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REVIEW ARTICLE **OPEN ACCESS**

Niosomes : A Future of Targeted Drug Delivery System

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ABSTRACT
Niosomes are characteristically alternative to the liposomes and are referred as non-ionic surfactant vesicles. They are structurally similar to liposomes and biodegradable, relatively non-toxic, biocompatible, more stable, in-expensive & also exhibit flexibility in their structural characterization. The niosomes can exhibit encapsulate different type of drugs i. e both hydrophilic & lipophilic drugs within their multi environmental structure. The niosomes are the vesicular system with their bilayer structure assembled by non-ionic surfactants and able to enhance the bioavailability of a drug to a pre-determined area for a period. The entrapment efficiency is promoted due to the amphiphilic nature of niosomes& other additives such as cholesterol can be used to maintain the rigidity of niosomal structure. Niosomes are also preferred in diagnostic imaging and as a vaccine adjuvant. As being non-ionic they also improves the therapeutic index of the drug by restricting its action to target cells. This narrative review focuses on the fundamental aspects of the niosomes including their structure, methods of preparation, advantages, disadvantages & applications.
Key words: Niosomes, Cholesterol, Hydrophilic & lipophilic drug, surfactant, NSVs.

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INTRODUCTION:

Niosomes are the surfactant based vesicles consist of unilamellar/multilamellar structures enclosing lipophilic components and an adequate solution of solutes are called niosomes. These are the non-ionic surfactant vesicles produced by self-assembly of the hydrated surfactant monomers [1]. These are the structure of niosomes formed by mixing non-ionic surfactant, cholesterol & diethyl ether along with the subsequent hydration in aqueous media comprising the lamellar structures of the size ranges between 10 to 1000nm. The various advantages of niosomes over the liposomes are stability associated problems which includes oxidation, high economy, a purity that influences on size and shape as it consist of non-immunogenic, biodegradable & biocompatible surfactants [2]. The non-ionic surfactant such as span-60 can be usually stabilized by the addition of the small amount of anionic surfactant such as diacetyl phosphate. The main reason for preferring niosomes over liposomes is because of the high chemical stability & economy. These non-ionic surfactants offer several advantages and are

- Higher patient compliance when compared with other dosage forms.
- The non-ionic surfactant vesicles act as a depository, which results to a controlled manner for releasing of drug.
- Solubility's varying with wide range can be accommodated by drug molecule [3].

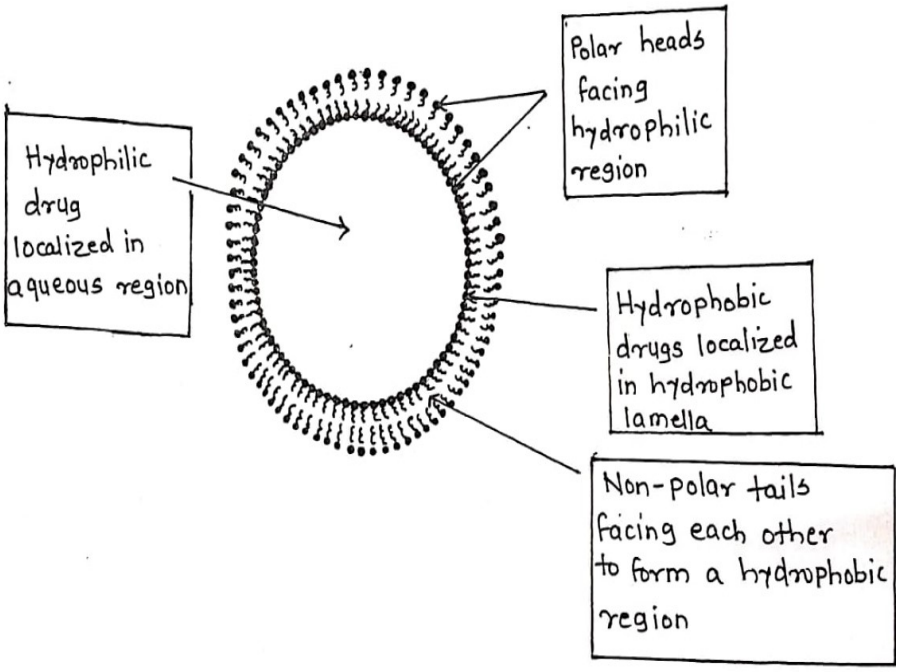

Fig. 1: Structure of Niosome

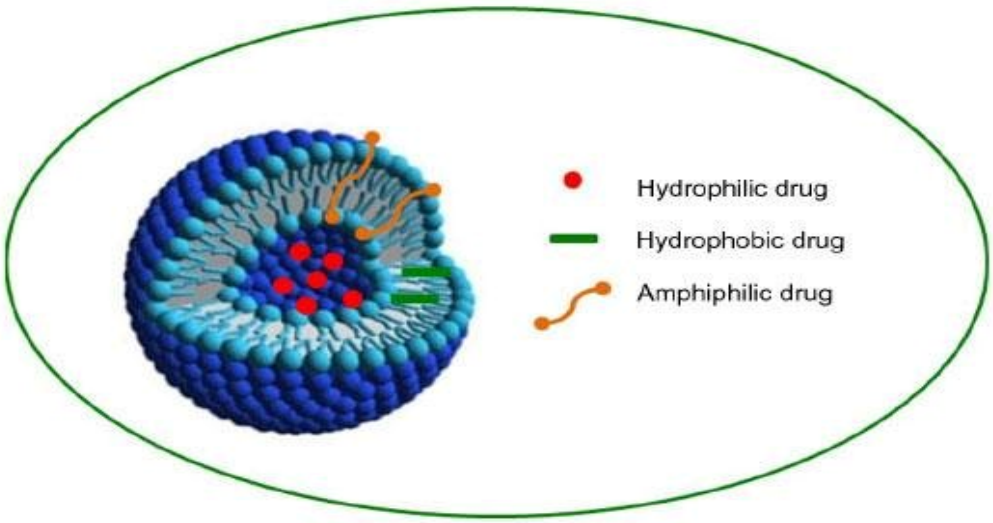

Fig. 2: Schematic Presentation of Niosomal Vesicle [6]

COMPOSITION OF NIOSOMES

There are two components which are used in niosomes preparation are,

a) Cholesterol
b) Non-ionic surfactant

A. Cholesterol is referred as an steroid derivative, which is preferred to provide rigidity and proper shape, confirmation to niosome form. It also increases the entrapment efficiency but these are usually added to the non-ionic surfactants used to give adaptable & orientational order to the niosomal bilayer. Cholesterol is also responsible for liquid phase transition of niosomal system resulting in niosomes and also called as abolish gel.

B. The non-ionis surfactants which are generally used for the preparation of niosomes are,
   Ex.Tween 20, 40, 60 &80.
   Spans 20, 40, 60, 80 & 85.

C. Other additives : It includes the charge inducers which increases which are responsible for the surface charge density & prevent flocculation, aggregation and fusion of the niosomes. The two types of negatively & positively charged molecules are intended for induction of charge in niosomes. The

use of diacetyl phosphate (DCP) & stearyl amine (SA) is preferred which includes negative or positive charge on membrane and thereby helps to stanilize the formulation [5,6].

Table 1: Different types of Non-ionic Surfactants [8]

Type of Non-Ionic Surfactants	Example
Fatty Alcohol	Cetyl alcohol, Stearyl alcohol, cetostearyl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl alcohol, Trixon X-100, Nonon Xymol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block Copolymers	Poloxamers

Types of Niosomes:

The various types of niosomes are as follows,

i. Multi lamellar vesicles (MLV)
ii. Large unilamellar vesicles (LUV)
iii. Small unilamellar vesicles (SUV)

Table 2: Types of Niosomes

	MLV	SUV	LUV
Parameters	Greater than 0.05µm	0.025-0.05 µm	Greater than 0.10 µm
Methods of Preparation	Hand shaking method	Sonication Extrusion method Solvent dilution tech.	Reverse phase evaporation method

Salient features of Niosomes

- These are osmotically active.
- The bioavailability of the particular drug can be increased just by computing the drug moiety from biological environment.
- These are less in toxicity and the therapeutic efficacy of drug can also be improved by blocking its acion to target cells.
- They also improves the therapeutic action of the drug by blocking its acion to target cells with less toxicity.
- They alter the organ distribution & metabolic stability by extending the circulation of entrapped drug moiety.

Applications of Niosomes [9, 10]

- It is an vehicle suspension with water-based vehicle. Due to this property it gives high patient compliance when related to other oily dosage forms.
- It consists of an infrastructure which is hydrophilic, amphiphilic & lipophilic moieties together and as a result could adopt drug moieties with a wide range of solubilities.
- Niosomesare osmotically stable and active and arealso responsible for the increase in the stability of entrapped drug.
- Niosomes enhances the oral bioavailability of the poorly absorbed drugs and helps for the skin penetration of the skin.
- Niosomes causes delayed clearance of drug from the circulation which leads to improve in the therapeutic performance of the drug.
- They are also refrred as carriers for iobitridol, a diagnostic agent used for x-ray imaging.

Advantages of Niosomes [11]

- Niosomes can adopt a variety of drug moieties such as hydrophilic, lipophilic and amphiphilic.
- By altering the composition of vesicle size, surface charge and concentration vesicle characteristics can be controlled.
- They can increase bioavailability of poorly soluble drugs when administered orally.
- Niosomes allows controlled release of the drug due to the depot formulation.
- Niosome released drug in both sustained and controlled manner.
- the drug moiety can be protected from enzyme metabolism.
- The entrapped drug stability enhances due to the niosomal formulations.

- Increases permeation of drug through the skin.
- Suitable for all routes of drug administration.

Disadvantages of Niosomes [12]

- Not suitable for aqueous formulations because of problems such as fusion, aggregation, leaking of entrapped drug.
- Time consuming method and require specialized equipments for processing.

Table 3. Comparison between Niosomes and Liposomes [8]

Liposomes	Niosomes
More expensive	Less expensive
Require special methods for handling and storage of the final formulation.	No special methods require for such formulation
Phospholipids may be neutral and charged.	Non-ionic surfactant is uncharged.

METHODS AND TECHNIQUES OF PREPARATION OF NIOSOMES:

1. **Sonication**

Typical method of preparation of niosomes in which drug solution in buffer is added to the aqueous solution of surfactant/Cholesterol in a 10ml glass vial. Then the mixture is kept for sonication at 60 ^{0}C for 3 minutes using a sonicator which in turn leads to the formulation of unilamellar vesicles [13].

Mixture containing drug solution in the surfactant, cholesterol & buffer

⇓

To yield niosomes sonicated with a titanium probe sonicator at 60□ for 3 minutes

2. **Ether Injection Method**

In this method of niosomes preparation is done by slowly introducing a solution containing a particular ratio of cholesterol & surfactant in diethyl ether into warm water maintained at 60□. Then into aqueous solution of drug through 14-gauze needle the resultant surfactant mixture in ether is injected. Afterwards formation of unilamellar vesicles of surfactants containing drug occurs due to the vaporization of ether. Depending upon he formulation variables and conditions used vesicle ranges from 50 to 1000nm[14].

A specific particular ratio of cholesterol and surfactant were dissolved in diethyl ether into warm water maintained at 60^{0}C

⇓

The above prepared mixture in ether is then transferred through 14-gauge needle into an aqueous solution of material

⇓

As ether vaporizes it leads to the formation of the single layer vesicles

⇓

Depending upon the conditions use the diameter of the vesicles ranges from 50-1000 nm

3. **Reverse phase evaporation technique**

In this method cholesterol and surfactant are dissolved in the mixture of organic solvent such as ether and chloroform. Then to the above solution the aqueous phase having drug solution is added and sonicated at 4-5℃. After the addition of a small amount of phosphate buffered saline (PBS), the clear gel is obtained which is again followed by sonication. The organic phase is removed by at 40^{0}C under low pressure. Then the resulting viscous niosomal preparation is diluted with PBS & heated on a water bath at 60^{0}C for 10 min to yield niosomes [15].

4. **The Bubble method**

The Bubble method is used for the preparation of niosomeswhich dont have any use of organic solvents. The bubbling unit is formed by round bottomed flask with three necks and to control the temperature it is held in water bath. Then the thermometer and water-cooled reflux is positioned in the first and second neck respectively and through the third neck nitrogen is supplied. Then the cholesterol and surfactant are dispensed in the buffer (pH 7.4) at 70^{0}C and with high shear homogenizer the dispersion is mixed for 15 seconds and immediately afterwards bubbled at 70^{0}C using nitrogen gas [16].

Bubbling unit involves round-bottomed flask with three neck position in water bath to control the temperature

Water-cool reflux is positioned in the first neck and the nitrogen supply occurs through the third neck as the thermometer is positioned in the second neck

Surfactant and Cholesterol are dissolved in the buffer (pH 7.4) at 70^0C high shear homogenizer is used for the dispersion mixing for 15 seconds

"Bubbled" at 70^o using nitrogen gas

5. **Thin film hydration technique/ Hand shaking method**

Vesicle forming ingredients such as surfactant and cholesterol are mixed together in a round bottom flask and dissolved in a volatile organic solvent such as methanol, diethyl ether or chloroform. Afterwards the organic solvent is evaporated at room temp by using a rotary evaporator at 20^0C which leads to the formation of a thin layer of solid mixture. Then the surfactant film (dry) is rehydrated by using aqueous phase at 0-60^0C with gentle agitation, which leads to the development of niosomes [17].

The mixing of ingredients - charge inducer, surfactant and cholesterol

The above mixture is dissolved in a round bottom flask containing a volatile organic solvent (chloroform, diethyl ether or methanol)

The organic solvent is then evaporated at room temperature 20°C by using rotary evaporator

Forming a thin layer of solid mixture

With gental agitation dry surfactant film formed is re-hydrated using an aqueous phase at 0-60°C

Formation of niosomes

6. **Multiple membrane extrusion method**

In this method a blend of surfactant, cholesterol and di-acetyl phosphate are dissolved in chloroform and the solvent is evaporated using a thin film evaporator. Afterwards using aqueous drug solution the film is re-hydrated and the resultant suspension is extruded through polycarbonate membrane, which are kept in a series up to 8 passages. This is the novel method for controlling niosomal size.

7. **Ethanol injection method**

Usually for the preparation of small unilamellar vesicles the ethanol injection method is preferred without sonication. In this method, in the excess of saline or other aqueous medium an ethanol solution containing surfactant is injected rapidly through a fine needle. Afterwards the formation of vesicles occurs due to the evaporation of the ethanol [18].

An ethanol solution containing surfactant is injected rapidly through a fine needle

Into excess of saline or other aqueous medium

Vaporization of ethanol

Formation of vesicles

8. **Micro Fluidization**

The technique followed in this method involves the submerged jet principle in which two fluidized streams interact with each other at ultra high velocities and in the micro channels within the interaction chamber. Afterwards the thin liquid sheet impingements along with common front are arranged such as that the energy supplies remain same within that of the area of niosomes formulation, followed by the formation of niosomal vesicles of greater uniformity, smaller size & better reproducibility [19].

9. **Trans membrane pH gradient drug uptake process**

First organic solvent were taken in which cholesterol and surfactant were dissolved referred as remote loading process

(chloroform)

⇓

Under reduced pressure solvent gets evaporates and the thin film is produced upon the wall of round bottom flask

⇓

By using 300 mm citric acid (pH4.0)the film was hydrated which is then followed by vortex mixing

⇓

Multilamellar vesicles are frozen and thawed 3 times and later sonication

⇓

Aqueous solution with drug concentration 10 mg/ml of drug is added and vortex for niosomal suspension

⇓

The pH of the sample is maintained to 7.0-7.2 using 1M disodium phosphate

⇓

To yield niosomes the mixture is then kept for heating at 60°C for 10 minutes [20]

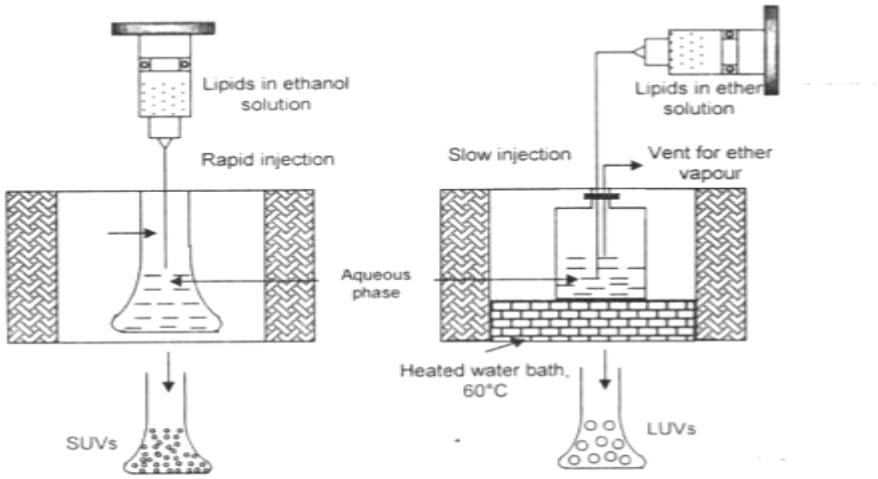

Fig. 3: Diagrammatic Representation of Ether Injection Method and Ethanol Injection Method for Preparation of Niosomes

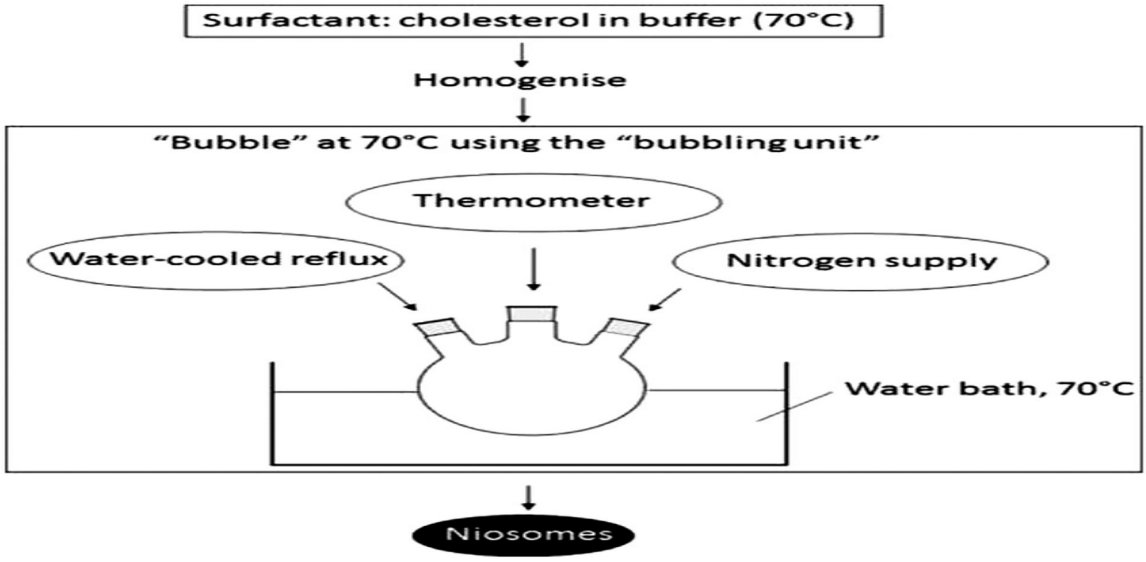

Fig. 4: Diagrammatic Representation of Bubble Method of Preparation of Niosomes

FACTORS INFLUENCING NIOSOMAL FORMULATIONS:

1) **Nature of surfactant**

As the HLB value of surfactants increases it leads to increase in the mean size of niosomes due to decrease in the surface free energy with an increase in the surfactant hydrophobivity.

Ex, Span 60 with higher TC exhibits better entrapment.

The surfactants having HLB value which varies from 14 to 17 are not suaitable for the niosomal preparation. Decrease in the HLB value of surfactants from 8.6 to 1.7 decreases the entrapment efficiency and highest entrapment efficiency is found with the HLB value of 8.6 [20].

Table 4.HLB values of surfactants [6]

Sr. No.	Surfactant	Chemical Name	HLB
1.	Span 20	SorbitanMonolaurate	8.6
2.	Span 40	SorbitanMonopalmitate	6.7
3.	Span 60	SorbitanMonostearate	4.7
4.	Span 80	Sorbitan Mono-oleate	4.3
5.	Tween 20	Polyoxytethylene(20)sorbitanmonolaurate	16.7
6.	Tween 60	Polyoxytethylene(20)sorbitanmonostearate	15
7.	Tween 72	Polyoxytethylene(2)stearyl ether	4.9
8.	Tween 76	Polyoxytethylene(10)stearyl ether	12.4
9.	Tween 78	Polyoxytethylene(20)stearyl ether	15.3

2) **Nature of encapsulated drug**

The nature of drug affects the charge and elasticity of the niosomal bilayer due to the physicochemical properties of the niosomes. The degree of entrapment is also influenced by the HLB of drug. The drug entrapment occurs by interacting with the surfactant head groups leading to the increasing charge & produces the mutual extension of the bilayer of surfactant and thus increases the vesicle size [21].

3) **Hydration temperature**

The temperature of hydration affects the size and shape of the niosomes. The hydration temperature should be above the liquid phase transition temperature. Sometimes the change in assembly of surfactants into vesicles and vesicle shape modification occurs due to the modification in temperature. Volume of hydration medium and hydration time are also responsible and preferred for the modification. Improper selection of the hydration medium, time, hydration temperature and volume produces fragile niosomes or drug leaking problems may arise [23].

4) **Cholesterol Content**

The entrapment efficiency & hydro-dynamic diameter of niosomes can be increased by the incorporation of the cholesterol. The increase in the concentration of the cholesterol causes an rising in the bilayers rigidity and decreasein the release rate material which is encapsulated. Mainly cholesterol acts in two ways :

- Increase in the chain order of bilayers of the liquid state.
- The chain order of the gel state bilayers gets decreased due to the cholesterol content [22].

5) **Charge**

The presence of charge leads to the increase in the inter lamellar distance successive bilayers in multi lamellar vesicle structure and greater overall entrapped volume.

6) **Resistance to osmotic stress**

The use of hypertonic solution results in the trimming in the vesicle diameter. In hypertonic solution, reticence of eluting fluid from vesicles results in slower release and initially followed by the faster release due to the instinctive slacken of vehicle structure under osmotic pressure [27].

Table 5.Nature of drug and its effect on its stability [32]

Nature of the drug	Leakage from the vesicles	Stability
Hydrophobic drug	Decreases	Increases
Hydrophilic drug	Increases	Decreases
Amphiphilic drug	Decreases	-
Macromolecules	Decreases	Increases

CHARACTERIZATION OF NIOSOMES:

Different parameters are used for the evaluation of niosomes, such as measurement of vesicle size, optical microscopy, vesicle charge, entrapment efficiency, freeze-fractur, bilayer rigidity & homogenicity, thermal analysis *etc.*

1. **Bilayer rigidity &Homogenecity**

As the bio-distribution and biodegradation of niosomes are influenced by rigidity of the bilayer. Homogenecity occur both in niosome dispersion also in niosome structure & identified by D.S.C, F.T.I.R & P-NMR [24].

2. **Size and Shape**

Different methods are used for the determination of mean diameter such as laser light scattering method beside that it can also be determined by Optical microscopy, photon correlation microscopy, molecular sieve chromatography, Electron microscopy [24].

3. ***In-vitro* release**

The *in-vitro* release study can be done by the use of,

a) Dialysis tubing
b) Reverse dialysis
c) Franz diffusion cell

a) Dialysis tubing : In this method a dialysis sac is washed with distilled water. Then the prepared vesicle suspension is pipetted into a bag which is made up of tubing dialysis and after that the bag is sealed. After that the bag with the vesicle suspension placed in 200ml of buffer solution in a 250ml beaker with continuous shaking at 25^0C as it is an convenient assay method.

b) Reverse Dialysis : The proniosomes are placed in a 1ml of dissolution medium as the number of small dialysis.The proniosomes are then kept into the dissolution medium. The direct dilution of the proniosomes can be possible with this method and the rapid release cannot be calculated by using this method.

c) Franz diffusion cell : The *in-vitro* diffusion study can be carried out by Franz dissusion cell. Theniosomes are kept in the donor compartment of a frantz diffusion cell with cellphane membrane. The proniosomes are then subjected against a favourable dissolution medium at desirable room temperature. The withdrawal of the samples from the medium at favourable intervals & analyze for drug content using U. V. Spectroscopy, HPLC *etc* [25].

4. **Vesicle charge**

In the behaviour of niosomesi.e both in *in-vivo* & *in-vitro* the vesicle surface charge play an important role. Because in general the charged niosomes has been seen more stable against the fusion & aggregation when compared with uncharged vesicles. This can be achieved by microelectrophoresis. Is is an alternative approach to the use of pH-sensitive flurophores. In recent advanced techniques, dynamic light scattering have been used to measure the zeta potential of niosomes [26, 22].

5. **SEM (Scanning electron microscopy)**

After the preparation of niosomes they were observed under a SEM.

6. **Niosomal drug loading & Encapsulation efficiency**

For the determination of the drug loading and encapsulation efficiency, the niosomal aqueous supernatant was removed & sediment was washed twice with distilled water in order to remove the absorbed drug [23, 31].

7. **Freeze – fracture**

The niosomes were examined by means of the freeze-fracture microscopy technology. Samples are impregnated in 30% glycerol and then frozen into partially solidified Feron 22, freeze-fractured in a freeze-fracture device(-105℃, 10-6 mmHg) and replicated by evaporation from a platinum/carbon gun. The replicas were thoroughly washed with distilled water, picked up onto formvarcoated grids and examined with a Philips Cm 10 transmission electron microscope [29].

8. **Transmission ElecrtronMicroscopy(TEM)**

By using TEM the morphology of hydrated noisome dispersion can be examined by TEM. For about 1min a drop of dispersion was stratified onto a carbon coated grid and should be kept to adhere on the carbon substrate. By usinga piece of filter paper the dispersion present in excess should be removed. A drop of 2% phosphotungstic acid solution was stratified and again the solution in excess was again removed by a tip of filter paper. The sample should be air-dried and observed under electron microscope at an accelerating voltage of 80kV [32, 36].

9. **Thermal Anlysis**

Differential scanning calorimetry (DSC) were performed to investigate gel-liquid transition temperature of niosomes. The phase transition temperature was also referred as the temperature that instigate a conversion of the gel phase to a liquid physical state with the closely packaging of molecules, to liqiid crystalline phase, loosely packed molecules and fluid. A small amount of freezed-dried niosomes was sealed in 40 µl aluminium crucible. For the conservation of freeze-dried samples, 1 ml of niosomal suspension was chilled or frozen in liquid nitrogen and freeze dried all over night in a lyophilizer. A second crucible having the equivalent correspondent mount of PBS (pH 7.4) h as been sealed as the reference cell. The temperature of the pans was raised from 20-80℃.At the rate of 5℃/min and a calorimeter. With indium the heat flow calibration can be performed. By broadcasting the temperature cycle three times for each sample the reliability of the thermograms can be determined [32, 34, 37].

10. **Stability study**

The niosomal formulation were treated for the stability studies by storing at 4℃, 25℃& 37℃ in the thermostat oven for the time period of about three months. After every one month group, drug content of all the formulation were checked by entrapment efficiency parameter[37].

Table 6. Marketed formulations of Niosomes [14]

Sr. No.	Brand	Name of the product
1.	Lancome- Foundation and complexation	Flash retouch Brush on concealer
2.	Britney Spears – Curious	Curious Coffert: Edp Spray 100ml + DualendedParfum& Pink Lipgloss + Body soufflé 100ml
3.	Loris Azzaro _ Chrome	Chrome Eau De Toilette Spray 200 ml
4.	Orlane – Lipcolor and Lipstick	Lip gloss

Table 7.List of drug formulated as Niosomes [14]

Routes of administration	Examples of drugs
Intravenous route	Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin,Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
Peroral route	DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
Transdermal route	Flurbiprofen, Piroxicam, Estradiol Levonorgestrol,Nimesulide,Dithranol, Ketoconazole, Enoxacin, Ketorolac
Ocular route	Timolol Maleate, Cyclopentolate
Nasal route	Sumatriptan, Influenza Viral Vaccine
Inhalation	All-trans retinoic acids

CONCLUSION

Niosomes are the nop-ionic surfactant vesicles and alternative to liposomes. They have several advantages over liposomes, such as their improved purity, relatively lower cost and higher chemical stability when compared with liposomes. Niosomes are preferred as one of the great revolution in drug delivery technologies. The concept of encapsulating the drug in the niosomes and to target niosomes at the specific site is extensively welcomed by the researchers and academicians. The niosomes are also responsible for altering the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of drug.

FUTURE ASPECTS

Niosomes represent an encouraging and promising and drug delivery molecule. As it is having lot of scope for encapsulating the various anti-cancer, anti-infective, anti-viral drugs *etc.* in niosomes for minimizing the toxicity and undesirable effects of that drug. When compared with charged drug carriers they are safer because charged drug particles are relatively toxic and unsuitable.

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