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A Review on Formulation and Evaluation of Niosomal Gel

Mr.S.Md.Fazal UI Haq[1*] N.shirisha*
Centre for Pharmaceutical Sciences, JNTUH, Kukatpally, Telangana.
Centre for Pharmaceutical sciences, Institute of Science and Technology, Hyderabad, Telangana, 500085.

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ABSTRACT
Niosomes are the novel drug delivery system composed of vesicular nanocarriers. Niosomes are bilayerd, microscopic and nonionicformed by the self-assemblyof non-ionic surfactants in the aqueous phase. They are biocompatible, biodegradable, nontoxic, more stable, inexpensive and have a tendency to load different types of drugs. They show sustained drug release and the bio adhesion, enhance the contact time of gel. Niosomes are prepared mostly by thin film hydration method by using different ratios of non-ionic surfactants and cholesterol, then evaluated for entrapment efficiency, particle size and shape, invitro release studies. They are used in treatment of several diseases like psoriasis, Parkinson, migraine and fungal infections. Niosomal gel sustains the drug release for a prolonged period of time by protecting drug from enzyme metabolism.
Key words: Niosomes, Bio adhesion, Sustained release, Bilayerd.

I. INTRODUCTION

Niosomes are bilayered microscopic lamellar structures with a size range between 10-10000nm. They are formed by self-association of non-ionic surfactants in aqueous phase. They are spherical in shape and consists of lamellar (unilamellar & multilamellar) structures. Encapsulation of the drugs in niosomes improves the drug permeation. They can encapsulate bothhydrophobic and hydrophilic drugs. Hydrophilic drugs can be delivered by adsorbing on the surface of the bilayer or by entrapping the drug in aqueous core of particle, hydrophobic drugs are delivered by encapsulating the drug into bilayer of non-ionic surfactants.[4]Niosomes are composed of non-ionic surfactants, lipids and polymers where surfactants act as penetration enhancers and lipids are used to provide rigidity and proper shape. Niosomes are obtaining much attention because of their advantages like physical and chemical stability, content uniformity, low cost, convenient storage and various surfactants are available forniosomal formulations.[5]Niosomal formulations minimizes drug degradation, inactivation of drug after administration and prevents side effects. Niosomal gel formulations are used in treatment of various diseases like arthritis, gout, psoriasis and antifungal infections. zetasizer and metasizer are used for size determination of niosomes.[4]

1.2 ADVANTAGES[3-10]

- Drug release in sustained and controlled manner.
- Enhances permeation of drug through skin.
- Niosomal surfactants are biocompatible, biodegradable and low immunogenic.
- Enhances oral bioavailability of poorly soluble drugs.
- Protects drug from enzyme metabolism.
- Niosomes are osmotically active and stable as well as they increase the stability of drug.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The vesicles may act as a depot, release the drug in a controlled manner.
- They can protect the active moiety from biological circulation.
- Handling and storage of surfactants requires no special conditions.

1.3 DISADVANTAGES[14]

- Multilamellar vesicles prepared by extrusion and sonication method is time consuming and requires specializedequipment's.
- Limited shelf life for aqueous suspension of niosomes due to fusion, aggregation and leaking of entrapped drugs.

II. COMPOSITION OF NIOSOMES[7-10]

The two main components used for the preparation of niosomes are:

- Nonionic surfactants
- Cholesterol.

2.1 Nonionic surfactants

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Nonionic surfactants are the surface-active agents used in preparation of niosomes due to more benefits like stability, biocompatibility and less toxiccompared to anionic & cationic surfactants. They are amphiphilic molecules consists of hydrophilic head group and hydrophobic tail which affect the entrapment efficiency of drug. Most frequently used nonionic surfactants for the preparation of niosomes are Tweens (tween 20,40,60,80), Spans (span 60,40,20,85,80), Brijs (brijs 30,35,52,58,72,76).

Table 1: Examples of Nonionic surfactants[7]

TYPE OF NONIONIC SURFACTANT	EXAMPLES
Ethers	Brij, Lauryl glucoside, Decyl glucoside, Nonoxynol-9
Esters	Glyceryl laurate, Spans, Polysorbates
Fatty alcohol	Stearyl alcohol, Cetyl alcohol, Oleyl alcohol
Block polymers	Poloxamers

Selection of surfactants is based on hydrophilic-lipophilic balance(HLB) and critical packing parameter values.

HLB (Hydrophilic Lipophilic Balance)

HLB indicates the solubility of the surfactant which is dimensionless parameter. The lower the HLB value indicates the more lipophilic nature of the surfactant and higher the HLB value denotes the hydrophilic nature of surfactant. HLB value between 4 and 8 were found to be compatible with vesicle formation.

CRITICAL PACKING PARAMETER(CPP)[16]

CPP is used to determine the geometry of vesicle to be formed from surfactants is affected by its structure.The geometry of vesicle to be formed can be predicted on the basis of critical packing parameters of surfactants. It can be defined by the following equation:

$$CPP=V/lc\times a_0$$

Where V= hydrophobic group volume

Lc = the critical hydrophobic group length

a_0 = area of hydrophilic head group

2.2 Cholesterol

Cholesterol is a steroid derivative, which provides proper shape and rigidity to niosome form. cholesterol in niosomes increases membrane stability and decreases the fluidity of the membrane.

III. TYPES OF NIOSOMES[7-20]

Niosomes are classified into three groups based on vesicle size and preparation method.

a) Multilamellar vesicles(MLV).
b) Large unilamellar vesicles (LUV).
c) Small unilamellar vesicles (SUL).

Table 2: Types of Niosomes.

Parameters	Multi lamellar vesicles	Large unilamellar vesicles	Small unilamellar vesicles
Vesicle size	> 0.5µm	> 0.10µm	0.025-0.05µm
Preparation method	Hand shaking method	Reverse phase evaporation method	Sonication, extrusion method, solvent dilution technique

IV. PREPARATION OF NIOSOMES[3-7]

The method of preparation influences the size, size distribution and number of bilayers, entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

a) Thin film hydration method
b) Reverse evaporation technique
c) Ether injection method
d) Sonication
e) The bubble method
f) Micro fluidization
g) Membrane extrusion method
h) Formation from pro-niosomes

4.1 Thin film hydration method (TFH):

TFH method is one of the most widely used and simple method for preparation of niosomes. In TFH method drug is dissolved in an organic solvent such as chloroform or a mixture of organic solvents in a round bottomed flask; surfactant and cholesterol are added at different ratios. The organic solvent is removed under vacuum at 60^0 C by rotary evaporator till the thin film formation. The film is dried for 5min under

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vacuum to remove residual solvents. Furthermore, the dried film is hydrated with phosphate buffer pH 7.4 at 60^0 C. Hydration of lipid film leads to formation of niosomes. The resulting niosomal suspension was mixed by vortex mixing and sonicated by probe sonicator.

4.2 Reverse phase evaporation:

In this method, accurately weighed quantities of cholesterol and surfactants (1:1) are dissolved in a mixture of ether and chloroform. Then an aqueous phase containing drug is added to it, resulting two phases are sonicated at 4-5℃. The clear gel formed is again sonicated by adding small amount of phosphate buffer saline (PBS). Then the organic phase is removed at 40^0 C under low pressure. The resulting niosomal suspension is diluted with PBS and heated at 60^0 C for 10 min on a waterbath to yield niosomes. The niosomal suspension formed is stored in refrigerator in a closed container.

4.3 Ether injection method:

In this method niosomes are prepared by dissolving nonionic surfactant and cholesterol in diethyl ether then drug is dissolved in above lipid solution. Then this solution is taken into a syringe and injected slowly through a needle into aqueous phase (phosphate buffer pH7.4) held in beaker and agitated slowly. Vaporization of solvent results in formation of niosomes and separated by ultracentrifugation.

4.4 Sonication:

In this method, an aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a 10ml glass vial. Then the mixture is probe sonicated at 60^0 Cfor 3 minutes using sonicator with titanium probe to yield niosomes.

4.5 Bubble method:[10]

It is a novel technique for preparations of niosomes, consists of round bottomed flask with three necks positioned in water bath to control the temperature, Water cooled reflux and thermometer are placed 1^{st}&2^{nd} necks and nitrogen supply though 3^{rd} neck. Cholesterol and surfactant are dispersed in buffer (pH 7.4) at 70^0 C, nitrogen gas is bubbled at 70^0 C to yield niosomes.

4.6 Micro fluidization:

The principle involved in this technique is submerged jet principle, in which two fluidized streams interact with each other at ultra high velocities, in the micro channels within the interaction chamber. Impingement of thin liquid sheet along with a common front is arranged so that the energy supplied to the system remains within the area of niosomes formation. It results in the formation of niosomes with greater uniformity, smaller size and better reproducibility.

4.7 Membrane extrusion method:

Desired size of niosomes can be prepared by this method. The mixture of surfactant, cholesterol and diacetyl phosphate in chloroform forms thin film rotary evaporator. Then the film is hydrated with aqueous drug polycarbonate membranes and the resultant suspension extruded by which it isplaced in series of 8 passages.

4.8 Formation from pro-niosomes:

Proniosome is a dry formulation in which each water-soluble particle was covered with a thin film of dry surfactant. The niosomes were recognized by adding the aqueous phase at T>Tm with brief agitation.T is the temperature and Tm is the mean phase transition temperature.

4.9 SEPERATION OF UNENTRAPPED DRUG[16]

The removal of unentrapped solute from the vesicles can be done by various technique, which include:

Dialysis:

The aqueous niosomal dispersion is dialyzed in a dialysis tube against phosphate buffer or glucose solution.

Gel filtration:

The unentrapped drug is removed by gel filtration of niosomal dispersion through sephadex-G-50 column and elution with phosphate with phosphate buffer saline.

Centrifugation:

The niosomal suspension is centrifuged and then supernatant is separated. The pellet is resuspended to give a niosomal suspension free from unentrapped drug.

The prepared niosomes are incorporated into an appropriate gel base made up of polymers (Carbopol-R-940) and stirred with mechanical stirrer until no lumps are observed, then allowed it to hydrate for overnight. Then the ph. of the gel was adjusted by adding triethanolamine.

V. EVALUATION OF NIOSOMES[5-6]

5.1 Entrapment efficiency:

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Entrapment efficiency is to determine the amount of drug loaded in niosomes by centrifugation method. Niosomes containing drug was separated from unentrapped drug by centrifugation. After, separation niosomal pellets are washed with distilled water for 2 times. The supernatant separated each time was estimated by UV spectroscopy. Encapsulation efficiency was calculated by the following equation:

EE% = (amount of entrapped drug/total drug added) *100

5.2 Particle size:

The shape of niosomal vesicles is assumed to be spherical and various techniques used to determine the mean diameter of vesicle like optical microscopy, laser light scattering method, Dynamic light scattering.

Optical microscope: A drop of niosomal formulation was taken on a glass slide and placed a cover slip over it then, observed under optical microscope to evaluate the vesicle size of niosomes.

5.3 IN VITRO DRUG RELEASE[7-19]

In vitro drug release study can be characterized by the following methods:

1. Dialysis
2. Reverse dialysis
3. Franz diffusion

1.Dialysis

A dialysis sac is washed and soaked in distilled water. Then the niosomal suspension is placed into the dialysis sac which is hermetically sealed and placed in 200ml buffer solution in 250ml beaker with constant shaking at 25℃. The samples are withdrawn at various time intervals and drug content analysis is done by suitable method.

2. Reverse dialysis

In this method, 1ml of dissolution medium is taken in number of small dialysis tubes into which niosomes are added then the niosomes are displaced from the dissolution medium.

3.Franz diffusion cell

Niosomes are placed in the donor chamber of Franz diffusion cell fitted with cellophane membrane, where, niosomes were dialyzed against a suitable dissolution medium at room temperature. Then the samples are withdrawn at various time intervals and analyzed for drug content by using suitable method like UV spectroscopy, HPLC (High Performance Liquid Chromatography).

5.4 Surface morphology:

The niosomal formulation was determined for shape and surface morphology by using TEM (Transmission Electron Microscope) at an accelerating voltage of 100kv.

5.5 Organoleptic characters:

Niosomalformulations were visually inspected for color,clarity and presence of any foreign particles.

5.6 Viscosity:

Viscosity of niosomal gel was measured by using Brookfield viscometer with spindle number 4 and 50rpm rotation speed,25^0 c. This measurement was done for 3 times and average readings are calculated.

5.7 Spreadability:

The spreadability of gel formulation was determined by placing 1.0g of gel sample on the lower slide and upper slide was placed on the top of the sample. It was determined by the formula:

$$S=M*L/T$$

Where S is spreadability, M is weight tied to the upper slide, L is length travel by upper slide and T is time.

5.8 PH:

Digital PH meter is used to measure the pH of niosomal gel by using standard buffer solutions of pH 4. Average of three readings was taken to calculate the ph.

5.9 Drug content:[6]

The amount of drug present in niosomal formulation was determined by dissolving the formulation in a solvent and absorbance is measured at 311nm to calculate the drug content.

5.10 Stability:

The stability study was performed at different storage conditions for few weeks and evaluated for particle size, drug content, entrapment efficiency at various time intervals.

VI. APPLICATIONS OF NIOSOMAL GEL[10-19]

Niosomal drug delivery is applicable to many pharmacological agents for the action against various diseases.

a) Ophthalmic drug delivery

The major drawback of ocular dosage forms like ophthalmic solution, suspension and ointments is difficult to achieve excellent bioavailability due to tear production, transient residence time and impermeability of corneal epithelium. But niosomal drug delivery can be used to achieve excellent bioavailability of the drug.

b) Transdermal drug delivery

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Increase in penetration rate can be achieved by transdermal delivery system of niosomes with good bioavailability and enhances therapeutic efficiency. Where, slow penetration of drug through skin is the major disadvantage of transdermal dosage forms.

c) Immunological application of niosomes

Niosomes are used for studying the nature of immune response provoked by antigens. Brewer and alexander reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

d) Niosomal formulations are used in treatment of various diseases: arthritis, schizophrenia, antifungal diseases.[4]

e) Topically applied niosomal gel increases the residence time of drugs in stratum corneum.

f) Niosomal gel used in glaucoma treatment has improved bioavailability.

g) Sustained and control release of drugs is the major application of niosomal gel.

Table 3: List of drugs formulated as Niosomes[19-21]

Routes of administration	Examples of drugs
Transdermal route	Piroxicam, Estradiol,Levonorgestrol, Ketoconazole, Ketorolac, Nimusulide, Flurbiprofen
Intravenous route	Dichlofenac sodium, Methotrexate, Rifampicin, Zidovudine, Cisplatin, Doxorubicin, Indomethacin, Colchicine, Flurbiprofen, Amarogentin
Peroral route	Proteins, Peptides, DNA Vaccines, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin
Ocular route	Cyclopentolate, Timolol Maleate
Nasal route	Sumatriptan, Influenza viral vaccine
Inhalation	All trans retinoic acids

VII. CONCLUSION

Niosomes are novel drug carriers with a size range from 10-1000nm. They are prepared by different methods which provides sustainedand prolonged drug delivery with enhanced bioavailability and improved patient compliance. Niosomal gel formulations shows better drug release, prolonged action and stable at different storage conditions than non niosomal formulation.These niosomal formulations enhances the permeation of drug through skin due to bio adhesive property of the gel.

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