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A Review Article Niosomal Drug Delivery for Oral Route

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Abstract: *Niosomes are artificial vesicles with potential technological advantages. They are non- ionic surfactant vesicles. As efficient drug delivery systems with a wide range of uses, niosomes have the same potential benefits as phospholipid vesicles (liposomes), including the capacity to hold both water- and lipid-soluble pharmaceutical molecules. Niosomes can also be thought of as more cost-effective, chemically stable, and occasionally physically stable alternatives to liposomes. Simple preparation techniques and commonly used surfactants in pharmaceutical technology can be employed to create niosomes. Numerous studies have covered noisome physicochemical characteristics and their uses as drug delivery vehicles. This review article focuses on the concept of niosomes, advantages and disadvantages, composition, method of preparation, factors influencing the niosomal formulation and characterization, application of niosomes. Niosomes can be utilized in the treatment of several diseases like Psoriasis, leishmaniasis, cancer, migraine, Parkinson etc. Niosomes can be used as diagnostic aid. Niosomal technology is widely used in cosmetics. Still researchers have to focus a lot on the commercial utility of niosomes in drug delivery.*

Keywords: Niosomes, surfactant, vesicles

I. INTRODUCTION

Niosomes are non ionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. Niosomesare either unilamellar or multilamellar vesicles that have a better stability than liposomes. Niosomes are formed on admixture of nonionic surfactant, cholesterol with subsequent hydration in aqueous medium.

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he investigate a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, & niosomes.

Defination of Niosomes

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionicsurfactants, with or without incorporation of cholesterol or other lipids.

The sizes of niosomesare microscopic and lie in nanometric scale. The particle size ranges from 10nm-100nm.

Structure of Niosomes

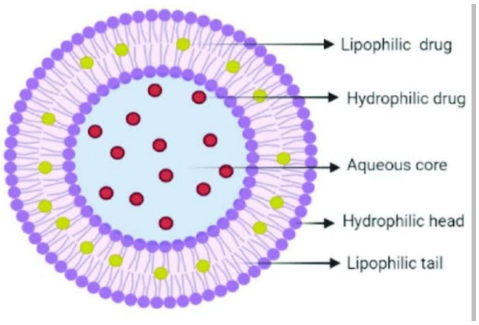

Fig.1.struture of Niosomes

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The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself.

Advantages of Niosomes

- They are osmotically active and stable.
- They increase the stability of the entrapped drug
- Handling and storage of surfactants do not require any special conditions
- They increase the oral bioavailability of drugs
- They enhance the skin penetration of drugs
- They be used for oral, parenteral as well topical route.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- The vesicle suspension being water-based vehicle offers high patient compliancewhen compared to oily dosage forms.
- Drug molecules of wide range of solubilities can be accommodated in the niosomes provided by the infrastructure consisting of hydrophilic, lipophilic and amphiphilic.
- They can release the drug in sustained/controlled manner.
- Storage and handling of surfactants oblige no special conditions like low temperature and inert atmosphere.
- They can act as a depot formulation, thus allowing the drug release in a controlled manner.
- They enhance the oral bioavailability of poorly soluble drugs.
- They possess stable structure even in emulsion form.
- Therapeutic concert of the drug molecules can be improved by tardy clearance from circulation.
- They can protect the active moiety from biological circulation.

Disadvantages of Niosomes

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion

FORMULATION OF NIOSOMES

Composition

Niosomes mainly contains following types of components:

1. Non-ionic surfactants:

Selection of surfactant should be done on the basis of HLB value.As Hydrophilic Lipophilic Balance (HLB) is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. It is also reported that the hydrophilic surfactant owing to high aqueous solubility, on hydration do not reach a state of concentrated systems in order to allow free hydrated units to exist aggregates and coalesced to form lamellar structure.

E.g. Spans (span 60, 40, 20, 85, 80)
Tweens (tween 20, 40, 60, 80) and
Brijs (brij 30, 35, 52, 58, 72, 76).

2. Cholesterol:

Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer

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characteristics can not be discarded. In general, incorporation of cholesterol affect properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity. As a result of this, the niosome become less leaky in nature.

3. Water or buffer solution:
This serves as the continuous phase in which the niosomes are dispersed.

4. Active pharmaceutical ingredients (APIs):
are the drugs that you want to deliver using the niosomes, which can include various therapeutic agents like:
Anticancer drugs (e.g., doxorubicin) Antibiotics (e.g., gentamicin) Antifungal agents (e.g., amphotericin B) These Anti-inflammatory drugs (e.g., diclofenac)

5. Classes of Surfactants Utilized in the Niosomal Formulation
Ether linked:-
Hydrophilic and hydrophobic moieties are ether linked in these surfactants11. Eg: polyoxy ethylene alkyl ethers (CnEOm)

Dialkyl chain surfuctant:-
It has the molecular weight of 972.It is used in the sodium stibogluconate niosomal formulation.

Ester linked surfactant:
Hydrophilic and hydrophobic moieties are ester linked in these surfactants.

Sorbitan esters:
They are H-C-OH mixtures of the partial esters of sorbital

poly-sorbates:
Polysorbates are used in the niosomal entrapped methotrexate pharmacokinetics studies.

Types Of Niosomes
The niosomes are classified as a function of the number ofbilayer (e.g. MLV, SUV) or as a function of size. (e.g.LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below:

- Multilamellar vesicles (MLV)
- Large unilamellar vesicles(LUV)
- Small unilamellar vesicles (SUV)

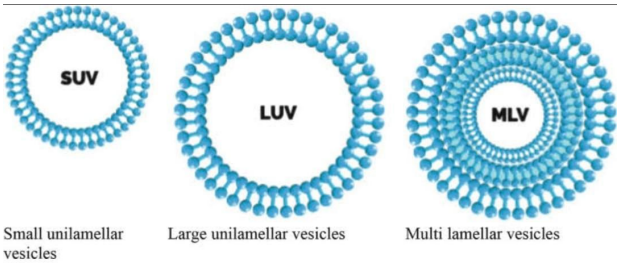

Fig .2 Types of Niosomes

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Multilamellar Vesicles (MLV)

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.thin film hydration method and transmembrane ph gradient method was used for the preparation of multilamellar vesicles.

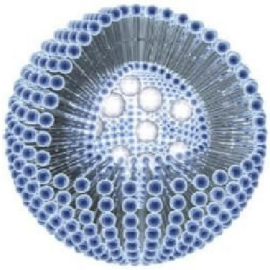

Fig.3.Mulitilamellar Vesicles (MLV)

Large Unilamellar Vesicles (LUV)

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids the sizeof large unilamellar vesicles is more than 100 nm, Ether injection method and reverse phase evaporation method was used for the preparation of large unilamellar vesicles

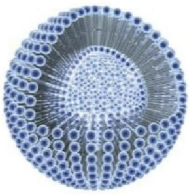

Fig.4.Large Unilamellar Vesicles (SUV)

Small Unilamellar Vesicles (SUV)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion.the size of small unilamellar vesicles is upto 100 nm i.e 20-50 nm

Fig.5.Small Unilamellar Vesicles (SUV)

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Factors Affecting Niosomes Formulation

Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups. In polyoxyethylene glycol (PEG) coated vesicles; some drug isentrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment. The physicochemical properties of encapsulated drug affect charge and rigidity of the niosome bilayer. Here drug interacts with surfactant head group and develops the charge which creates mutual repulsion between surfactant bilayer and hence increase vesicle size [1,14] Another factor to be considered is whether the drug to be encapsulated is amphiphilic. The best example of such a drug is doxorubicin. When encapsulated in niosomes,aggregation occurred and was overcome by the addition of asteric stabilizer. The increase in encapsulation of a drug that occurs when more is added could be the result of saturation of the medium.

Amount and Type of Surfactant

The mean size of niosomes increases proportionally with increase in the HLB surfactants likeSpan 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.

Cholesterol Content and Charge

Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment. 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.

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 probablys 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.{1}

Effect of Additives

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 noisome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24- oxyethylene ether), which prevents aggregation due to development of stearic hydrance. 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

Method of Preparation

1. Hand Shaking method
2. Reverse phase evaporation technique
3. Ether Injection method
4. Multiple membrane extrusion method
5. Bubble method
6. Sonicatio
7. Proniosomes

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1. Hand Shaking method

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask.

The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask.The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation.This process forms typical multilamellar Niosomes.

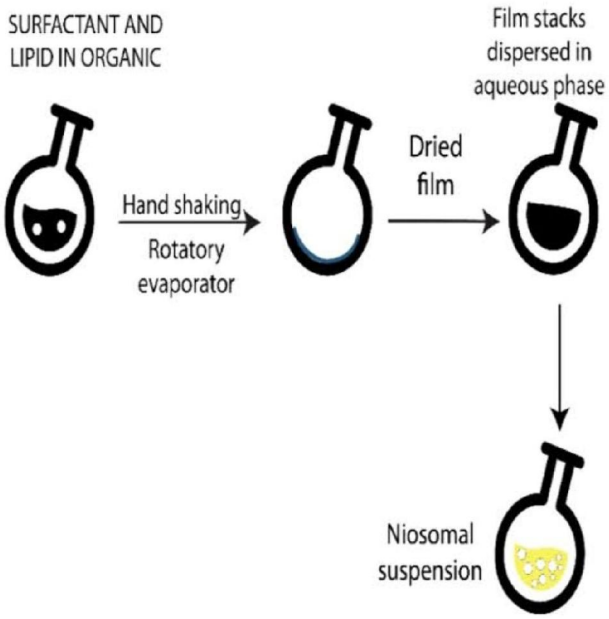

Fig.6. Hand Shakig Method

2. Reverse phase evaporation technique

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C.The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C underlow pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at60°C for 10 min to yield Niosomes

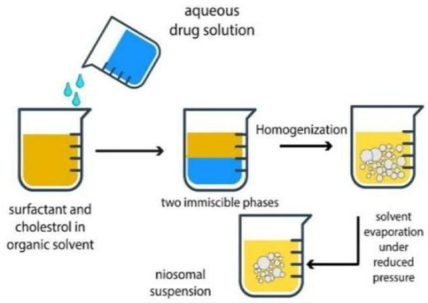

Fig.7. Reverse phase evaporation technique

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3. Ether Injection method

This method provides a means of making Niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C.The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material.Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm

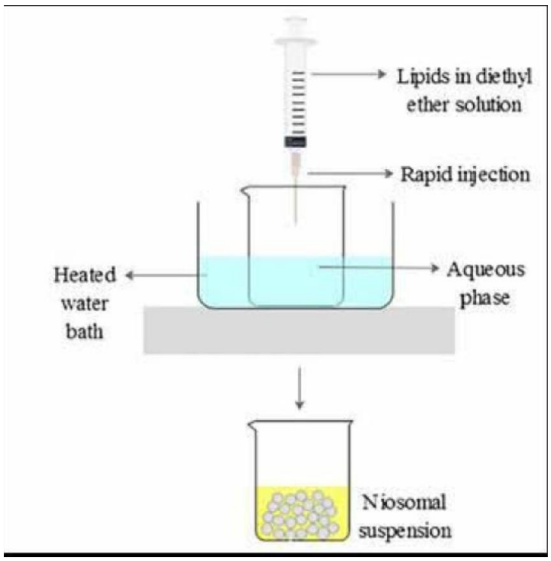

Fig.8..Ether Injection method

4. Multiple membrane extrusion method

A mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a good method for controlling niosome size.

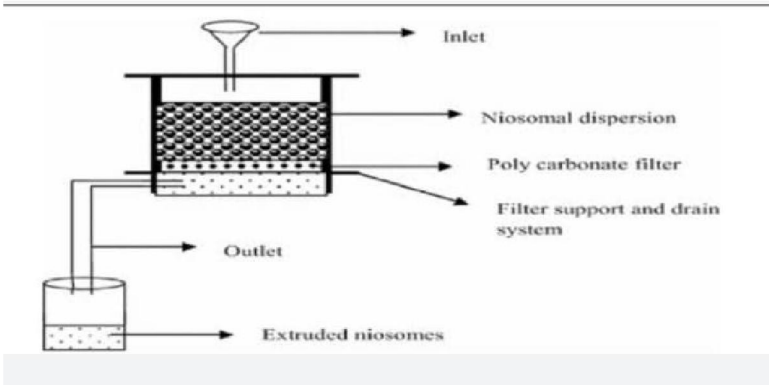

Fig.9. Multiple membrane extrusion method

5. Bubble method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

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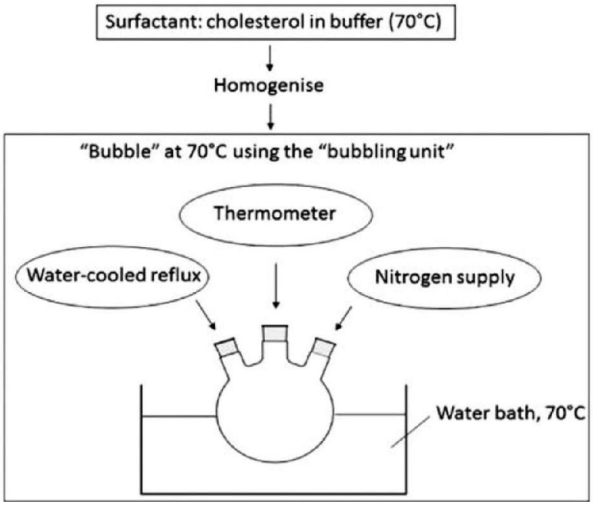

Fig.10. Bubble method

6. Sonication

A typical method of production of the vesicles is by Sonication of solution. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10- ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield Niosomes.

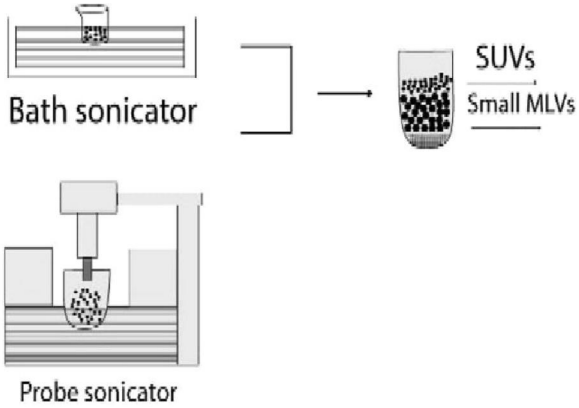

Fig.11.Sonication

7. Proniosomes

The niosomes are recognized by the addition of aqueous phase at T>Tm and brief agitation (where T- Temperature and TM-Phase transition temperature) Another method of producing niosomes is to coat a water soluble carrier such as sorbitol with surfactant The result of the coating process is a dry formulation. In which each water soluble particle is covered with thin film of dry surfactant This preparation is called as "proniosomes"

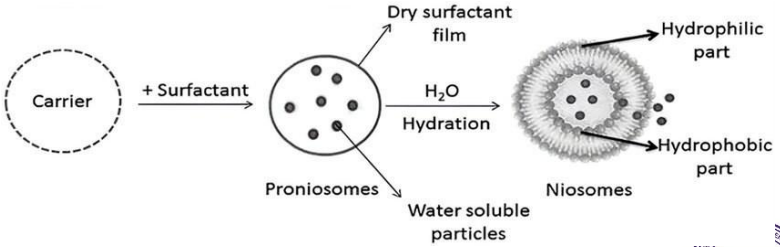

Fig.12. Proniosome

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8. Delivery strategies

The administration of niosomes by various routes has been reported and it is clear that the route is important in designing a vesicular formulation. For example, enoxacin, a fluoroquinolone antibiotic with a broad spectrum of activity, has a plasma half-life after oral administration of only 3–6 h such that frequent dosing is necessary for effective antibiotic therapy. Subsequently, the oral formulation was withdrawn due to a high frequency of drug interactions and adverse effects and a transdermal delivery system based on niosomes was developed. This is now the preferred formulation because it reduces the adverse effects of oral administration and provides a long duration of action.

1. Oral Route

The oral route is generally preferred leading to a research emphasis on delivery of niosomes via the oral route. A niosome formulation of acyclovir providing a Higuchi pattern of drug release was found to enhance sustained release of drug in an in vivo study in rabbits. In this study, the oral bioavailability and MRT of acyclovir were increased more than 2-fold compared to a tablet dosage form. Similarly, a Span 60 niosome formulation of fluconazole with an encapsulation efficiency>91% showed sustained release by zero order followed by first order kinetics.Griseofulvin loaded niosomes have been subjected to an in vitro–in vivo correlation study, which showed that niosomes were an efficient way to enhance the bioavailability and sustained delivery of griseofulvin via the oral route. These studies all indicate that niosomes are a promising delivery systems for sustained drug release. However, the main obstacles to oral delivery are hepatic first pass metabolism and GI irritation, limitations that can be overcome using other routes of administration. For oral immunization, mannosylated nonionic surfactant based vesicles have been developed for the efficient delivery of plasmid DNA encoding small subunit proteins of hepatitis B virus. Rifampicin and gatifloxacin loaded niosomes were effective against the tubercle bacilli for prolonged periods and were better than the conventional dosage form because of the reduced dose and greater patient compliance.

Characteristics of Niosomes:

- Vesicle diameter and morphology.
- Vesicle charge.
- Bilayer formation.
- Number of lamella
- Drug loading and encapsulation efficiency.
- In-vitro drug release.
- Stability studies

Vesicle diameter:-

Niosomes are spherical in shape and the size range from 20nm to 50µm. Techniques used to determine the vesicle size and size distribution include light microscopy, coulter counter, and photon correlation microscopy and freeze fracture electron microscopy. Scanning electron microscopy, atomic force microscopy and cyto transmission electron microscopy are used to determine the shape and surface characteristics of the niosomes

Vesicle Charge

The vesicle surface charge plays a major role in the stability and behaviour of niosomes. Charged niosomes are found to be more stable than uncharged niosomes against aggregation and fusion. Surface potential of niosomes can be estimated by the zeta potential measured by micro electrophoresis or dynamic light scattering. PH sensitive fluorophores can be used as an alternative method.

Bilayer formation

Bilayer vesicle formation can be characterized by x-cross formation due to the assembly of non-ionic surfactants under light polarization microscopy.

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Number of lamellae:-

Number of lamellae in vesicles is characterized by NMR spectroscopy, electron microscopy and small angle Xray scattering.

Drug loading and encapsulation efficiency:-

Drug loading and encapsulation efficiency of niosomal dispersion is determined after the separation of unentrapped drug. The unentrapped drug is separated by dialysis or centrifugation or gel filtration.

In-vitro drug release

In-vitro drug release of niosomes can be characterized by the following methods :

- Dialysis
- Reverse dialysis
- Franz diffusion cell

Dialysis:

It is the simplest method used to determine the invitro release kinetics of the niosomal loaded drug. Dialysis tubing is used.

Reverse dialysis:

1 ml of dissolution medium is taken in a number of small dialysis tubes into which niosomes are added. Then the niosomes are displaced from the dissolution medium.

Franz diffusion:-

Niosomes are dialyzed against suitable dissolution media through a cellophane membrane at room temperature in Franz diffusion cell. Now-a-days FRET is used to monitor the release of encapsulated matter in niosomes.

Stability of niosomes:

Stability of niosomes is indicated by the constant particle size and constant concentration of entrapped drug. Stability of niosomes depends upon the concentration and type of surfactant, cholesterol.

E.g.: Sonicated spherical niosomes are stable at room temperature. Sonicated polyhedral niosomes are instable at room temperature but stable at the temperature above the phase transition temperature.

II. CONCLUSION

From the past few decades, there is a great revolution in development of novel drug delivery system. The technology of utilizing niosomes as promising drug delivery system is still in its infancy. Niosomes have shown a profound influence in targeting the particular organ and tissue. Niosomes can serve as better diagnostic agents, vaccine delivery system, tumour targeting agents, ophthalmic, nasal and transdermal delivery systems. Research has to be carried out extensively to have commercially available niosomal formulations. Oral formulation has been preferred and most common route of drug delivery.In the begining of the work, drug authentication was performed. The authentication study showed that the obtained sample of Glimepiride was pure and complied with IP limit.Niosomes are versatile in structure, morphology and size; they can entrap hydrophilic drugs in aqueous compartments to decrease the degradation of durg.Glimepiride niosmes were prepared with an provide the drug prolonged period of timein the stomach.Glimepiride was targeted to stomach because it has the absorption window in upper part of GIT so it has been provided for prolonged period of time in stomach for better therapeutic activity by increasing its bioavailability. Glimepiride is an Antidibetic drug of BCS class II having low solubility and high permeability.

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