

Niosome in Ocular Drug Delivery: An Update Review

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Abstract:-With the recent advancement in the field of ocular therapy, drug delivery approaches have been superior to a new concept in terms of nonionic surfactant vesicles (NSVs), that is, the ability to deliver the therapeutic agent to a patient in a staggered profile. However the major drawbacks of the conventional drug delivery system like lacking of permeability through ocular barrier and poor bioavailability of water soluble drugs have been overcome by the emergence of NSVs. Niosomes have the same potential advantages of phospholipid vesicles (liposomes) of being able to accommodate both water soluble and lipid soluble drug molecules control their release and as such serve as versatile drug delivery devices of numerous applications. The drug loaded NSVs (DNSVs) can be fabricated by simple and cost-effective techniques with improved physical stability and enhance bioavailability without blurring the vision. The increasing research interest surrounding this delivery system has widened the areas of pharmaceuticals in particular with many more subdisciplines expected to coexist in the near future. This review gives a comprehensive emphasis on NSVs considerations, formulation approaches, physicochemical properties, fabrication techniques, and therapeutic significances of NSVs in the field of ocular delivery and also addresses the future development of modified NSVs.

Keywords: - nonionic surfactant, physical stability, bioavailability.

I. INTRODUCTION

Ocular drug delivery has been a foremost challenge for researchers because of the distinctive anatomy and physiology of eye which contains different barriers such as different layers of cornea, sclera and retina in addition to blood retinal barriers, lachrymal fluid-eye barrier and also drug loss from the ocular surface. These obstacles cause a considerable challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye. The major challenge to the formulator is to outwit these barriers without causing any tissue damage. The cornea is the anterior layer of the eye, comprises of epithelium, stroma and endothelium. However, this layer represents a mechanical barrier restraining the delivery of drug molecules. Due to their high lipid content, the epithelium and the endothelium are considered as an obstruction to the passage of hydrophilic molecules. The stroma is characterized by a high water content that makes this layer impermeable to lipophilic molecules. Corneal barrier also plays a considerable role in low ocular bioavailability due to which only < 5% of the

applied drugs are able to penetrate through the cornea into the intra-ocular tissues .¹

Inconvenience in using conventional dosage forms are as follows:

- Limited permeability which leads to lower absorption.
- Rapid elimination.
- Frequent instillation.
- Lower bioavailability due to low precorneal residence time.
- Drainage of drugs from nasolacrimal duct.

Vesicular drug delivery systems such as liposomes and niosomes provided a promising alternative with some success being recorded by many authors. The fluidity of such formulations hindered the possibility of achieving prolonged effect. Authors employed vesicular systems dispersed with mucoadhesive polymers as a tool to solve this problem. However; there are many parameters which require further investigations. These include the effect of the rigidity of the vesicular membrane, the effect of vesicle size and the combination between vesicular system and the *in situ* gelling systems as a tool to improve ocular availability of drug. This work was thus undertaken to investigate these parameters.²

This problem can be addressed by use of suitable carrier systems. Niosomal vesicular system is one of the potential approaches, which can be suitably used. Niosomes, therefore, are promising drug carrier and have the potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. As of today more than 50 drugs are tried in niosome formulations by intravenous, per oral, transdermal, inhalation, ocular and nasal routes of administration.³

Niosomes in topical ocular delivery are preferred over other vesicular systems because of the following reasons: (1) chemical stability; (2) low toxicity because of their non-ionic nature; (3) handling surfactants with no special precautions or conditions; (4) the ability to improve the performance of the drug via better availability and controlled delivery at a particular site; (5) being biodegradable, biocompatible and non-immunogenic.⁴

The advantage of vesicular systems does not only reside in providing prolonged and controlled action at the corneal surface but also involves providing controlled ocular

delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface. Moreover, vesicles offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that has the convenience of a drop, but will localize and maintain drug activity at its site of action. The penetration of drug molecules into the eye from a topically applied preparation is a complex phenomenon. In vesicular dosage forms, the drug is encapsulated in lipid vesicles, which can cross cell membrane. Vesicles, therefore, can be viewed as drug carriers which can change the rate and extent of absorption as well as the disposition of the drug.⁵

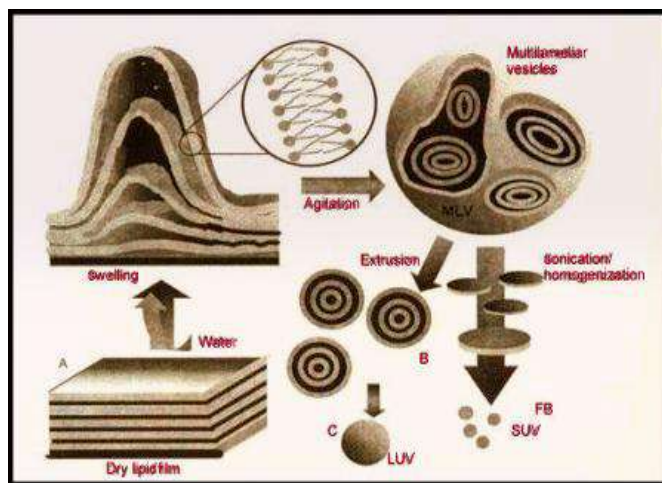
1.1 Niosomes as Nanocarrier Systems

Colloidal drug delivery systems such as liposomes and niosomes have distinct advantages over conventional dosage forms. These systems can act as drug reservoirs and provide controlled release of the active substance. In addition, modification of their composition or surface can allow targeting. Niosomes are non-ionic surfactant based vesicles that had been developed as alternative controlled drug delivery systems to liposomes in order to overcome the problems associated with sterilization, large-scale production and stability. The first niosome formulations were developed and patented by L'Oreal in 1975. They are liposome-like vesicles formed from the hydrated mixtures of cholesterol, charge inducing substance, and nonionic surfactants such as monoalkyl or dialkyl polyoxyethylene ether. Basically, these vesicles do not form spontaneously. Thermodynamically stable vesicles form only in the presence of proper mixtures of surfactants and charge inducing agents. The mechanism of vesicle formation upon use of nonionic surfactants is not completely clear. The most common theory is that nonionic surfactants form a closed bilayer in aqueous media based on their amphiphilic nature. Formation of this structure involves some input of energy, for instance by means of physical agitation (e.g. using the hand-shaking method) or heat (e.g. using the heating method;). In this closed bilayer structure, hydrophobic parts of the molecule are oriented away from the aqueous solvent whereas the hydrophilic head comes in contact with the aqueous solvent. It resembles phospholipid vesicles in liposomes and hence, enables entrapment of hydrophilic drugs. The low cost, stability and resultant ease of storage of nonionic surfactants has led to the exploitation of these compounds as alternatives to phospholipids. The superiorities and advantages of niosomes, compared to other micro and nanoencapsulation technologies can be summarized as follows:⁶

- ❖ Compared to phospholipid molecules used in liposome formulations, the surfactants used in the formation of niosomes are more stable.
- ❖ Simple methods are required for manufacturing and large-scale production of niosomes.
- ❖ As the excipients and equipments used for production are not expensive, niosome manufacturing process is cost-effective.

- ❖ Niosomes possess longer shelf-life than liposomes and most other nanocarrier systems.
- ❖ Unlike liposomes, they are stable at room temperature and less susceptible to light.

Fig no. 1.1: Vesicle Formation



1.2 Advantages of Niosomes⁷

1. Niosomes are economically cheap among the colloidal drug carrier.
2. Niosomes entrap solute in manner analogous to liposomes.
3. They are more stable than liposomes, because the phospholipid, present in the liposomes gets easily oxidized.
4. Niosomes are osmotically active and stable as well as they increase the stability of entrapped drug.
5. They improve oral bioavailability of poorly absorbed drugs.
6. They can enhance the skin penetration of drugs.
7. They are biodegradable, biocompatible and non-immunogenic.
8. They can be made to reach the site of action by oral, parenteral as well as topical routes.
9. Niosomes can accommodate drug molecule with a wide range of solubilities because of the presence of hydrophilic and hydrophobic moieties together in their structure.
10. The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.
11. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
12. The vesicles may act as a depot, releasing the drug in a controlled manner.
13. They improve the therapeutic performance of the drug molecules by delayed clearance from the

circulation, protecting the drug from biological environment and restricting effects to target cells.

14. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

Considering above information in view, their requirement of some vesicular system to treat ocular infection for better patient compliance. Apart from this vital information, some of the clinical aspects which contribute poor bioavailability of ophthalmic dosage forms should be accounted. Firstly, the nature of chemical agents which are employed for treatment of ocular diseases like open angle glaucoma, closureangle glaucoma, mydriasis, miosis, accomodation, cycloplegia, zonules, cataract, dacryodentitis, conjunctivitis, keratitis, endophthalmitis, viral rheinitis, toxoplasmosis

A number of disorders can affect the structure of the eye, with outcomes ranging from moderate discomfort to significant loss of vision. The health care provider should be familiar with the signs and symptoms of common eye disorders and understand the decision making process behind treatment Inflammatory conditions 1. Hordeolum and Chalazion 2. Blepharitis 3. Dacryocystitis 4. Conjunctivitis 5. Trachoma 6. Anterior Uveitis 7. Corneal ulcer, 8. Glaucoma .⁸

Ocular infections may be caused by bacteria, fungi, parasites, or viruses, and each of these may produce a spectrum of disease. It is usually challenging to determine the causative agent based on clinical features because they may or may not be distinctive. Many a time, it may not even be possible to discriminate between infective or non-infective conditions. In addition, the prevalence and distribution of type of infectious agents associated with eye infections widely vary and are dependent on variety of factors. In recent times, *in vivo* methods, such as confocal microscopy, have come a long way in putting clinical diagnosis on firmer grounds, especially for *Acanthamoeba* and fungal keratitis. However, apart from its limited application, the equipment may not be available in all settings. Therefore, confirmation by microscopic examination and culture of the clinical samples remain the gold standard for etiological diagnosis. Currently, molecular diagnosis has added the sensitivity, specificity, and speed that have been the concerns with the conventional techniques of microscopy and culture. This review will describe the role of various methods that are currently available for the diagnosis of ocular infections.⁸

Fungal keratitis is one of the major causes of ophthalmic mycosis and is difficult to treat. Filamentous fungi were long considered as a major cause of fungal keratitis. Keratitis caused by these filamentous fungi may involve any part of the cornea. Dematiaceous fungi such as *Curvularia*, *Bipolaris*, and *Exserohilum* species have also been reported to cause fungal keratitis.

After *Aspergillus* and *Fusarium* species, *Curvularia* and *Bipolaris* species are the third most common keratitis-causative fungi worldwide. The ultimate goal in the treatment of fungal keratitis is to conserve vision. This requires timely diagnosis of the infection and administration of the appropriate antifungal therapy. Patient with fungal keratitis can be treated with either medical or surgical therapy. Whilst surgical procedures are more effective in patients with acute corneal perforation, antifungal agents are still the major therapeutic option in fungal keratitis. The range of common antifungal agents available for fungal keratitis remains inadequate and is generally associated with poor clinical outcomes. Voriconazole is a new generation triazole antifungal agent. Only marketed in systemic formulation and, The general predisposing factors for fungal keratitis include ocular trauma, prolonged use of topical or systemic immune suppressants, pre-existing corneal surface disease, underlying systemic disease (eg, diabetes mellitus), and contact lens wear. The voriconazole concentration in the aqueous humor was 53% of the concentration obtained in the plasma, and was sufficiently high to be effective against most common fungi associated with fungal keratitis.⁹

The clinical efficacy of an antifungal agent in ophthalmic mycoses depends, to a great extent, on the concentration achieved in the target ocular tissue. This, in turn, depends on a number of factors, including the molecular mass and concentration of the drug and the route by which it has been administered, the duration of contact with the target ocular tissue, and the ability of the compound to penetrate the eye. Poor bioavailability of antifungal drugs due to the various protective mechanisms of the eye is a serious concern for the treatment of corneal fungal infections in today's world. The use of noisome that can improve the bioavailability of these antifungal drugs is relatively a new idea being conceived and here we have synthesized voriconazole loaded niosome which can be used for the treatment of corneal fungal infections.¹⁰

1.3 Anatomical and physiological considerations

Eye is the most marvelous of the sense organs as it makes us aware of various objects all around us, near and far away. Eye is nearly spherical in shape except that its front portion i.e., transparent cornea bulges a bit forward. The eye is protected by the eyelashes, eyelids, tears and blinking. The eyelashes catch foreign materials as the blink reflex prevents injury by closing the lids, blinking occurs frequently during waking hours to keep the corneal surface free of mucous and moistened by the tears secreted by the lacrimal glands. Tears wash away irritating agents and are bactericidal preventing infections. The protective operations of the eye lids and lacrimal system are such that, there is a rapid removal of material instilled into the eye unless the material is suitably small in volume, chemically and physiologically compatible with surface tissues. The eye is one of the most delicate and yet most valuable of the sense organs and is a challenging subject for topical administration of drugs to the eye.¹¹

A) Accessory structures of the eye

The accessory structures of the eye include the eyelids, eyelashes, eyebrows, the lacrimal (tearing) apparatus and extrinsic eye muscles. The lacrimal apparatus is a group of structures that produces and drains lacrimal fluids or tears.

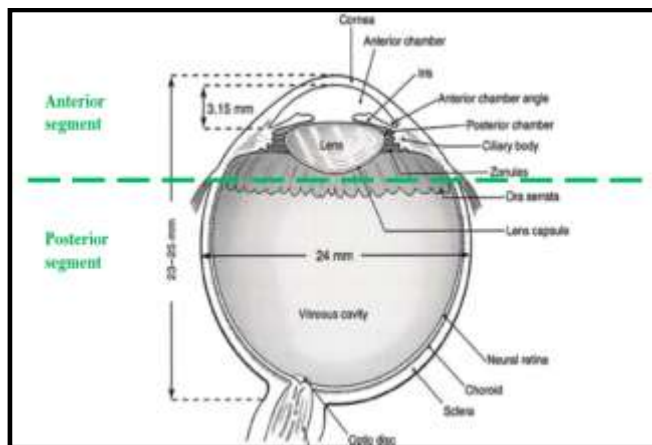
B) Anatomy of the eyeball

The eyeball measures about 2.5 cm in diameter, only a small portion (about 1/6th part) of the globular eye is exposed in front, the rest is hidden in bony socket of the orbit on a cushion of fat and connective tissue. The wall of the human eyeball consists essentially of three layers: **Fibrous tunic, vascular tunic and Retina.**

i) Fibrous tunic :-

Fibrous tunic, the outermost coat of the eyeball, consists of the anterior cornea and posterior sclera. The **cornea** is a transparent coat that covers the colored iris. Cornea mainly consists of the following structures from the front to back, **(I) Epithelium, (II) Bowman's membrane, (III) Stroma, (IV) Descemet's Membrane, (V) Endothelium.** The cornea is 0.5 to 1mm in thickness and normally it possesses no blood vessels except at the corneoscleral junction. The **sclera**, the "white" of the eye, is a layer of dense connective tissue made up densely of collagen fibers and fibroblasts. The sclera covers the entire eyeball except the cornea. At the junction of the sclera and cornea is an opening known as the scleral venous sinus (canal of Schelmm).

Figure no. 1.2 Cross anatomy of the anterior& posterior segment of the human eye



ii) Vascular tunic

This middle layer is mainly vascular, consisting of the **choroid, ciliary body and iris.**

Choroid lines the posterior five-sixths of the inner surface of the sclera. It is very rich in blood vessels.

Ciliary body is the anterior continuation of the choroids consisting of ciliary muscle and secretory epithelial cells. The major function of the ciliary body is the production of

aqueous humor. Systemic drugs enter the anterior and posterior chambers largely by passing through the ciliary body vasculature and then diffusing in to the iris where they can enter the aqueous humor. The ciliary body is one of the major ocular sources of drug-metabolizing enzymes, responsible for drug detoxification and removal from the eye. **Iris** is the visible colored part of the eye and extends anteriorly from the ciliary body lying behind the cornea and in front of the lens. The pigment granules of the iris epithelium absorb light as well as lipophilic drugs. As a result the iris can serve as a reservoir for some drugs, concentrating and then releasing them for longer than otherwise expected(5, 7) The innermost layer is the retina, consisting of the essential nervous system responsible for vision. Retina lines the posterior three quarters of the eyeball and is the beginning of the visual pathway.

iii) Retina

The retina is situated between the clear vitreous humor in its inner surface and the choroids on its outer surface. Retina consists of two distinct chambers, anterior and posterior behind the pupil and iris, within the cavity of the eyeball, is the lens. Protein called crystallins, arranged like the layers of an onion, make up the lens. The lens is held in place by the zonules, which run from the ciliary body and fuse into the outer layer of the lens capsule. The lens tends to develop cataract or opacities with age, interfering with vision.¹²

C) Conjunctiva

The conjunctiva membrane covers the outer surface of the white portion of the eye and the inner surface of the eyelids. In most places it is loosely attached and thereby permits free movement of the eyeball, this makes possible subconjunctival injection. The conjunctiva forms an inferior and a superior sac except for the cornea, the conjunctiva is the most exposed portion of the eye.¹³

D) Sclera

The sclera (the white part of the eye) is the outermost layer that covers the anterior surface of the eye. It protects the sensitive inner parts of the eye. The sclera is a firm and resistant structure (0.5-1 mm thick) composed of the same collagen fibrils as the corneal stroma. However, the sclera's collagen fibers are arranged in an irregular network rather than a lattice structure. This makes the sclera appear opaque compared with the transparent cornea. The sclera constitutes the posterior five-sixths of the globe, whereas the cornea comprises the remaining one-sixth.¹⁴

1.4 Ocular bioavailability from ophthalmic dosage forms

Topical ocular drug delivery is a commonly used and desired route for treating disorders that affect the anterior segment of the eye (the cornea, conjunctiva, sclera, iris and lens) (Figure 3). This is because of the fast and local effects, accessibility to the ocular tissue, absolute safety and patient acceptability, as well as the relatively lower risk compared with systemic routes of drug administration.

However, there are many anatomical and physiological barriers forming part of the eye's natural defence. These barriers and protective mechanisms prevent the administered ophthalmic formulations from residing on the eye surface for enough time to allow complete drug absorption. This prevents a significant portion of the instilled dose from being absorbed by the ocular tissue (ocular bioavailability). Therefore, the ocular bioavailability of topically applied drugs from simple solutions is often less than 1%.¹⁵

1.4.1 Anatomical and physiological considerations

The corneal and the conjunctival-scleral routes are the two major routes for ocular drug absorption from topically administered ophthalmic dosage forms.

A) Corneal route

The cornea is the transparent vascular dome-shaped structure at the anterior part of the eye. The anterior corneal surface is covered by the tear film and the posterior surface is bathed by the aqueous humor. The surface area of the cornea is approximately 1.3 cm², forming One-sixth of the surface area of the globe. The cornea is thinnest at the centre and its thickness gradually increases towards the periphery, with mean thickness of 0.5 mm and 0.7 mm respectively. Anatomically, it is divided into five layers. 1. Epithelium 2. Bowman's layer 3. Stroma. 4. Descemet's membrane 5. Endothelium.

B) Conjunctival-scleral route

The conjunctival-scleral route is the major pathway for polar and large-molecular weight drugs to reach the intraocular tissues. For example, high molecular weight drugs such as inulin (mol wt 5500) can gain access to the iris and ciliary body by diffusion via the conjunctival-sclera route. Further, drugs permeated through this route gain access directly to the posterior segment of the eye (choroid, vitreous humour and retina).¹⁶

1.5 Niosomes

Over the last three decades, liposomes of different compositions used for topical ophthalmic drug delivery have increased/prolonged the therapeutic effect while minimising toxic.

1.5.1 Non ionic surfactant vesicular system:-

Vesicles consisting of one or more surfactant bilayers enclosing aqueous spaces are called nonionic surfactant vesicles or simply niosomes. Niosomes are considered of particular interest as they offer several advantages over liposomes:

- Niosomes are more stable chemically.
- Niosomes acquire lower production cost due to the availability of starting materials.
- Niosomes are biodegradable and non-immunogenic .
- Niosomes do not require expensive handling (storing in a freezer and preparation under nitrogen gas).

Nevertheless, the formulation of niosomes can pose challenges due to possible physical instability and poor ability to encapsulate a considerable amount of water-soluble drug molecules. Niosomes should have certain attributes in relation to their potential use as vehicles for ocular drug delivery.¹⁷ These include:

- The size of the vesicle should be large enough to resist drainage by reflex tearing and eye blinking. For example, large multilamellar vesicles (MLV) were found to reside for a longer period on the ocular surface than small unilamellar liposomes. This was attributed to the ability of MLV to entrap a relatively higher amount of the drug and resist nasolacrimal . The same argument applies to niosomes. Ideally, it has been reported that niosome sizes > 10 µm are suitable for ocular delivery.²⁴
- The shape of the prepared niosomes should show some irregularities to fit properly into the *cul-de-sac* of the eye and lodge on the eye surface.
- Ocular niosomes should ideally be thermo-responsive in order to release drug content in a controlled, yet timely manner before being flushed by blinking and nasolacrimal drainage Complete abolishment of gel/liquid transition of surfactant forming niosomes could produce niosomes with an extremely low release rate to water soluble drugs, which does not suit the short residence time of ocularly administered ophthalmic products.¹⁸

1.5.2 Ideal properties of Non-ionic surfactant used in niosomes formation

Hydrophilic lipophilic balance & critical packing parameters of non ionic surfactant are important factors during vesicle formulation rather than micelles. The correlation among the surfactant structure containing size of polar head group plus length of non-polar region in vesicle preparation. Hydrophilic lipophilic balance (HLB) is a good indicator of the vesicle forming ability of any surfactant, HLB number should not be more than 8, if it is increased hydrophilicity will increase so stability of vesicle decreases. If Non-ionic surfactants like polysorbates (tween) are used in formation niosomes have HLB more than 10, thus large concentration of cholesterol requires for stability of niosomes and which in turn results decrease in entrapment efficiency.¹⁹

1.5.3 Classification of non-ionic surfactants

They are characterized as amphiphilic (hydrophobic head and hydrophilic tail) molecules capable for forming vesicle after hydrated in water or solution.²⁰

A. Sorbitan esters

They are prepared by sorbitol esters along with oleic acid anhydrides. Sorbitan esters are water insoluble as reflected by their lower HLB values.

For example; Sorbitan monolaurate , Sorbitan monopalmitate.

B. Polysorbates

They are poly-oxy -ethylene derivatives of sorbitan ester. They are prepared by condensation of sorbitol ester with ethylene oxide moles. Polysorbates are water miscible due to high hydrophilic lipophilic balance value greater than 10.

For example: Poly-oxyethylene Sorbitan tristearate

C. Poly-oxy ethylated glycol mono-ethers

Poly-oxy ethylated glycol mono-ethers are available as Brij series which includes Poly-oxy ethyl lauryl ethers (Brij 30, 35) and Poly-oxy ethyl cetyl ethers (Brij 52, 56)

D. General formula: Cx Ey

X: alkyl chain length and Y: ethylene oxide chain length

E. Poly-oxy ethylated alkyl phenols

Poly-oxy-ethylated t-alkyl phenols are available as Triton-X series which includes X-114 (E 7-8), X-100 (E 9-10) and X-102 (E 12-13).

F. Poloxamers

They are Poly-oxy-ethylene—Poly-oxy-propylene derivatives.

They are commercially available under trade name 'Pluronics'. Pluronic F68 [Polyoxy propylene mol.wt.(1501-1800)+140 mol. ethylene Oxide]

G. Bola- surfactant

These novel surfactants are made up of azacrown ether units connected with longalkyl chain group and capable to form colloidal structure after addition of cholesterol.²¹

Table no. 1.1: HLB values of non-ionic surfactants

Chemical name	Commercial name	HLB Values
Poly-oxyethylene Sorbitan monolaurate	Tween 20	16.7
Poly-oxyethylene Sorbitan monopalmitate	Tween 40	15.6
Poly-oxyethylene Sorbitan monostearate	Tween 60	14.9
Poly-oxyethylene Sorbitan tristearate	Tween 65	10.5
Poly-oxyethylene Sorbitan mono-oleate	Tween 80	15.0
Sorbitan monolaurate	Span 20	8.6
Sorbitan monopalmitate	Span 40	6.7
Sorbitan monostearate	Span 60	4.7
Sorbitan tristearate	Span 65	2.1
Sorbitan mono-oleate	Span 80	4.3
Polyoxyethylene 2 stearylether	Brij 72	4.9
Polyoxyethylene 4 lauryl ether	Brij 30	9.7

1.5.4. Methods of niosomes preparation

A. Ether injection method

In this method vesicles are made by injection or slowly introduction of lipids i.e. non ionic surfactants and cholesterol in ether into aqueous phase heated at 60-65°C. Mechanism of vesicle formation can be attributed to slow evaporation of solvent resulting in ether gradient between surfactant-cholesterol monolayer on interface of ether and water. Consequently may form vesicles from folding of bilayer sheets. Vaporisation of ether leads to formation of single layered vesicle with highest entrapment efficiency.²²

B. Ethanol injection method

In this method slow injection of surfactant: cholesterol: stearic acid and drug in ethanol through a needle into pre-heated aqueous phase. Mechanism of vesicle formation can be attributed to slow evaporation of ethanol solvent resulting in ethanol gradient across surfactant and cholesterol layer at ethanol –water interface and afterwards there is formation of vesicles.²³

C. Film hydration method

In this method non ionic surfactant & membrane stabilizer lipid are mixed in organic solvent like chloroform, methanol, and diethyl ether in round bottom flask. There is formation of thin film of solid mixture by evaporation of volatile solvent on the wall of round bottom flask. Afterwards rehydration of that film occurs by addition of solvent with gentle agitation. Film hydration method forms multi-lamellar niosome.²⁴

D. Sonication

Lipid mixture is added into the water or aqueous solvent and sonicated for specific time interval at definite temperature. Previously multi-lamellar vesicles are formed which undergo vibrations to produce uni-lamellar vesicles.²⁵

E. Reverse phase evaporation

Equimolar ratio of surfactant and lipid are added into organic solvent like chloroform, ether. Hydrophilic drug incorporated in to aqueous phase and sonication of lipid & aqueous phase at low temperature. Due to that gel was formed undergo sonication after adding up phosphate buffer saline. Volatile solvent is removed by application of heat. Produced suspension is diluted with phosphate buffer saline & heated at 60-65°C for 15 min to give niosome.²⁶

F. Aqueous dispersion

It involves lipid dispersion in water having hydrophilic moiety for encapsulation with continuous agitation under controlled temperature conditions leads to homogenous vesiculation. Dispersion may be homogenized or ultra-centrifuged. Homogenization may be followed by bubbling of nitrogen till vesiculation is complete. Bubbles possibly provide spherical gas/air interface for niosome to get organize as per thermodynamic stability requirement. Nitrogen is

subsequently release and allows hydration of amphiphiles to form vesicles.²⁷

G. Micro fluidization

In this method jet principle was used for niosome formation. Two phases i.e. lipid and aqueous phase interact with each other at high velocities. High velocity jet principle give rise to niosome having nano size, good uniformity and reproducibility.²⁸

H. Multiple membrane extrusion method

Extrude technique was used for niosome formation. In this technique thin film was made by evaporation of lipid mixture i.e. surfactant-membrane stabilizer. Lipid film hydrated with water or phosphate buffer saline having hydrophilic API and resulting mixture extruded via membrane filter made by polycarbonate. Extrusion takes place serially to obtain niosome of desired size.²⁹

I. Trans membrane pH gradient process

Lipid mixture dispersed in organic solvent subsequently lipid film was obtained on wall of round bottom flask. Hydration of film takes place with addition of acid like citric acid by vigorous agitation. Produced multilamellar vesicles undergo freeze thaw cycle and later go through sonication. Later API aqueous solution is added and agitated. Mixture pH was raise to 7.0 – 7.2 by disodium phosphate 1M addition. Finally mixture is heated at 65°C to give niosome.³⁰

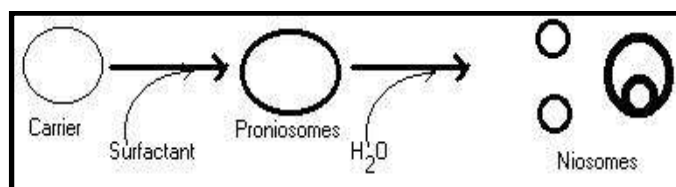
J. Bubble method

This is innovative technique used in niosome preparation excluding organic solvent. Round bottom flask contain three neck areas for reflux, thermometer and nitrogen supply inlet respectively. Lipid mixture was dispersed in phosphate buffer saline later on undergoes high pressure homogenizer. Instantly supply of nitrogen gas at 65-70 °C owing to bubble formation and obtained the vesicle.³¹

K. Niosomes from proniosomes

In this method surfactant coating on the sorbitol or water soluble carrier, output of this method is dry formulation. Niosome was prepared form proniosome by the addition of water phase at elevated temperature which was greater than mean phase transition temperature.³²

Fig no.1.3 Mechanism of niosome formation



1.5.5 Factors affecting niosomes formulation

1. Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. In polyoxyethylene glycol (PEG) coated vesicles; some drug is entrapped in the long PEG, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

2. Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

3. Cholesterol content and charge

Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

4. Resistance to osmotic stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

5. Membranes Composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral

niosome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24- oxyethyleneether), which prevents aggregation due to development of stearic unhydrance. In contrast spherical Niosomes are formed by C16G2: cholesterol: solution (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solution C24 in ration (91:9) having bigger size (8.0 ± 0.03 mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solution C24 in ratio (49:49:2) (6.6 ± 0.2 mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from niosome.³³

1.5.6 Characterization of niosomes

1.5.6.1 Micromeretic properties

i) Size

Niosome is sphere in shaped and vesicle size could be find out by microscope technique, Beckmann's particle size analyzer etc. This parameter is important because it has been observed that release rate; shelf life of preparation depends on vesicle size.³⁴

ii) Shape and morphology

It is determined by microscopic techniques under 400X magnification. Such studies are important because the composition and concentration of bilayer affects the shape.

E.g. Vesicles prepared with C16G2 (Hexadecyl diglycerol ether) and Solulan C24 (Stearic stabilizer cholesteryl-poly-24-oxyethylene ether) alone formed polyhedralniosomes. Cholesterol, in addition, formed spherical- tubular niosomes. Also, the method adopted for vesicle preparation is found to influence their final morphology. E.g. Hand shaking technique forms MLVs whereas ether injection method produces unilamellar vesicles.³⁵

1.5.6.2 Entrapment efficiency

It was find out by removals of free drug as of the niosomal dispersions by dialysis, centrifugation or using sephadex columns. Direct estimation is carried out by use of markers and disruption of vesicles by surfactants like Solulan C-24, Triton X-100 or 50 % propanol.³⁶

In case of centrifugation method untrapped drug can be determined from clear supernatant. Formula of entrapment efficiency (%) is given as bellow.

$$\text{Entrapment Efficiency (\%)} = (A-B/A) \times 100 \text{ OR}$$

$$\text{Entrapment efficiency (\%)} = (C/A) \times 100$$

A = Initial concentration drug

B = Drug in supernatant

C = Drug entrapped in niosomes

1.5.6.3 In-vitro release

API release rate was determined using dialysis method. Non ionic surfactant dispersion was filled in dialysis sac which is previously washed and sinks in phosphate buffer or water. Afterwards dialysis sac was placed in phosphate buffer solution maintained at 37°C. On specific duration buffer sample was withdrawn and find out drug concentration using suitable analytical method.³⁷

II. CONCLUSION

Niosomes, a nonionic surfactant vesicular system, is a novel and efficient approach to drug delivery. With the incorporation of appropriate nonionic surfactant and cholesterol in the vesicular membrane, a wide range of drugs can be encapsulated into niosomes. In addition, niosomes possess enhanced stability and reduced toxic drug effects, with sustained release of the encapsulated drug. Furthermore, no special conditions are required for handling and storage of niosomes, compared with other drug-delivery systems such as liposomes. Appropriate modifications of niosomes, resulting in structures such as proniosomes, enable them to be used in special routes of administration. In summary, niosomes represent a highly effective tool for drug delivery in the therapeutic regime of numerous diseases and have the potential to provide more efficacious treatment than conventional drug-delivery platforms.

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