasting lubrication.[9]

2.3. Cholesterol

Cholesterol functions as an extra lipid, which enhances the robustness of the nanoparticle and results in interaction with the cell membrane. A cholesterol concentration of 40 is essential for optimal maintenance of particle stability, functionality & structural integrity and ensure vaccine efficacy. Recent findings have highlighted a dynamic role of cholesterol in lipid nanoparticles, i.e. cholesterol migrates from LNP core to lipid shell upon exposure to apolipoprotein E.

The result suggests that even though cholesterol is relatively inert when compared to ionizable lipids, cholesterol, and its derivatives can influence the cellular recognition and trafficking pathways potentially affecting biodistribution and efficacy. Patel and his team have created a series of LNPs that incorporate bile acids instead of cholesterol, using varying

amounts of these bile acids. They have shown that these modified nanoparticles (VNPs) can enhance the transport of mRNA from the liver to the spleen, both in vitro and in vivo.[10]

2.4. PEGylated lipids

PEGlipids make up a small part of LNP, usually 1.5%. Despite this, they also strongly impact key properties like the size, and distribution of particles preventing them from clumping and improving their stability during preparation and storage. Polyethylene glycol lipids play an important role in regulating the encapsulation efficacy of nucleic acids, extending the circulatory half-life of NP, influencing in vivo biodistribution, enhancing transfection efficiency, and regulating immune responses towards LNP formulations.[11]

Another purpose of PEG ligands is to modify the surface of the LNPs. "Functionalized PEGlipids allow lipid nanoparticles bind with ligands or biomolecules. PEG is generally considered as non-immunogenic but anti-PEG antibodies have been found. These antibodies increase the removal of LNP from the blood stream and activate the immune system. Researchers are exploring alternatives to PEG, but it is still the most widely used lipid to extend the circulation time of LNPS.[12]

3. PHYSICOCHEMICAL PROPERTIES OF DRUGS USED FOR OCULAR DISEASE

Studying a drug's physicochemical properties is the 1st step in developing a drug delivery system for NLC.

(nanostructured lipid carriers) and SLNC (solid lipid nanoparticle). One of the key factors to check is the drug's lipophilicity, lipophilicity of the drug is important because the drug must be evenly dissolved and distributed in the lipid matrix. These types of formulations typically consist of 10-22 % of lipid phase and 80-90% of aqueous phase. If the drug has high water solubility, it might not property encapsulate in the lipid nanoparticle. As a general guideline, drugs with a log p of at least 2 are considered good candidates for lipid formulation. The ideal drug physicochemical properties of these systems include the drug molecule must be base or neutral, have a low melting point (less than 150^0), and have few polar groups. The melting temperature is linked to the crystal lattice energy, which affects the drug solubility in both the aqueous and lipid phases.[13]

Drugs lipophilicity and water solubility are important for preparing of lipid based nano system. But they are not the only factor which affect the drug loading and encapsulation

efficiency. Other factors, such as the type of lipid used, its concentration and the method of preparation also plays a crucial role in the drugs entrapment in NLC and SLN formulation.[14] Prepared amphotericin B NLC for ocular delivery had a log D -2.31 at PH 7.4, the lipid phase consisted of precirol®ATO 5 as the solid lipid, castor oil as the liquid lipid, and PEG (mPEG-DSPE, for PEGylated NLC) or che-mophor®EL (for non-PEGylated NLC) as surfactants, aqueous phase includes tween® 80 and poloxamer 188 as surfactants. Then NLC was prepared by using hot emulsification followed by high-pressure homogenization. The amount of amphotericin B, castor oil, PEG, and the number of cycles was optimized using a box-behnker design to improve the formulation. "Lipid formulations are complex mixtures of drugs, lipids, surfactants, and co-solvents. This type of formulation can be prepared using various methods, each with different parameters like temperature, pressure, cycles, and agitation. As a result, various factors need to be studied to optimize the critical quality attributes of nanoparticles which can affect the drug product's performance for ocular delivery.[15]

4. DEVELOPMENT OF LNP

Preparation method

The introduction of enhanced strategies for (LNP) formulation, leveraging conventional preparation methodologies, represents a significant advancement in drug delivery. The T-junction blending method, for instance, facilitates the controlled and efficient combination of the organic and aqueous phases. This approach resulted in the generation of lipid nanoparticles that encapsulated plasmid DNA (pDNA) or small interfering RNA (siRNA) which are crucial for the delivery of genetic material to the target cell. Microfluidic techniques like "Microfluidic hydrodynamic focusing" (MHF) and "staggered herringbone mixing" (SHM) have been further modified to improve LNP production. These microfluidic methodologies allow precise control over the mixing and formation of particles at a microscale which leads to better control over size and homogeneity of the NPs.[16] These rapid mixing methodologies used in the production of lipid nanoparticles indeed after several notable advantages, like improved control over the physicochemical properties of nanoparticles, enhanced encapsulation efficiencies, and greater stability of nanoparticles. These advantages make rapid mixing an alternative to conventional methods.

Incorporation of larger quantities of organic solvents during the production of nanoparticles is a significant disadvantage. Ethanol is often used as a solvent because it is easy to remove

through dialysis, but the presence of ethanol in the final product poses a potential risk. The residual solvent quantities are tightly regulated by guidelines to ensure patient safety especially for non-enteric therapies. Another disadvantage of the rapid mixing system is the limited solubility of certain lipids in ethanol, which leads to a low concentration of LNP in the final solution which affects the efficiency and feasibility of the production. Balancing solvent removal, lipid solubility, and LNP concentration remains a critical challenge in optimizing rapid mixing processes for industrial and therapeutic applications.[17,18]

Ultrafiltration particularly "Tangential flow filtration" (TFF) is an effective technique for concentration in LPN suspension. TFF is commonly employed to increase the concentration of the nanoparticles after their formulation, especially in large-scale production. TFF allows the separation of excess solvents and impurities, while concentrating nanoparticles, which is important for higher production of nanoparticles and ensures the quality of final formulation.

"lyophilization" or "freeze-drying" is indeed a powerful strategy for increasing the shelf life of the LNPs. By removing the internal moisture under controlled conditions, lyophilization helps to preserve the stability of NP. The development of rotary freeze-drying technology introduces an innovative approach to the synthesis of lipid nanoparticles.

Cryoprotectants are essential during freeze drying process of lipid nanoparticles. Cryoprotectants help preserve the structure of nanoparticles and biological activity by preventing damage to cells during the freezing and drying phase. The choice of cryoprotectants significantly influences the final product. A variety of cryoprotectants have been evaluated for use with lipid nanoparticles which include monosaccharides (glucose, fructose, mannitol, etc), disaccharides (sucrose, lactose, maltose, etc), polysaccharides, and various hydrophilic polymers (polyvinylpyrrolidone, gelatine).[19]

5. POTENTIAL RISK OF LNP IN EYE CARE

LNP has shown great promise in the treatment of eye conditions, especially for delivering RNA. Base therapeutics such as mRNA and small interfering RNA (siRNA), however, the potential hazards that are associated with LNPs in ocular application should not be overlooked. One of the concerns is the risk of inflammatory disease in the eye, over time which leads to various complications. Inflammatory responses in the eye can be concerning because the ocular environment is delicate and persistent inflammation results in complications like compromised vision, tissue damage, and long-term conditions such as

retinal degeneration on macular edema. LNP-associated inflammatory damage is rarely reported, but the use of RNA-LNP in an inflammatory condition leads to increased inflammation.[20]

Another potential risk which is associated with the use of intraocular LNP is thrombosis which is independent.

Upon the formulation of LNP. Thrombosis in the eye can lead to significant complications including macular edema and neovascular glaucoma. The anticoagulant therapy is a standard treatment to reduce the risk of thrombosis. It is important to carefully evaluate the properties of each anti-coagulant to ensure that LNP activity is preserved.

LNP must remain stable in the ocular environment for effective drug delivery. The ocular surface is complex and various factors, such as enzyme activity, salt concentration and tear film components can potentially impact the stability of LNP.[21] This can lead to either premature (or) uncontrolled drug release, which would undermine the therapeutic efficacy of the treatment. In addition, LNP is generally considered to be relatively safe nanocarriers, but it's crucial to investigate their long-term safety and potential toxicity.[22]

6. FUTURE OF LNP IN OPHTHALMOLOGY

LNP can be targeted to specific eye tissues by altering their surface properties, such as modifying lipid composition or by adding targeting ligands. This improves the local effectiveness of the treatment while reducing the systemic side effects. LNP's can be used in eye drops or for drug delivery to treat ocular diseases.[23] The nano size of LNP allows them to pass through the cornea and the ocular tissues, which improves drug absorption and enhances therapeutic efficacy. LNP vectors can also deliver gene-modified therapies to the ocular tissue which help to treat both hereditary and non-hereditary eye diseases.

LNP can aid retinal regeneration by encapsulating stem cells or other regeneration therapeutic agent in LNP. This LNP's are targeted to damaged retinal tissues to promote retinal regeneration and repair.[24]

Table 1: marketed products.

S.NO	Name of the product	Drug (active ingredient)	Lipid used	MFG by company	Formulation
1.	Refresh mega-3	Carboxymethyl cellulose sodium (0.5%) Glycerine (1%) Polysorbate 80 (0.5%)	Flaxseed oil & castor oil	Allergan	Liquid solution
2.	OPTASE MGD advanced dry eye drop	Glycerine (0.9%)	Olive oil	Scope Health Inc	Lipid microemulsion
3.	Refresh optive advance	Carboxymethylcellulose (0.5%) Glycerine (0,9%) Polysorbate 80 (0.5%)	Castor oil	Allergan	Emulsion eye drop
4.	Systane ® complete	Propylene glycol (0.6%)	Mineral oil	Alcon laboratories Inc.	Emulsion
5.	Freshkote	Polyvinyl alcohol (2.7%) Povidone (2.0%)	Mineral oil	Eyevance pharmaceuticals	Solution

CONCLUSION

The eye is the only organ of the central nervous system, that reaches the body's surface and it has several protective mechanisms to protect the body against external threats. These include structures like cornea, conjunctiva & sclera, which make it challenging to deliver drugs directly to the affected areas of the eye. Dry eye can be divided into aqueous tear-deficient dry eye & evaporative dry eye. Although the available data shows potential for lipid-based eye drops to treat evaporative dry eye by improving the lipid tear film structure and thickness. Developing new lipids or improving the existing ones with unique properties for lipid nanoparticle therapy could help to make the treatments more effective and targeted. Various lipids that are used in the formulation of lipid-based eye drops include ionizable cationic lipids, mineral oil, cholesterol, PEGylated lipids, etc. Lipid nanoparticles with their nanoscale size and suitable lipid matrix, can cross the ocular barriers effectively and potentially reduce the required dose for the desired effect. Using “lipid-based eye drops" along with treatment like cyclosporine, omega-3 supplements, and lid wipes may help to improve the treatment of evaporative dry eyes.

In conclusion, lipid-based eye drops show promise in managing evaporative dry eye by improving tear film’s structure and thickness. However, more research innovative, and well-

designed clinical trials are needed to enhance their effectiveness and ensure better treatment outcomes.[25]

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