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The Niosomes: An Overview In Ocular Drug Delivery System As An Advanced Approach

Devesh Singh*[1], Kuldip Kumar Savita[2], Akhilesh Kumar Mishra[3], Khushboo Mishra[4],Deepika Shakya[5]

[1,2,3,4,5,]Smt. Vidyawati College of Pharmacy, Gora Machhiya Kanpur Road, Jhansi, U.P. (284121)
Email id-kuldeep.academic04@gmail.com and singhdeveshjhansi1998@gmail.com

ABSTRACT

Eye infections are a common issue in primary care and a significant healthcare concern. Conditions such as conjunctivitis, epithelial keratitis, and glaucoma represent prevalent infectious diseases affecting the eye. Patients afflicted with these infections commonly experience symptoms such as inflammation, eye pain, redness, watery release, and unclear vision. Topical formulations are recommended for treating eye infections due to their ease of use. However, effectively delivering drugs to various eye structures and addressing ocular problems presents challenges.Presently, topical eye drops are the primary method for treating anterior eye conditions. Regrettably, these ophthalmic solutions are quicklyeliminated from the eye's surface, resulting in limited drug availability. Therefore, the progress of innovative drug delivery systems capable of sustaining drug concentration over extended periods is essential. Nanotechnology has emerged as a promising field in ophthalmology, offering specialized carriers like Niosomes, Liposomes, and polymer-based vesicles to enhance drug transfer and release, thus improving drug effectiveness.Niosomes, in particular, have garnered attention due to their stability in comparison to Liposomes, which can degrade under specific conditions. Niosomes are created by the mixture of non-ionic surfactants and cholesterol using different strategies such as Thin Film Hydration, Ether Injection, Sonication, Reverse Phase Evaporation, Bubble Formation, Hand Shaking, Heating, Freeze and Thaw, among others. These Niosomes can then be transformed into Niosomal Gel by incorporating Carbopol 934. The prepared Niosomal Gel is subject to evaluation through various parameters, including Transmission Electron Microscopy, Entrapment Efficiency, pH Determination, Stability Analysis, Viscosity Measurement, and In Vitro Drug Release, among others.

Keywords: Niosomes, Niosomal Gel, Infection, Eye, Technique,Bioavailability, Liposomes.

Abbreviations:PBS- Phosphate buffer solution, TFH- Thin film Hydration, SUV- Small unilamellar vesicle, LUV- Large unilamellar vesicle, MLV- Multilamellar vesicle.

1. Introduction:

Ocular drug delivery poses significant challenges for drug scientists because of the novel and pharmacokinetically explicit climate of the eye. The eye's particular life structure considers uniquenature that allows local drug delivery and non-invasive medicaltreatment of disease. **Biswas Roy Gopa et al., (2017)**

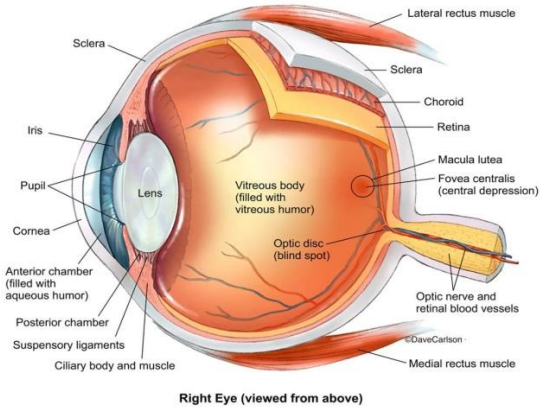

Figure 1: Anatomy of Eye

Delivering drugs topically to different compartments of the eye is a complex task. Topical eye drops are commonly used for anterior ocular therapy, targeting areas such as the conjunctiva, cornea, sclera, and anterior uvea. **Urtti A. et al., (2016)**. However, the absorption time for drugs administered through eye drops is approximately two to three minutes, leading to quick drainage from the eye's surface and resulting in poor bioavailability. **Durak Saliha et al., (2020).**

Conventional ophthalmic dosage forms like ointments and suspensions have limitations in treating ocular diseases due to their poor bioavailability. **Baranowski P. et al., (2014).** These forms generally result in low drug absorption through the cornea and face challenges such as tear formation and non-productive absorption. Their limited permeability further contributes to lower absorption, reduced bioavailability, and rapid elimination. **Biswas Roy Gopa et al., (2017)**.

Thus, there is a must to grow novel drug delivery systems that can maintain optimal drug concentrations for prolonged periods. **Del Amo E. M. et al., (2008)**Nanotechnology provides specialized carriers that offer improved strategies for transportation and controlled release of drugs, thereby enhancing their therapeutic effectiveness. **Yetisgin A. A. et al., (2020)**Among these vesicular carriers such as Niosomes, Liposomes, polymer-based vesicles, and micelles have emerged as prominent options due to their advantageous properties. **Tagalakis A. A. et al., (2018)**These vesicles play a crucial role in safeguarding drugs from degradation during circulation and storage, consequently long lasting the serum half-life of medications by preventing their sequestration within the reticuloendothelial system. Especially, Niosomes exhibit significant potential as nanocarriers for treating various ocular disorders owing to their biocompatibility, biodegradability, structural versatility, and capability to entrap both hydrophobic & hydrophilic medication. **Durak Saliha et al., (2020)**

1.2. Priority of Niosomes over Liposomes:

Niosomes have emerged as a promising alternative to liposomes in ophthalmic drug delivery due to several advantages. One significant problem associated with liposomes is the powerlessness of phospholipids to oxidative degradation in air. **Nicholas J. D. Gower et al., (2016).** The use of liposomes requires purified phospholipids, which should be put away and taken care of in a latent air, making them costly. **Melis Cagdas et al., (2014).** Alternatively, synthesizing phospholipids is still more expensive than naturally occurring lipids. Whereas, Niosomes composed of non-ionic surfactants, offer greater stability as drug carriers and are comparatively cheaper than liposomes. Niosomes can be delivered for a huge scope without the utilization of unsatisfactory solvents, making their production process simpler. **Biswas Roy Gopa et al., (2017).**

1.3. Niosomes- A brief note:

Niosomes represent a type of vesicle formed by hydrating non-ionic surfactants, irrespective of the inclusion of cholesterol or other lipids.**Handjani Vila et al.,(1979)** These structures possess a lower degree of harm and contribute to the enhanced therapeutic effectiveness of drugs by facilitating targeted effects. This innovative drug delivery approach involves the entrapment of medications within vesicular structures. Although the majority of surfactants when introduced to water form micellar arrangements, certain surfactants have the ability to organize into bilayer vesicles, which are referred to as niosomes.**Yadav D. Jaydeep et al.,(2011)** Niosomes can be categorized based on their size or the number of bilayers they possess. For instance, Small Unilamellar Vesicles (SUVs) typically exhibit sizes ranging from 10 to 100 nm, while Large Unilamellar Vesicles (LUVs) span dimensions of 100 to 3000 nm. On a larger scale, Multi-Lamellar Vesicles (MLVs) exceed dimensions of 5 µm in size. **Durak Saliha et al., (2020)**

1.4. Niosomes take advantages over other nano-carriers because:

- Niosomes exhibit osmotic activity. **Biswas Roy Gopa et al., (2017).**
- They contribute to the increased stability of the entrapped drug. **Okore V. C. et al., 2011).**
- Niosomes can possibly upgrade drug penetration. **Biswas Roy Gopa et al., (2017).**
- These vesicles offer controlled release of drugs. **Yadav D. J. et al., (2011)**.
- Niosomes protecting drugs from the natural climate and limit their effects to target cells.**Gharbaviet al., (2018)**

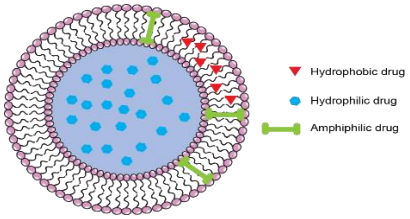

Figure 2: Structure of Niosomes

1.5. Components of Niosomes:

- **Non-ionic surfactants:**

Non-ionic surfactants assume a significant part in the development of Niosomes. These surfactants comprise of a hydrophilic head and a hydrophobic tail. **V Pola Chandu et al., (2012)**. They act as permeability enhancers and further improved solubility by decreasing surface strain. The entrapment efficiency of medication can be expanded by utilizing non-ionic surfactants with longer alkyl chains. **Das K. G. et al., (2013)** The types of non ionic surfactants and their some applications in Niosomal preparations have been summarised in Table 1. **Aparajay P. et al., (2022**)

Table 1: Surfactants commonly used in Niosomes preparation

S. No.	Class of non ionic surfactants	Applications
1	Sorbitan fatty acid esters (Span 20, 40, 60, 80 & 85)	Lowest transition temperature, act as a gelator, improve solubility. **Manosroi et al., (2012)**
2	Polyoxyethylene fatty acid esters (Tween 20, 40, 60, & 80)	Stable for poorly soluble drugs, stabilize protein derivative. **Akbari et al., (2015); Ruckmani et al., (2010)**
3	Alkyl ether &alkyl glyceryl ether (Brij 30, 52, 56, 58, 72, 76 & 92)	No instances of skin allergies have been reported. The broad spectrum of Hydrophilic-Lipophilic Balance (HLB) values enables the creation of both inverse and multilamellar vesicles. **Manosori et al., (2003)**
4	Block copolymer (pluronic L64, P105 etc.)	Biodegradable, pH sensitive, helps in delivery of protein and peptide through oral route. **Alexandridis et al., (1994)**

- **Cholesterol:**

Cholesterol is incorporated into noisome arrangements to give inflexibility and proper shape. **V Pola Chandu et al., (2012).** It settles the construction of non-ionic surfactant vesicles, lessening spillage. The increased concentration of cholesterol additionally increased the entrapment efficiency of the medication, with higher concentrations of cholesterol providing greater efficiency. **Agarwal S. et al., (2003).** Cholesterol also helps in improving the permeability of drug in the membrane. It has amphipathic nature, OH group bind with the aqueous phase while aliphatic changed with parallel with hydrocarbons. **Shrividya V. et al., (2016)**

- **Organic Solvent:**

The selection of organic solvent has a main impact on vesicle size and penetration rate. **Ishii F. et al., (1995).** Various alcohols like ethanol, methanol, acetone, propanol, butanol, and isopropanol can be utilized. In the planning of niosomes, a fluid stage containing phosphate support (pH 7.4), glycerol (0.1%), or boiling water is utilized alongside the natural dissolvable**. Soujanya C. et al., (2012)** Formation of vesicles Depends on the alcohols and vesicles diameter depends on their solubility in water. Solubility in water increase the size of vesicles. **Parikh D. K. et al., (2005); Annakula D. et al., (2010)**

2. Preparation methods of Niosomes:

2.1. Thin-Film Hydration (TFH) Method:

The thin film hydration technique is a straightforward method utilized for Niosome formulation. Non-ionic surfactants, renowned for their compatibility, stability, and low toxicity, are commonly employed in vesicle creation. **Thabet et al., (2022).** Cholesterol, acting as a lipid component, functions as both a membrane stabilizer and penetration enhancer. Ethanol is often favoured for its ability to facilitate the formation of larger vesicles with enhanced drug entrapment. **Aparajay P. et al., (2022)**

To execute the thin film hydration technique, essential ingredients like surfactant, cholesterol, & drug are mixed in ethanol within a round basejar. The mixture is agitated by stirring by a glass rod and then evaporated utilizing a rotational evaporator, resulting in the creation of a dry layer on the inner surface of the jar. Subsequently, this layer is hydrated using PBS at pH 7.4, leading to the formation of drug-loaded niosomes. **Jain V. et al., (2021); Kaur V. et al., (2015).**

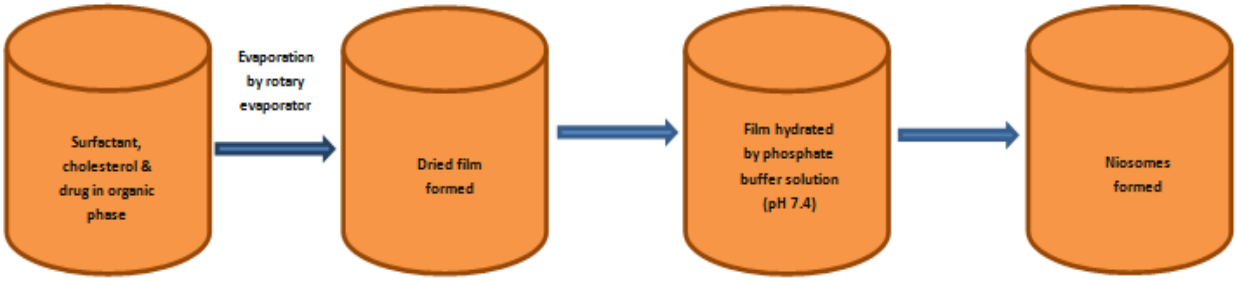

Figure 3: Representation on thin film hydration.

2.2. Ether Injection Method:

The ether injection method is a generally involved procedure for getting ready Niosomes. In this strategy, a combination of surfactant, cholesterol, and methanol in various proportions is ready. **Choudhary D. Praveen et al., (2019)**This subsequent arrangement is then slowly infused utilizing a microsyringe into a phosphate buffer solution (pH 7.4) that as of now contains the medication. During the injection, the rate is maintained at 0.25 ml/min.**Rogerson A. et al., (1998)**The solution is continuously stirred using an attractive stirrer, while the temperature is kept over 60 °C.The stirring process is continued for about 1-1.5 hours. As the solvent evaporates, unilamellar spherical niosomes are formed. **Baillie A. J. et al., (1986); Yadav D. J. et al., (2011)**

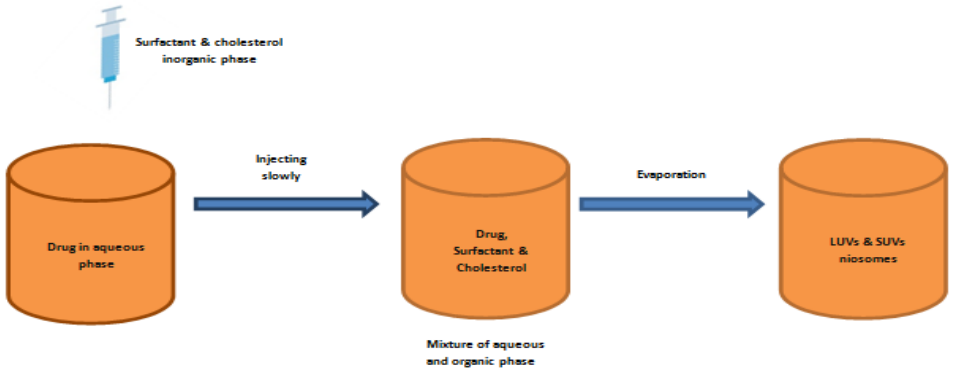

Figure 4: Representation on ether injection method.

2.3. Sonication Method:

The sonication strategy is a regularly utilized procedure for the creation of niosomes. In this technique, the medication is added to a buffer solution, and afterward a mixture of surfactant and cholesterol is added to the solution. The subsequent mixture is exposed to sonication at 60°C for 3 minutes utilizing a sonicator outfitted with a titanium test. This sonication cycle helps in the development of niosomes.**V PolaChanduet al., (2012); AparajayP.et al., (2022); Alamet al., (2013); Yadav D. J., et al., (2011); Baillie A. J. et al., (1986).**

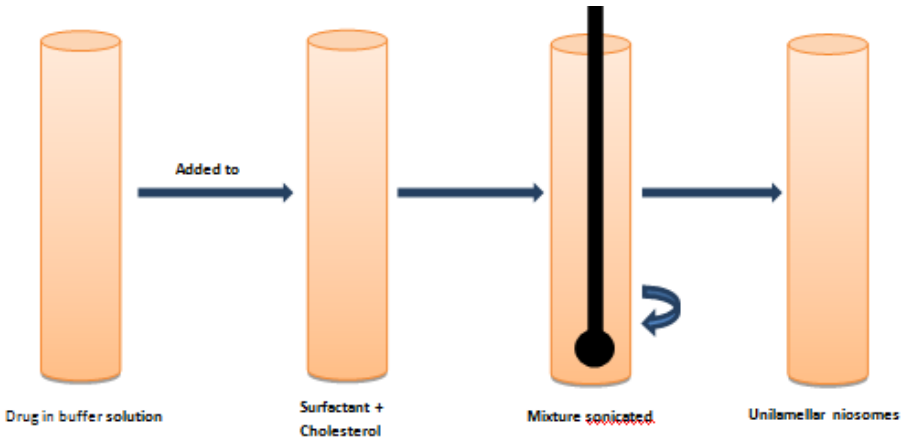

Figure 5: Representation on sonication method.

2.4. Reverse phase evaporation method:

This method is typically employed for the generation of large unilamellar vesicles (LUVs). It involves dissolving non-ionic surfactant and cholesterol in an organic solvent, while the drug is introduced into the aqueous phase. The two phases are subsequently mixed, and the resulting mixture is subjected to sonication to create an emulsion. This emulsion is then evaporated using a rotary evaporator at a temperature range of 40-60°C,bringing about the development of LUV niosomes. **Aparajay Priyadarshi et al., (2022); Raja Naresh R. A. et al., (1994); Yadav D. J., et al., (2011); Jain S. et al., (2005); Bendas E. R. et al., (2013).**

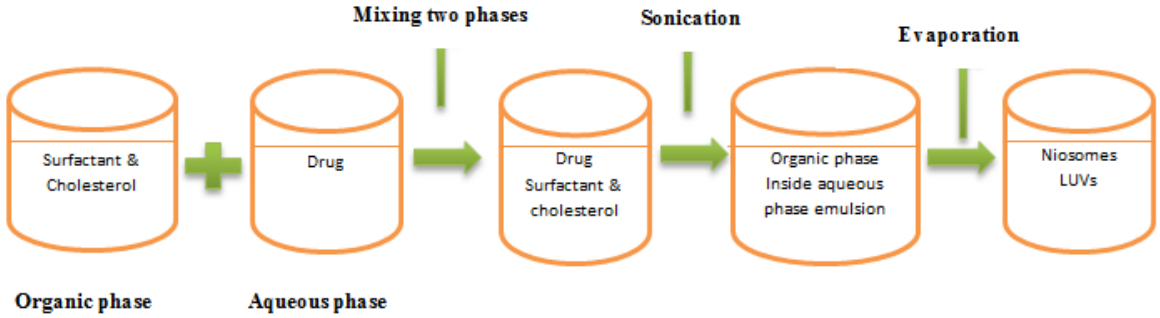

Figure 6: Representation on reverse phase evaporation method.

2.5. Bubble method:

This technique is a organic solvent free methodology for the formation of niosomes. In this strategy, the surfactants, cholesterol, and medication are mixed in a watery stage, for example, phosphate buffer solution (PBS). The subsequent solution is then moved into a three-neck round-base jar, which isset in a water bath to control the temperature. The diffusion of surfactants and added substances happens at 70°C. To start the interaction, a high shear homogenizer is utilized to accomplish a homogeneous scattering by blending for 15-30 seconds. Consequently, nitrogen gas is risen through the arrangement at 70°C. **Durak Saliha et al., (2020); Moghassemi S. et al., (2014); Talsma H. et al., (1994).**

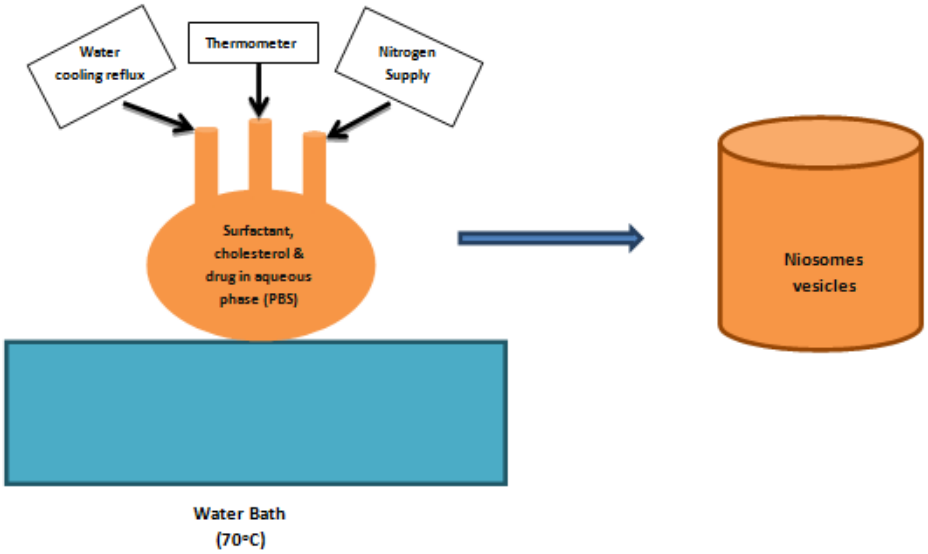

Figure 7: Representation on bubble method.

2.6. Hand Shaking Method:

In the described technique, a blend comprising surfactant, cholesterol, and the drug is disintegrated within an organic solvent. Subsequently, the combination is subjected to evaporation utilizing a rotary evaporator to eliminate the organic solvent. The resulting lipid film is then hydrated by employing a phosphate buffer solution and subjecting it to mechanical shaking, resulting in the formation of a white suspension. This process ultimately leads to the development of multilamellar vesicles.**Aparajay P. et al.,(2022); Kerr D. J. et al., (1988)**

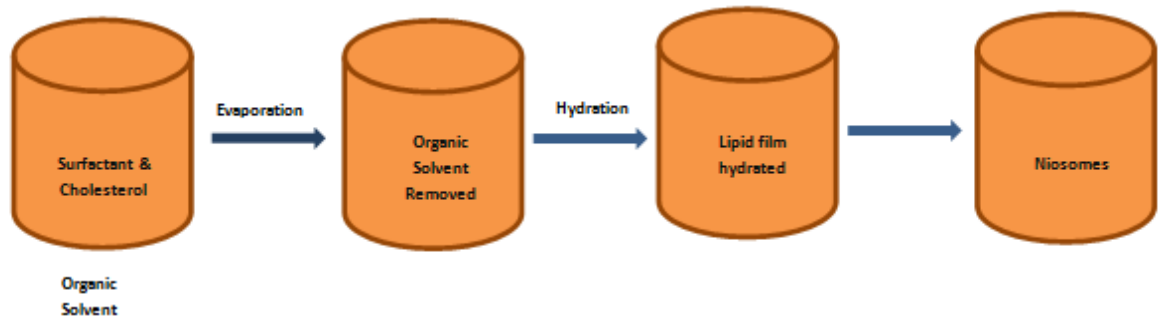

Figure 8: Representation on hand shaking method.

2.7. Heating Method:

The niosomes are prepared utilizing this technique by adding the surfactants, cholesterol, and medication independently to a watery stage, like PBS. Every solution is warmed at a temperature of 120°C for of 15 minutes. In this way, the solutions are combined as one at a lower temperature of 60°C and mixed for 15 minutes to create niosomes. This specific strategy does not utilize any harmful and volatile organic solvents and offering a helpful one-step process. **Aparajay Priyadarshi et al., (2022); Mortazavi S. M. et al., (2007); Mozafari M. R. et al., (2007)**

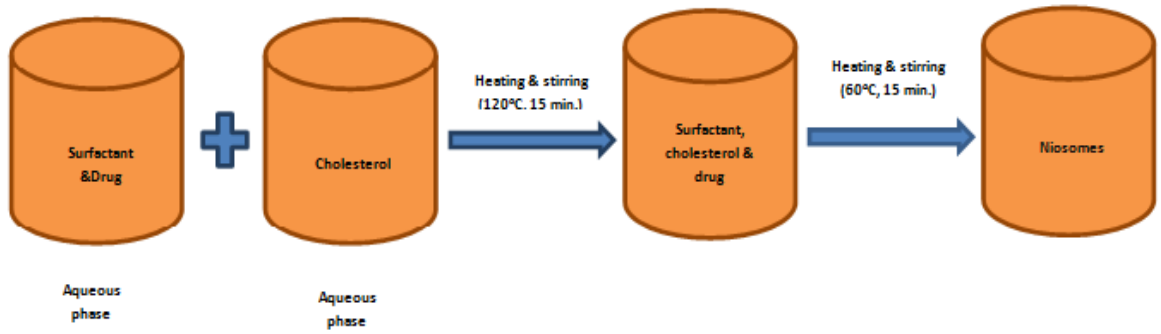

Figure 9: Representation on heating method.

2.8. Freeze and thaw method:

The freeze and thaw technique, similar to the thin film hydration approach, represents an enhanced method for niosome creation. In this process, the multilamellar vesicle (MLV) niosome suspension obtained from the thin film hydration technique is goes through a freezing process using liquid nitrogen. Subsequently, it is thawed through defrosting in a water bath, repeating this cycle over multiple cycles with brief intervals. **Durak Saliha et al., (2020); Abdelkader H. et al., (2011)**

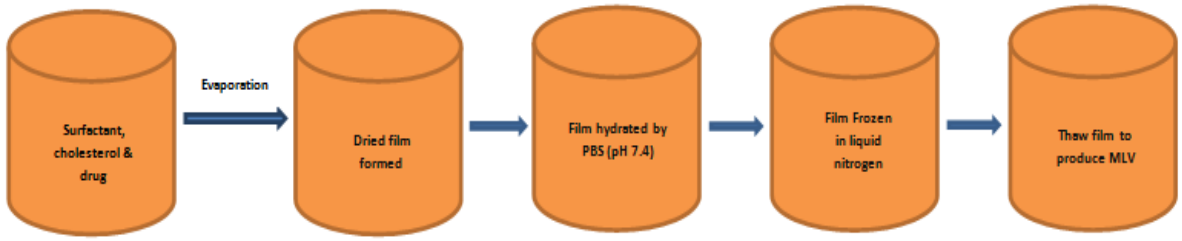

Figure 10: Representation on freeze and thaw method.

3. Gel preparation:

Hydroalcoholic gels have gained increasing popularity due to their excellent dispersal properties. The preparation of hydroalcoholic gels involves the utilization of a direct method. **Ubaid M. et al., (2016)** For the preparation of gel first of all, take the Carbopol 934 and mixed with distilled water through the magnetic stirrer after the well mixing of Carbopol in water prepared Niosomes will be slowly added in the solution on the magnetic stirrer after that few

drops of triethanolamine added in the mixture and convert Niosomes into niosomal gel formulation. Triethanolaminealso used as a pH adjuster. **Choudhary H. et al., (2013); Jain V. et al., (2021)**

4. Evaluation Parameters for niosomal gel:

4.1. Transmission Electron Microscopy:

The Transmission Electron Microscopy (TEM) is employed to analyze the surface characteristics, encompassing size, shape, and structure, of Niosomes.**Tangari P. et al., (2011)** The size of niosomes can range from 10 to 5000 nm, contingent upon the preparation method. Notably, nano-sized vesicles are Small Unilamellar Vesicles (SUV) and micron-sized vesicles are Large Unilamellar Vesicles (LUV) and Multi-Lamellar Vesicles (MLV) play a crucial role in ocular treatment. **Gharbavi M. et al., (2018**) For TEM analysis, a sample is prepared by applying a droplet onto a carbon-coated copper grid. After 15 minutes, a solution of 1% phosphotungstic acid is applied. The sample is then dried and observed using transmission electron microscopy. **Muzzalupo R. et al., (2008); Jain V. et al., (2021)**

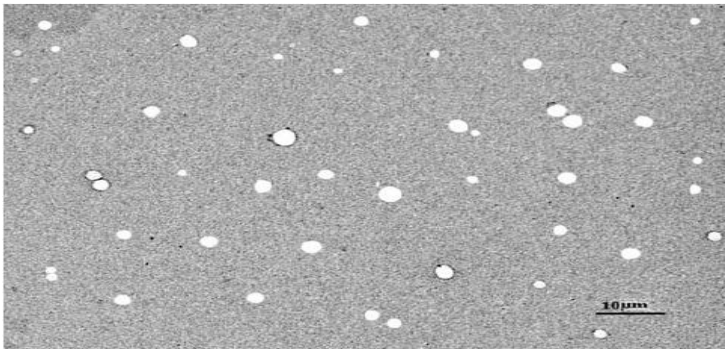

Figure 11: Transmission electron microscopy of niosomes.

4.2. Drug content:

Drug content in the formulation is calculated by the calibration curve. For the measurement of drug content take 100 mg of Niosomal gel and mixed 50 ml methanol in 100 ml volumetric flask and shake well for 15 minutes. Now make up the volume 100 ml with methanol. **Radha G. V. et al., (2013)** Now take the 10 ml solution and and dilute with 100 ml methanol. Then absorbance of prepared dilution measured by the uv spectrophotometer and drug content evaluated by the following formula. **Kesarvani R. K. et al., (2011); Shirsand S. R. et al., (2012)**

$$Y = mX + C$$

Where Y is absorbance, m is slope, C is intercept and X is concentration.

4.3. Entrapment efficiency:

This parameter is utilized to quantify the percentage of incorporated medication within the vesicles. **Aparajay P. et al., (2022)** To determine the entrapment efficiency and calculate the amount of drug captured in Niosomes, unentrapped drug is initially separated using various techniques such as centrifugation, gel filtration, or dialysis. **Blazek et al., (2001)** Among these techniques, centrifugation is the most commonly employed for drug separation. In this method, drug-loaded Niosomes are placed in a centrifuge tube and diluted with distilled water. The mixture is then subjected to centrifugation for 20 minutes, resulting in the separation of unentrapped medication from the formulation. The concentrations of both the supernatant (containing unentrapped drug) and the sediment (containing entrapped drug) are measured individually after dilution with PBS, utilizing a UV spectrophotometer. The entrapment efficiency percentage is subsequently calculated by utilizing the following equation. **Kaur V. et al., (2015); Jain V. et al., (2021).**

$$\% \text{ Entrapment efficiency} = \text{Entrapped drug} / \text{Total drug} \times 100$$

4.4. pH Determination:

For the determination of pH take the specific amount of formulated Niosomal gel in a beaker and dilute with the distilled water now measured its pH by digital pH meter. **Shirsand S. R. et al., (2012); Jain V. et al., (2021)**

4.5. Viscosity:

In this evaluation parameter Viscosity of prepared sample measured by the Brookfield viscometer equipped with the helipath stand and T bar spindles of different no. like (1, 2, 3, 4). Viscosity determined at the different

temperatures from 25-40 ºC and variable shear rate. **ChaudhariDesai P. et al., (2019)** Taken the gel formulation in a beaker and measured the viscosity by stirring T-bar spindle, at the specific rpm at the constant temperature. The same process done almost three times and final viscosity obtained. **Jain V. et al., (2021); Zaki N. M. et al., (2007)**

4.6. In vitro drug release:

In vitro drug release assessments are commonly determined by using a Franz Diffusion Cell Apparatus, which consists of two primary segments: the acceptor compartment and the donor compartment. **Durak Saliha et al., (2020)** An artificial dialysis membrane is positioned between the donor and receptor compartments and securely held in place using external clamps. The receptor compartment is loaded with a phosphate buffer solution at pH 7.4, while the donor compartment is loaded with the Niosomal gel. **Abdelkader H. et al., (2011)**

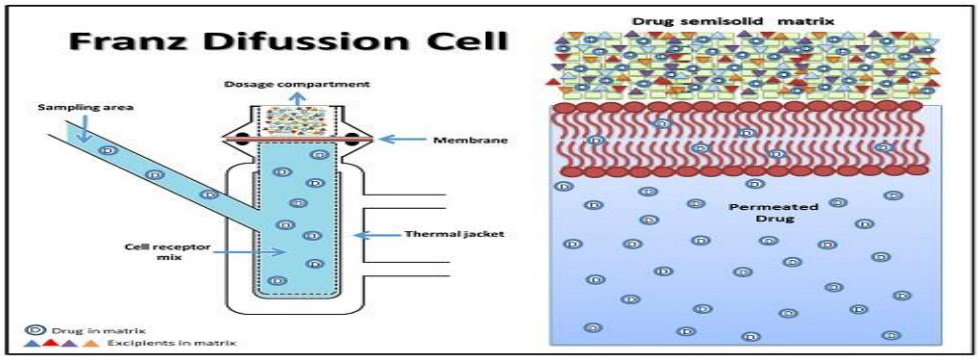

Figure 12: In vitro drug release by franz diffusion cell technique.

Kinetic analysis of release data:

To analyze the release kinetics of the drug, the results obtained from in vitro drug release experiments displayed various delivery patterns, encompassing zero-order, first-order, Higuchi's model, and Korsmeyer and Peppas model. **Srinivas et al.,(2010)**In the context of these models, the zero-order model depicts a consistent rate of release over an extended duration, while the first-order model describes a logarithmic rate of release over time. **Durak Saliha et al., (2020**) Higuchi's model illustrates a linear relationship between the total rate of release and the square root of time, whereas the Korsmeyer and Peppas equation characterizes the logarithmic quantity of medication released in relation to the logarithm of time. The drug release kinetics were determined through the application of various release models to the in vitro release study data, employing the following equations.

Zero order:

$$W_t = W_0 - K_0 t,$$

The drug release kinetics can be described using various models. One of the commonly used model is the zero-order model, which relates how much medication delivered (W_t) at a particular time (t) to the underlying quantity of medication in the solution (W_0) and the zero order constant (K_0).**Jafariazar Z. et al., (2015)**

First order:

$$\ln W_t = \ln W_0 - K_1 t,$$

This model relates how much medication delivered (W_t) at a particular time (t) to the underlying amount of medication in the solution (W_0) and the first order constant (K_1).

Higuchi's model:

$$W_t = K_h \sqrt{t},$$

The Higuchi model serves as a tool for describing drug release kinetics, establishing a relationship between the amount of medication released (W_t) at a specific time (t) and the Higuchi release constant (K_h). Furthermore, Higuchi's model suggests that the rate of medication release decelerates as the distance traversed by the drug molecule increases. **Higuchi T. et al., (1963); Durak Saliha et al., (2020)**

Korsmeyer and Peppas model:

$$M_t/M_\infty = K_{kp} t^n,$$

The Korsmeyer and Peppas model is employed for the analysis of drug release kinetics. It encompasses the fractional amount of medication released (M_t/M_∞) at a specific time (t), the Korsmeyer and Peppas release constant (K_{kp}), the release exponent (n), and the mechanism of drug release (t^n). **Subrizi A. et al., (2019)**

4.7. Stability study:

The primary objective of this assessment parameter is to determine the stability of the Niosomal formulation over specific time intervals under various temperature conditions. For stability assessment, the formulation is subjected to three distinct temperature environments: refrigeration (2-8°C), room temperature (25±0.5°C), and elevated temperature (45±0.5°C), over a minimum duration of 90 days. **Ojeda E. et al., (2015); Shahiwala A. et al., (2002)** To execute this evaluation, the Niosomal gel is encapsulated within a glass vial and securely sealed with aluminum foil. Following the lapse of at least one month, samples are withdrawn from the vials for analysis. During this assessment, several parameters are examined, including entrapment efficiency, particle size, appearance, assay, and pH. **Shrividya vardhani C. H. et al., (2016)**

5. Some basic applications of Niosomes in ocular drug delivery:

In ocular drug delivery, Niosomal gel addresses several challenges encountered with the administration of conventional eye solutions. **Deepika et al., (2020)** These advancements include enhanced drug efficacy, protection of drugs from degradation caused by enzymes found in tears and the corneal epithelial surface, improved drug bioavailability, and an extended habitation time of the drug within the eye. Additionally, Niosomes offer the advantage of sustained drug release. **Rawia M. et al., (2016); Alla E. E. et al., (2019)**

6. Some ocular Diseases in which Niosomal gel is better than conventional eye drops:

6.1. Conjunctivitis:

Conjunctivitis refers to the infection or inflammation of the conjunctiva, a translucent mucous membrane situated on the sclera. **Azari A. A. et al., (2013)** It commonly manifests as redness in the eye and can affect individuals of all ages. **Ryder E. C. et al., (2011)**Conjunctivitis can be categorized as infectious or non-infectious, encompassing various types such as viral, bacterial, fungal, allergic, toxic, and irritation-induced conjunctivitis. Viral, bacterial, and fungal conjunctivitis, occurring in acute or chronic forms, fall under infectious conjunctivitis. **Alfonso S. A. et al., (2015)**Non-infectious conjunctivitis includes allergic conjunctivitis, toxic conjunctivitis, and irritation-induced conjunctivitis. **Skevaki C. L. et al., (2011)** Conjunctivitis can also stem from sexually transmitted diseases like chlamydial infection and gonorrhoea. **Morrow G. L. et al., (1998)**Topical medication administration is the primary treatment for conjunctivitis. **Yasin M. N. et al., (2012)** The advancement of nanotechnological formulations has emerged as a promising approach to enhance medication bioavailability in the treatment of conjunctivitis, particularly in comparison to traditional ophthalmic solutions. **Durak Saliha et al., (2020)**

6.2. Glaucoma:

Glaucoma, a prevalent neurodegenerative condition of the eye, requires lifelong treatment. It is characterized by the death of retinal ganglion cells, leading to the degeneration of nerve axons and resulting in visual field defects **Geyer O. et al., (2020)** The primary contributing factor to glaucoma is elevated intraocular pressure (IOP). This rise in IOP is caused by the accumulation of aqueous humor in the anterior chamber due to increased fluid production or blockage in the drainage system **Emad Eldeeb A. et al., (2019)**

Niosomal formulations offer several advantages for glaucoma treatment. These include an extended ability to lower IOP, enhanced ocular bioavailability, controlled and sustained drug delivery, and reduced ocular toxicity. **Sahoo R. K. et al., (2014); Durak Saliha et al., (2020)**

6.3. Keratitis

Keratitis, which involves inflammation of the corneal surface, is primarily caused by infections resulting from pathogens such as bacteria, fungi, and viruses. **Sharaf M. G. et al., (2014)** The clinical presentation of keratitis can vary based on the specific infectious agents involved. Common symptoms experienced by keratitis patients include eye redness, pain, excessive tear production, and blurred vision**. Lakhundi S. et al., (2017); Durak Saliha et al., (2020)**

While topical eye drops are the most common treatment for these infections, their efficacy can be hindered by high tear production, leading to reduced residence time at the targeted tissue site. Recent research has highlighted the potential of nanotechnology to enhance ocular residence time and significantly increase drug bioavailability. **Sharaf M. G. et al., (2014)**

6.4. Retinal diseases:

Inherited Retinal Diseases (IRDs) constitute a diverse group of disorders with both clinical and genetic heterogeneity, primarily marked by retinal degeneration or dysfunction. This phenomenon stands as a predominant cause of blindness in adults and is also prevalent in childhood. **Georgiou M. et al., (2021)** These conditions are characterized by mutations in genes that are specific to the inner retinal layer, leading to the manifestation of inherited retinal diseases.Retinitis pigmentosa is the most prevalent variant of inherited retinal disorder. This condition has been associated with a minimum of 30 different genes. **Mc Clements M. E. et al., (2013)**

Table 2: Some Niosomal formulations for ocular drug delivery treatment:

Disease	Surfactants	Additives	Drug	Methods	Result
Glaucoma	Span 60	Cholesterol	Atenolol	T.F.H.	Higher E.E.% (80.7%), long-lasting medication release & IOP- lowering action more than 8 hour was observed. **Abu H. et al., (2014)**
	Span 60	Cholesterol	Brimonidin-e tartrate	T.F.H.	Higher E.E.% (>32%), IOP-lowering action 3 hour longer than commercial drug. **Prabhu P. et al., (2010)**
	Span 40, 60	Cholesterol	Acetazola-mide	T.F.H.& R.E.V.	Higher E.E.% (>32%) & these niosomes long-lasting IOP-lowering activity. **Guinedi A. S. et al., (2005)**
	Span 60	Cholesterol	Dorzolami-de HCL	TFH	Higher E.E.% (31%) &long-lasting drug release more than 8 hours. **Hashemi D. M. et al., (2017)**
	Span 60	Cholesterol, Chitosan, Carbopol	Timolol Maleate	REV	The Niosomal formulation exhibits an extended reduction in intraocular pressure (IOP) when compared to carbopol-coated niosomes,**Aggarwal D. et al., (2005)**
Conjuncti-vitis	Span 60	Cholesterol	Azithromy-cin	S.I., T.F.H., Hand shaking	E.E.% of niosomes (>30%) & niosomal in situ gel (>63%), long-lasting drug release up to 12 hour with increased permeability. **Akhtar N. et al., (2017)**
	Span 60	Cholesterol	Chloramph-enicol	S.I.	Higher E.E.% (>83%), long-lasting drug release more than 10 hour was observed. **Yasin M. N. et al., (2012)**
	Span 20, 60, 80, Tween 40, 60, 80	Cholesterol	Lomefloxa-cin HCL	TFH	E.E.% of tween niosomes (>41%) was greater than span niosomes (40%) and drug release of tweens was also higher than spans. **Khalil R. M. et al., (2017)**
	Span 60 Tween 60	Cholesterol	Azithromy-cin	TFH	Higher E.E.% (74%), Improved corneal permeability, No any ocular irritation. **Eid M. H. et al., (2021)**
	Tween 60	Cholesterol	Lomefloxa-cin HCL	TFH	Higher E.E.% was (68%) with the sustained release more than 8 hours, no sign of ocular irritancy. **Khalil M. R. et al., (2017)**
Ocular Infections	Span 20, 80, 60	Cholesterol	Lomefloxa-cin HCL	T.F.H.	Higher E.E.% (>78.1%), long-lasting drug release more than 8 hour with higher antimicrobial activity. **Abdelbary A. et al., (2017)**
	Span 60	Cholesterol Chitosan	Gatifloxaci-n	S.I.	Higher E.E.% (>68.9%), chitosan coating improved permeability. **Zubairu Y. et al., (2015)**
	Tween 40 Span 60	Cholesterol	Vancomyci-n Hydrochlor-ide	TFH	The E.E.% of the niosomes was found to be greater than 46%. Additionally, the antibacterial effectiveness of the gel surpassed that of the solution, primarily attributed to the extended ocular residence time. **Allam A. et al., (2019)**
	Span 60, 80	Cholesterol	Fluconazol-e	TFH	Higher E.E.% (84%) obtained by span 60, formulation shows sustained release and increase in permeability. **Fetih G. et al., (2016)**
	Tween 60, 80 Brij 35	Cholesterol, Dicetyl phosphate	Gentamicin sulfate	TFH	The E.E.% of niosomes was in wide range and all the niosomes shows long-lasting drug release more than 8 hours. **Abdelbary G. et al., (2008)**
Keratitis	Span 20	Cholestero-l	Natamyci-n	RPE	Higher E.E.% (96%) obtained with prolonged drug release. **El-Nabarawi M. A. et al., (2019)**
	Span 60	Cholesterol	Natamycin	TFH	E.E.% of Niosomal formulation obtained (83.31%), extended drug release up to 24 hours and increased corneal retention time. **Paradkar U. M. et al., (2017)**
	Span 40, 60, 80	Edge activators, Cholesterol	Fluconazol-e	SI	Highest E.E.% was (65.73%) and permeability of niosomes were higher than marketed solutions. **Kaur I. P. et al., (2012)**
	Span 60	Cholesterol, Bile salts, Edge activator	Tercanazol-e	SI	High conc. Of edge activator decreased E.E.% and selected formulation had E.E.% (95.47%) and also increased corneal permeation. **Abdelbary A. A. et al., (2016)**
	Span 40, 60	Cholesterol, Pluronic L64, Pluronic F127	Voriconazo-le	TFH	E.E.% of formulation was (>49%) with long-lasting drug release up to 8 hour. **Shukr M. H. et al., (2016)**
Ocular Inflamma-	Span 60	Cholesterol	Flurbiprofe-n	TFH	Niosomal in situ gel formulation produced long-lasting drug release more than 7 hour. **EI-Sayed M. M. et al.,**

tion					**(2017)**
	Span 60	Cholesterol	Prednisolo-ne	TFH, SI	Niosomes prepared by TFH has greater E.E.% in comparison of SI, extended drug release more than 8 hour, decreased inflammation more than drug solutions. **Gaffar P. M. et al., (2014)**
	Span 20, 80, 60 Tween 80	Cholesterol	Resveratrol	EIM	The higher E.E.% of Niosomal formulation was (90%) with sustained release pattern over 24 hour. **EI-Haddad M. E. et al., (2021)**
	Span 60	Cholesterol	Prednisolo-ne sodium phosphate	TFH	Higher E.E.% obtained (83.4%) with sustained release, Increase the drug bioavailability. **Choudhary D. P. et al., (2019)**

7. CONCLUSION:

Incorporating drugs into niosomes offers a promising strategy for achieving targeted drug delivery to specific sites of action. Niosomes possess distinct advantages over liposomes, including cost-effectiveness and enhanced stability, rendering them superior as targeting agents. In the context of treating ocular infections via the ophthalmic route, niosomal gel formulations exhibit superior efficacy compared to alternative formulations.These formulations enhance drug permeability and shield the medication from degradation by enzymes present on the tear/corneal epithelial surface. Furthermore, niosomes contribute to the improved stability of the encapsulated drug and extend its residence time on the ocular surface, leading to enhanced bioavailability. Additionally, niosomes enable controlled release of the drug over an extended period at the corneal surface. The topical application of medication on the ocular surface aids in enhancing patient compliance.Niosomes are versatile, biocompatible nanocarriers that are relatively straightforward to prepare. Their utilization represents a valuable advancement in the field of drug delivery, particularly for ocular treatments.

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