



# **Niosomes: A Promising Novel Nano Carrier for Drug Delivery**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

Niosomes are vesicles, which are formulated by hydrating the mixture of cholesterol, non-ionic surfactant and other biodegradable lipids. Niosomes increase the drug activity as compare to their conventional dosage form of a drug. Niosomes can be used as carrier of amphiphilic and lipophilic drugs. Niosomes may overcome the issues related to instability, fast degradation, low bioavailability, and insolubility of medications. The structure of niosomes either multilamellar or unilamellar, is depends on the method of formulation. Niosomes contain very efficient drug delivery potential for site-specific delivery of anti-cancer, anti-infective agents, etc. Niosomes are stable as well as cost effective carriers as compared with other drug formulations. Niosomes also have various applications in parental drug delivery system, topical drug delivery system, oral drug delivery system and novel drug delivery system such as targeted drug delivery system and controlled drug release system.

**Keywords:** Niosomes; amphiphilic; lipophilic; multilamellar; unilamellar; non-ionic surfactant.

## **1. INTRODUCTION**

Nowadays, there is no chance of any available drug delivery model to achieve the site-specific

delivery with controlled release kinetics of drug in desire manner. The present conventional dosage form often have side effects and complication

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due to their wide distribution throughout the body fluids. The localization of drug action in injured tissue is promising way to cure this tissue [1]. Drug targeting can be defined as the ability to specifically target the therapeutic agent to the desired site of action, with little or no interaction with non-targeted tissues. The purpose of drug targeting is to obtain a desired therapeutically response at a selected site without unwanted interaction at other sites [2]. In the modern era, number of drug-carriers was utilized to carry drug at the specific target organ/tissue such as immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes and many more. Among different carriers niosomes are well organised as well as documented drug delivery model to achieve goals. This is highly significant in cancer chemotherapy and in treatment of autoimmune disorders like Ankylosing spondylitis, Rheumatoid arthritis. Niosomes are the novel drug delivery system in which the hydrophilic drugs are entrapped in the core cavity, whereas hydrophobic drugs in to the non-polar region [1].

They are amphiphilic in nature. The drugs are encapsulated in a vesicle, which is made by non-ionic surfactant. The size of niosomes are very tiny. They have highly vesicular bilayer membrane made up of non-ionic surfactant with or without incorporation of non-ionic surfactant with or without incorporation of cholesterol and phosphate. The formation of vesicle aggregates requires some energy input, and all the pre-experimental methods studied involve hydrating the surfactant mixture on the gel at the liquid transition temperature of the system and then reducing the size to obtain a colloidal dispersion. Due to their potential ability to deliver various therapeutic agents, these vesicles are widely used as drug delivery systems to achieve targeted drug delivery, controlled release, and improved permeability. In fact, niosomes can work as therapeutic reservoirs for delivery of a drug in a controlled manner to amplify bioavailability, obtaining a desire therapeutic effect over a longer period of time, and can be

converted by altering the composition, concentration of various chemicals, and surface charge of vesicle components and membrane additives [3]. In addition, drug ionization has been shown to adjust the physical and chemical properties of vesicles and their percutaneous penetration curve; in the past few decades, niosomes have been widely studied as potential carriers for sustained and targeted drug delivery because they can easily reprivatisation to increase the versatility of the vesicles and the correct affinity for the target site [4].

### 1.1 Which One is better in Comparison between Niosomes and liposomes?

- Niosomes and liposomes are functionally the same, with similar physicochemical properties depending on the composition of the bilayer and the preparation methods used. They act as amphipathic vesicles and can be used for targeted and sustained drug delivery.
- Niosomes in the body is similar to that of liposomes. In addition, niosomal and liposomal vesicle structures have almost the same applications in the pharmaceutical and cosmetic fields, despite their different forms and chemical properties. Unit; Niosomes are composed of surfactants, while liposomes are mainly based on phospholipids, which means that niosomes are more balanced and do not have some of the risks associated with liposomes, as well as the high cost, low availability and variable purity associated with phospholipids[5].
- In addition, niosomes do not require special conditions such as low temperature or inert atmosphere during manufacturing and storage; these characteristics make niosome more attractive for industrial production. On the other hand, compared with liposomes, niosomes have many advantages, such as improving the intrinsic properties of skin penetration[6]

**Table 1. Comparison of niosomes and liposomes**

|                         | <b>Niosomes</b>                    | <b>Liposomes</b>                      |
|-------------------------|------------------------------------|---------------------------------------|
| Components              | Surfactants                        | Phospholipids                         |
| Component availability  | High                               | Low                                   |
| Component purity        | Good                               | Variable                              |
| Formulation and storage | No exceptional conditions required | Inert atmosphere and less temperature |
| Stability               | Fine                               | Less                                  |
| Cost                    | Less                               | More                                  |

## 1.2 Toxicity of Niosomes

- The toxicity of niosomes is related to their components, i.e., non-ionic surfactants are more biocompatible and less toxic than their anionic, amphoteric, and cationic counterparts. When the same surfactant exists in the form of a vesicle system, these properties are severely impaired. There are few published studies on the toxicity of niosomes and the types of surfactants they contain.
- Hofland evaluated the toxicity of the types of surfactants used in niosomes to human keratinocytes and showed that due to the enzymatic breakdown of ester bonds, the ester type surfactants are less toxic than the ether type [7].
- In addition, hemolysis tests are traditionally used to predict the toxicity of surfactants and derived vesicle systems. It has recently been shown that the ability of niosomes to destroy red blood cells depends on the length of the alkyl chain in the surfactant and the size of the colloidal aggregates in the solution. It is speculated that shorter carbon chains can better penetrate red blood cell membranes and destroy their molecular organization; Niosomes are more difficult to interact with biofilms, leading to significant hemolysis.
- Niosomes made with Boloform surfactants showed encouraging safety and tolerability data in human keratinocytes in vitro and in vivo tests. These volunteers did not use drug-free Boloform niosomes for topical treatment. Skin erythema will appear [7].

## 2. STRUCTURE OF NIOSOMES

Niosomes are spherical and consist of microscopic lamellar (unilamellar or multilamellar) structures. Niosomes are made up of a bilayer. Niosomal bilayer made up of non-ionic surfactants. Most of surfactants when immersed in water there is formation of micellar structures, however some surfactants are form bilayers which converts into niosomes [8]. The formation of bilayer is done by non-ionic surfactants, with or without cholesterol and a charge inducer. Various types of surfactants at variable combinations and molar ratios are used to form niosomes. Instance of surfactants include alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters. The addition of cholesterol maintains the rigidity of the double layer and makes niosomes

less leaky. At the same time, the loading sensor assists the loading of the vesicles, which increases the size of the vesicles and improves the efficiency of drug absorption. Negative charge inducers, including dicetyl phosphate, dihexadecyl phosphate, and lipoamino acid, and positive charge inducers, including stearylamine and cetylpyridinium chloride help to stabilize the vesicles [9]. Non-ionic surfactants in niosomes tend to orient themselves in such a way that hydrophilic end faces outward (toward the aqueous phase), and the hydrophobic ends point inward to each other, forming a closed two-layer structure, containing dissolved substances in the aqueous solution. Therefore, the closed bilayer structure of niosomes has hydrophilic inner and outer surfaces, with a sandwiched lipophilic area in between. To form a closed two-layer structure, energy such as heat or physical stirring is required. Various forces inside the vesicles were found to play a vital role to preserve the vesicular structure example such as, van der Waals and repulsive forces that exist among the surfactant molecules. They are form MLVs, LUVs, SUVs based on their preparation of methods. The niosomal bilayer have the hydrophobic chains are face each other within the bilayers and hydrophobic ends exposed on the outer side and inside of the vesicles [10].

### 2.1 Classification of Niosomes

Niosomes are classified based on following manner.

1. Based on number of bilayers
2. Based on the size of niosomes

According to these classification, niosomes are described as follows:

#### 2.1.1 Multilamellar vesicles (MLV)

Multilamellar vesicles (MLVs) contain number of bilayer surrounded by the aqueous lipid bilayers. The normal average sizes of multilamellar vesicles (MLVs) are 0.5-10  $\mu\text{m}$ . multilamellar vesicles (MLVs) are mostly used because of their simple preparation and stable for long periods of time. Multilamellar vesicles (MLVs) are used as drug carrier for lipophilic compounds.

#### 2.1.2 Large unilamellar vesicles (LUV)

LUV niosomes have size between 100-300 nm. They have a high aqueous phase to surfactants compartment ratio.

### 2.1.3 Small unilamellar vesicles (SUV)

The size of SUV are 10-100nm. SUV niosomes are produced from MLV by different methods, such as high-pressure homogenization, sonication and extrusion under high pressure. There are the some disadvantages of small unilamellar vesicles: they tend to aggregate, the drug loading in these vesicles are comparatively less and they are unstable thermodynamically.

### 2.1.4 BOLA-niosomes

BOLA surfactant compounds contain two hydrophilic heads and connected by one or two lipophilic tails.

### 2.1.5 Proniosomes

They obtained by a thin film of dry non-ionic surfactant from a water-soluble carrier. The carrier should be nontoxic, safe, poorly soluble in the mixture solutions, and have good water solubility.

### 2.1.6 Apsosomes

It is a combination of cholesterol, highly charged lipid diacetyl phosphate and acorbylpalmitate. It increase the transdermal permeation of drug.

### 2.2.1 Materials used in preparation of niosomes

### 2.1.7 Discomes

Under the certain condition non-ionic surfactant, some large disc like niosomes are form. This type niosomes are used for the ocular drug delivery system.

### 2.1.8 Elastic niosomes

They have ability of flexibility without destroying their structure. Therefore, they pass from the pores smaller than their size. Their structural flexibility improve their penetration capability through into the skin [11-13].

### 2.2 Composition of Niosomes [14,15]:

- i. Cholesterol: It is a steroidal derivative. It provide rigid and proper shape to niosomes.
- ii. Non-ionic surfactant: It used for formulation of niosomes.

Example:

- Tweens (20, 40, 60, 80)
- Spans ( 20, 40, 60, 80, 85)
- Brij ( 30, 35, 52, 58, 72, 76, 92)

**Table 2. Surfactants use for preparation of niosomes**

| Sr. No. | Non-ionic surfactants  | Examples   |
|---------|--|--|
| 1       | Alkyl ethers <ol style="list-style-type: none"> <li>i. Alkyl glycerol ethers</li> <li>ii. Polyoxyethylene glycol alkyl ethers (Brij)</li> </ol>                        | Hexadecyldeglycerol ether<br>Polyoxyethylene glycol alkyl ethers 30, Polyoxyethylene glycol alkyl ethers 52, Polyoxyethylene glycol alkyl ethers 72, Polyoxyethylene glycol alkyl ethers 76, Polyoxyethylene glycol alkyl ethers 78  |
| 2       | Alkyl esters <ol style="list-style-type: none"> <li>i. Sorbitan fatty acids esters (Spans)</li> <li>ii. Polyoxyethylene sorbitan fatty acid esters (Tweens)</li> </ol> | Sorbitan fatty acids esters 20, Sorbitan fatty acids esters 40, Sorbitan fatty acids esters 60, Sorbitan fatty acids esters 65, Sorbitan fatty acids esters 80, Sorbitan fatty acids esters 85<br>Polyoxyethylene sorbitan fatty acid esters 20, Polyoxyethylene sorbitan fatty acid esters 40, Polyoxyethylene sorbitan fatty acid esters 60, Polyoxyethylene sorbitan fatty acid esters 65, Polyoxyethylene sorbitan fatty acid esters 80, Polyoxyethylene sorbitan fatty acid esters 85 |
| 3       | Alkyl amides <ol style="list-style-type: none"> <li>i. Glycosides</li> <li>ii. Alkyl poly-glucosides</li> </ol>  | C-Glycoside derivative surfactants<br>Octyl-decylpolyglucoside, Decylpolyglucoside   |
| 4       | Fatty acids and Fatty alcohols <ol style="list-style-type: none"> <li>i. Fatty alcohol</li> <li>ii. Fatty acids</li> </ol>   | Myristyl alcohols , Stearyl alcohol, Cetyl alcohol<br>Myristic acid, Stearic acid, Palmitic acid   |
| 5       | Block copolymers <ol style="list-style-type: none"> <li>i. Pluronic</li> </ol>   | Poloxamer 188 , Pluronic P105  |
| 6       | Lipidic components<br>Cholesterol, 1- $\alpha$ -Soya phosphatidyl choline  |  |

| Sr. No. | Non-ionic surfactants | Examples   |
|---------|-----------------------|--|
| 7       | Charge molecule       |  |
|         | i. Negative charge    | Phosphatidic acid, Diacetyl phosphate, Lipoamino acid, Dihexadecyl phosphate |
|         | ii. Positive charge   | Stearylpyridinium chloride, Stearylamine, Cetylpyridinium chloride           |

### 2.2.2 Merits of niosomes

- Niosomes dispersion in an aqueous phase can be emulsified in non-aqueous phase to regulate the drug delivery rate and administered normal vesicle in external non-aqueous phase.
- The vesicle liquid/suspension is water-based vesicle. This give high patient conformity with viscus dosage forms.
- Niosomes can access the stability of entrapped drug, osmotically active in nature as well as stable.
- Handling of surface-active agent does not need any special conditions.
- Storage of surface-active agent does not require any other specific conditions for the same pharmacological effect.
- Skin penetration of drugs and increase oral bioavailability of poorly absorbed drugs problems solve by niosomes.
- They can be formulated in such a way that to reach the site of action by topical routes, oral routes and parenteral routes.
- The surface-active agents, which used for the niosomes are biocompatible, biodegradable and non-immunogenic.
- They enhance the therapeutic effects of the drug by covering the drug from biological environment, delayed clearance from the circulation and controlling effects to target cells.
- Niosomes are consist of lipophilic, hydrophilic and amphiphilic moieties because of that; they can help drug molecules with a broad spectrum of solubility.
- The characteristics of the vesicles development are fluctuating and handle able. Altering lamellarity, tapped volume, vesicle composition, size, surface charge and concentration can control the vesicle characteristics.
- The vesicle also acts as a releasing the drug in a controlled manner.
- They amend the therapeutic effect of the drug molecules by delayed clearance from the systemic circulation, restricting effect of target cells and protecting the drug from biological surrounded.

- They can also work as reservoir to release drug in granule form in controlled manner with proper suitable dosage form.
- Osmotically active and stability is acquired by niosomes in this state [11-13].

### 2.3 Demerits of Niosomes

- May exhibit fusion, thus limiting the shelf life of niosomal dispersion.
- Reason: aggregation leaching or hydrolysis of entrapped drug is done due to fusion of niosomal aqueous suspension; as a result, their shelf life is limited.
- Niosomes formation process was time consuming and tedious.
- Properly analysed, huge, specific and measurable equipment need for the authentic and effective production of drug-loaded niosomes.
- Sometimes, there is inefficient drug loading; which leads to improper or insufficient dose to targeted cells.
- Sometime there is problem of leaking in entrapped drug with niosomes vesicles; which is harmful for the other body parts and may chance of toxicity [16].

### 2.4 Preparation/Formulation of Niosomes

Niosomes can prepared by using non-ionic surfactants and lipid like cholesterol. Due to the entrapment efficacy of aqueous phase, number of bilayers and permeability of vesicle membranes, vesicle size and its distribution are influenced by the way of preparation. These parameters should be considered when deciding the best staging technique. Majority of the experimental methods consist of the hydration of a mixture of the surfactant and lipid at related temperature followed by effective size reduction to obtain a colloidal dispersion. Next, an untrapped drug can be separated from entrapped drugs by number of separation methods like dialysis, centrifugation or gel filtration. Here are the following methods, which are utilize for the preparation of niosomes.

#### 2.4.1 Ether injection method

In 1976, Deamer and Bangham invented this method, which is based on the slow release of

surfactant by injection. Cholesterol solution in ether added by injection (14-gauge needle). For this step, the aqueous solution / phase is preheated and kept at 60 ° C. Evaporation of ether leads to the formation of an ether gradient at the ether-water interface, which leads to the formation of single-layer vesicles. The diameter will be between 50 nm and 1000 nm. The ether injection method is used for some drug inclusions such as rifampicin (anti-tuberculosis). Niosomes made by this method have a slightly higher containment efficiency compared to niosomes made by manual shaking methods [17].

#### **2.4.2 Lipid layer hydration**

The surfactant and cholesterol are dissolved in a volatile organic solvent such as methanol, chloroform or diethyl ether in a round bottom flask. The organic solvent is then displaced under vacuum using a rotary evaporator, a thin film or layer of solid mixture adhering to the flask. All of this is done at room temperature with no further changes. The dry surfactant film can then be rehydrated with the aqueous phase at a temperature slightly above the phase transition temperature of the surfactant used, with gentle stirring. This process forms a large multilamellar niosomes, the size of which is between 300 nm and 500 nm with a low polydispersity index.

#### **2.4.3 Thin film hydration technique/ Hand shaking method**

The method of Hand stirring is similar to the methods of thin film hydration, this method forms MLV, in this method additives and surfactant are dissolved in organic solutions that are evaporated by rotary evaporator to form a thin film, after which this dry thin layer is mixed with an aqueous one hydrated solution. drug containing as PBS pH = 7.4; Shake this mixture for 1 hour with mechanical stirring to form niosomes [18].

#### **2.4.4 Bubble method**

The Bubble method is the modern novel technique for the niosomal products. The most benefits of this method is the niosomes can be prepared by only in one-step within a short period. In this method there is not using any organic solution for preparation of niosomes. The bubbling unit contain round bottom flask with three necks positioned in water bath to control the temperature in which, the Water is able to cooled reflux. The thermometer is positioned in

the second neck the nitrogen supply through the third neck. Surfactant and cholesterol are dispersed at the same time in the buffer pH 7.4 at 70°C, the dispersion mixed for 15 second and immediately afterword bubbled at 70°C using nitrogen gas.

#### **2.4.5 Reverse phase evaporation technique (REV)**

Szoka and Papahadjopoulos were written using a unique method in which surfactant and cholesterol (1: 1) are dissolved in a mixture of ether and chloroform, an aqueous phase containing the drug is added and the resulting two phases at 4-5. sonicated The clear gel formed is then sonicated after adding a small amount of PBS (phosphate-buffered saline solution) and then the organic phase is removed at 40 °C under low pressure. The resulting harmful suspension is diluted with phosphate buffer. Saline solution. Heated in a 60°C water bath for 10 min for noisy formulation. In addition, this technique is used to form mainly LUV [19].

#### **2.4.6 Sonication method**

In sonication method, a drug solution and buffer are added to the cholesterol/surfactant mixture in a 10 ml glass vial. The mixture is examination in sonicated at 60°C for 3 min using a sonicator. As a result, vesicles are of tiny unilamellar type niosomes.

#### **2.4.7 Multiple membrane extrusion method**

In this method, a mixture of diacetyl phosphate, surfactant and cholesterol are prepared. After this step, the solvent is evaporated using rotary vacuum evaporator to leave a thin film. In addition, the film is then hydrated with aqueous drug solution, the suspension thus obtained is force out the polycarbonate membrane and then placed in series up to eight passage to obtained uniform size niosomes [20].

#### **2.4.8 Trans-membrane pH gradient drug uptake process**

Cholesterol and surfactants are dissolved in chloroform. The mixture of cholesterol solvent, chloroform and surfactant was evaporated into a thin film in a round bottom flask under reduced pressure. The membrane was hydrated with 300 ml of citric acid pH 4.0 by shaking. Then the film was thawed three times and then sonicated. An aqueous solution containing 10 mg/ml of drug is

added to this harmful suspension. Then shake the solution. Then use 1 M disodium phosphate to increase the pH of the mixture to 7.0-7. Heat the mixture to 60°C and hold for 10 minutes until lumps are formed.

#### 2.4.9 Micro fluidization method

This method is work on submerged jet principle. In micro fluidization method two fluidized streams one containing drug and the other surfactant interact with each other at ultrahigh velocity. In precisely defined micro channel within the interaction chamber in such a way that the energy supplied to the system remain in the area of niosomes formations. This is called submerged jet principle. It result in better uniformity, smaller size and reproducibility in the formulation of niosomes [3].

#### 2.4.10 Niosomes formation from Proniosomes

Formulation of niosomes is done via coat of a water-soluble carrier such as sorbitol with surfactant. After coating them there are, form a dry formulation of film. In this case, each water-soluble particle is covered with a dry surfactant film. This preparation is termed as 'Proniosome'.

#### 2.4.11 Heating methods

In these methods, the mixture of non-ionic surfactants and additives are add to hydration solution in the presence of a polyol under nitrogen atmosphere at room temperature. Then this solution is heated up 120°C on a hot plate stirrer to dissolve additives. Then the temperature was down and the niosomes are form.

#### 2.4.12 Enzymatic methods

The enzymatic method was used to prepare MLVs. In enzymatic method, esterase cleave ester links, and cholesterol and surfactants are mixture with dicetyl phosphate and other lipids which produce MLVs niosomes [21].

### 3. FACTOR AFFECTING NIOSOMES FORMULATION

#### 3.1 Nature of the Drug

The drug, which are used in the formulation, is enhance charge and rigidity of the niosomes double-layer. The degree of entrapment was also affected by the Hydrophilic-lipophilic balance (HLB) of the drug and entrapment efficiency is depend on drug used in niosomes. The drug

entrapment efficiency can be affected by different factors like chemical structure, interaction between drug and membrane of the niosomes, molecular weight and hydrophilicity and lipophilicity of drug. Water-soluble drug show maximum drug loading in niosomes with Polyoxyethylene sorbitan fatty acid esters 60, whereas hydrophobic drugs show maximum drug loading with Sorbitan fatty acids esters 60.

#### 3.1.1 Amount and type of surfactant

As the surfactant value increase in niosomes formulation, there is also raise the mean size of niosomes; it happen because of the surface free energy decrease with the an increase in hydrophobicity of surfactant. In addition, a surfactant must have consist of hydrophobic tail and hydrophobic head. The hydrophilic tail contain one or two perfluoroalkyle or alkyl groups or in many case it consist one single steroidal group.

#### 3.1.2 Cholesterol content and charge

Cholesterols are increase the entrapment efficiency and hydrodynamic diameter of niosomes; it is also reduce the leakiness of membrane and its stabilizing activity. As the concentration of cholesterol is high in bilayer, there is reduce in the release rate of encapsulated material. Consequently, an expansion of the rigidity of the bilayers obtained.

#### 3.1.3 Resistance to osmotic stress

Hypertonic salt solution is used to reduce the diameter of niosomes with proper certain concentration.

#### 3.1.4 Temperature of hydration

Well organized maintain temperature is required during the whole process, which affect the shape and size of niosomes.

#### 3.2 HLB (Hydrophilic Lipophilic Balance)

Hydrophilic Lipophilic balance are Play crucial role in the selection of surfactants for the formation of niosomes. It affects the amount of drug loading capacity and size of niosomes. Surfactants which HLB value is 4 to 8 are compatible to vesicle formation, which more than eight are hardly able to form vesicles; thus, for formation of niosomes cholesterol is necessary to added [15,16,22].

### 3.3 Characterisation of Niosomes

#### 3.3.1 Size and shape

The shape of niosomes are assumed sphere shaped and there are numerous technique are utilized for their mean shape. Size of niosomes can be measure by electron microscope, ultracentrifugation, molecular sieve chromatography, laser light scattering method, optical microscopy, freeze fracture electron microscopy and photon correlation microscopy. Bilayer vesicles is characterized by light polarization microscopy. Moreover, Number of lamellar can be characterized by small angle X-ray scattering, NMR spectroscopy and electron microscopy.

#### 3.3.2 Zeta potential

Zeta potential is deeply crucial in the behaviour and properties of niosomes vesicles. The HLB value of surfactants are effective on zeta potential; if HLB value is high, there is more negative value of zeta potential.

#### 3.3.3 Entrapment efficiency

For checking this property, the niosomes is subjected to dialysis, centrifugation or gel filtration. After this process, the disrupt vesicles 50% n-propanol or 0.1% Triton X-100 are used for search out the entrapped drug in niosomes. The analysis of the niosomes can be done by any suitable assay method. Whereas, entrapment efficiency (EE) can be defined as:

$$\% \text{Entrapment efficiency (EE)} = \frac{\text{amount of drug entrapped drug}}{\text{total amount drug}} \times 100$$

#### 3.3.4 In-vitro release study by using dialysis

In-vitro release of niosomes can be studies with the help of dialysis tubing method. The sac was washed and put in water. Then, the suspension/solution of niosomes are pipette into

a bag made up of the tubing and then sealed it. Next, it is placed in a 250 ml beaker containing phosphate buffer (pH 7.4) of 200 ml with constant shaking at 37°C temperature provided with magnetic stirrer. Furthermore, the sink condition wash maintained by adding new buffer solution after withdrawing the sample after various time intervals. Drug content is analysed by an appropriate assay method.

#### 3.3.5 Angle of repose of niosomes

The angle of repose of niosomes dry powder is measured by a funnel method. The dry niosomes powder was poured into a funnel, which is fixed at a specific position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows come from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

#### 3.3.6 Osmotic shock

The change in the size of niosomes vesicle can be check by osmotic studies of niosomes. The niosomes solution was incubate with isotonic, hypotonic, hypertonic solution for 3hrs. Then the increase or decrease in the size of niosomes vesicles in the formulations was viewed under optical microscopy.

#### 3.3.7 Stability studies

For the stability studies of niosomes, the selected formulated batch is store in airtight sealed vials at various temperatures. In addition, there are mainly examine (%) drug retained and surface characteristics in niosomes. For this, the niosomes were sample at periodically of time 0, 1, 2, and 3 months observed for colour change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analysed by analytical methods [1,8,23].

**Table 3. Evaluation parameter for niosomes**

| Evaluation parameter                    | Generally used method in evaluation parameter   |
|---|---|
| Morphology                              | SEM, TEM, freeze fracture technique             |
| Size distribution, polydispersity index | Dynamic light scattering particle size analysis |
| Viscosity                               | Oswald viscometer                               |
| Membrane thickness                      | X-ray scattering method                         |
| Thermal analysis                        | DSC   |
| Turbidity                               | UV-Visible diode array spectrophotometer        |
| Entrapment efficacy                     | Centrifugation, dialysis, gel chromatography    |
| In-vitro release study                  | Dialysis membrane                               |
| Permeation study                        | Franz diffusion cell                            |



### 3.4 Application of Niosomes

- Niosomes act as haemoglobin carriers: Niosomes are used for the delivery of proteins peptide drugs (PPD). In the transdermal drug delivery system (TDDS), they work as boon for majority of the fungal-infection drugs. Niosomes are also beneficial for the ophthalmic drug delivery system (ODDS). Niosomes are gift for the biomedical science field because they are also used as diagnostic agent in various type of infection which is done by bacteria, virus, fungi and hazardous material [24,25].
- Immunological application: Niosomes are benefits for the study of immune response, which are provoked by antigens. Niosomes are also be utilized for targeting drugs in to the different body organs other than the Reticulo-Endothelial system. In this technique, the antibodies play as carrier system bind or attached to niosomes to target them to specific organs and measure the body-immune response.
- Sustained release: Drug, which have low therapeutic action and low solubility with water, are applied sustained release action in emergency treatment without any major adverse drug interaction. (Examples: theophylline, digoxin, lithium, warfarin) [11].
- Localized drug action: Niosomes are advantage able for the localization of drug performance because they have low penetrability through epithelium and connective tissue layers keeps the drug localized at the site of administration. Due to these circumstances, the very small size of niosomes are also effective as well as play a quick function with desire pharmacological response.
- Transdermal drug delivery through niosomes: It is irrefutable that, niosomes have optimum ability to carry the drugs, which is utmost for the any kind drugs to treat any of body surface infection with their half-life. Nevertheless, transdermal drug delivery has one of the drawback is drug have low permeability. If raise drug permeability with formation of their niosomes, which give effective effect on the particular part of the skin membranes [26].
- Niosomes as drug carriers: Because our body accept very fast, niosomes act as best drug loaded vehicles. They are

profitable for many diagnostic agents, which are used for X-ray imaging in scanning of body parts. Furthermore, niosomes are used as topical agent may show many advantages likes solubilisation matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate limiting membrane barrier for the inflection of systemic absorption of drugs.

- Delivery of peptide drugs: For oral peptides administration major disadvantage is their enzymatic degradation. Formulation of niosomal peptide, which cover the peptides from gastrointestinal peptide degeneration.
- Niosomes act as carrier for haemoglobin: remarkable used of niosomes is for the transport for haemoglobin in to the blood stream by crossing BBB (blood brain barrier) and other thick lipid layers.
- Drug targeting: The most powerful aspect of niosomes to capability to target to the drugs absorb in the RES (reticulo-endothelial system) [12].

#### 3.4.1 Future aspects of niosomes

- **Oral delivery:** For oral route, the most issues are digestive enzymes and acids in small intestine and stomach, different bioavailability of drug and poor absorption. Following this, to improve or increase bioavailability via new drug delivery system, such as niosomes. Example: improving the bioavailability of Cefdinir via the niosomes are reported [27].
- **Transdermal Drug delivery:** Transdermal drug delivery model technique is to protect the drug from the hepatic first pass metabolism as well as provide the controlled drug release in the particular tissue. However, the main disadvantage of this system is skin have many effective barriers which are made up from large protein-lipids. The drug, which have molecular weight, small to penetrate the stratum corneum of skin, can be delivered via this method [28].
- **Ocular delivery:** Ophthalmic drug delivery have many limitations like impermeability of corneal epithelium and precorneal tear film, which decrease or prevent the absorption of drugs. Nevertheless, niosomal ocular drug delivery is useful because their small size is enough to resist drainage by reflex tearing and eye blinking. Moreover, niosomes are remains on the

**Table 4. Niosomal preparation in TDDS**

| TDDS            | Drug                      | Reference |
|-----------------|---------------------------|-----------|
| Niosomes        | Ketoprofen                | [29]      |
|                 | Baclofen                  | [30]      |
|                 | Salidroside               | [31]      |
|                 | Capsaicin                 | [32]      |
|                 | Resveratrol, curcumin     | [33, 34]  |
| Niosomal gel    | Alpha-tocopherol          | [35]      |
|                 | Meloxicam                 | [36]      |
|                 | Rofecoxib                 | [37]      |
|                 | Simvastatin               | [38]      |
|                 | Propranolol hydrochloride | [39]      |
| Proniosomes     | Vinpocetine               | [40]      |
|                 | Simvastatin               | [38]      |
|                 | Nisoldipine               | [41]      |
| Proniosomal gel | Nifedipine                | [42]      |
|                 | Tenoxicam                 | [43]      |
|                 | Flurbiprofen              | [44]      |

Abbreviation: TDDS, transdermal drug delivery systems.

**Table 5. Niosomal drug delivery as Ocular DDS**

| Drug/compound(s)           | Effects  | Reference(s) |
|----------------------------|--|--------------|
| Doxorubicin                | Decreased proliferation of sarcoma cells                                       | [26]         |
| Daunorubicin hydrochloride | Destroyed Dalton's ascitic lymphoma cells                                      | [46]         |
| Bleomycin                  | Accumulated in higher levels at the tumour site                                | [47]         |
| Methotrexate               | Enhanced antitumor activity against sarcoma                                    | [48]         |
| 5-Fluorouracil             | Enhanced drug penetration in the treatment of skin cancer                      | [49]         |
| Vincristine                | Enhanced antitumor activity against sarcoma                                    | [50]         |
| Tocotrienol                | Enhanced cytotoxicity toward breast cancer cells                               | [51]         |
| Artemisinin                | Cytotoxic toward melanoma cells  | [52]         |
| Tamoxifen citrate          | Greater cytotoxicity against breast cancer cell line                           | [26]         |
| Mitoxantrone               | Greater cytotoxicity against human ovarian cancer and breast cancer cell lines | [50]         |
| Cisplatin                  | Enhanced cytotoxicity toward breast cancer cells                               | [53]         |

- eye surface. For instance there are some drug are used which are Tacrolimus and Gatifloxacin for the treatment of conjunctivitis [45].
- Pulmonary delivery: This route is very fascinating; in this route, large surface area of the alveolar region and it contains high permeability. Although, the limitation of this route is such as less drug mass per puff, low productivity of inhalation system, and less stability of drug. However, this problem is solving via niosomes and give more effective delivery of drug [54].
- Nasal route drug delivery: Nasal mucosa have extremely faster and high level of drug absorption in nasal cavity to brain. The advantages of this route system include fast onset of action, avoid first pass of metabolism, which is usually done by the liver, delivery the drug to systemic circulation. Although, the limitation of this system are absorption surface area is low, some drug has not achieve ideal dosing

- volumes. For preparation of this type drug delivery niosomes size was less. Example of niosomal nasal drug delivery system are Melatonin nano-niosomes [55].
- Cancer therapy: It is fact that, new drug delivery system are mainly formulated to decrease the dangerous adverse effects of anti-cancer drugs. The niosomes shown the promising carriers to achieve the desire goal in cancer treatment. Through niosomes prolong circulation, change in metabolism, half-life can reduce side effect and toxic effects of particular chosen drug, which is use in single form or in with combined. Paclitaxel (PCT) is antineoplastic agents, which is successfully entrapped in niosomes's various formulations. To following, the controlled or slow release of drug PCT that beneficial for reduce the toxic side effects. There are also used 5- fluorouracil to treat skin cancer and Doxorubicin for chemotherapy as niosomal form [56].

- Vaccine and Antigen Delivery: Some surfactants have immunostimulatory properties and can be used as vaccine adjuvants. (Niosomes adjuvant triggered by monopalmitoylglycerol: cholesterol: dihexadecyl phosphate (5:4:1) is a synthesis of ovalbumin or containing known T cell epitopes and bovine serum albumin by subcutaneous injection of mice Peptide preparation [57].

### 3.4.2 Route of administration of niosomal drugs

**Table 6. Different route of administration of niosomal drugs**

| Route of administration | Examples of drug   |
|-------------------------|--|
| Intravenous route       | cisplatin, rifampicin, insulin, zidovudine, Doxorubicin, comptotheicin |
| Inhalation              | All trans-retonic acids  |
| Transdermal route       | Piroxicam, estradiol, nimesulide                                       |
| Ocular route            | maleate, cyclopentol, Timolol  |
| Nasal route             | Sumatriptan, influenza viral   |

## 4. CONCLUSION

To sum up, niosomes have very important and key role in various types of drug deliveries; like targeting, topical, ophthalmic and parenteral. Niosomes are objectively useful in bright future for pharma industries. So far, only animal experimentation of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may service to exploit niosomes as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS etc. Furthermore, niosomes represent a promising drug delivery module, a structure similar to liposome and hence they can present alternative vesicular systems with respect to liposomes. Because niosomes can encapsulate different types of drugs in its multi-virtual structure. Based on various factors, such as cost, stability, targeting, ophthalmology, topical and parenteral, etc., Niosomes are considered to be the best drug delivery candidates compared to liposomes. By using new production, loading and modification methods, the potential of niosomes can be increased. These areas require further research and research to develop commercially available niosome drugs. At the end, the concept of comprehend the drug into niosomes or liposomes for a better targeting of the drug at specialized tissue location is widely accepted by academicians and researchers.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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