

## A Critical Analysis of The Niosomal Drug Delivery System: Overcome the Current Bottleneck

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### ABSTRACT

To achieve on-target delivery of medicaments to affected areas without undesirable interactions in other tissues, the clinical development of nanomaterials continues to seek safe and effective therapeutic drugs. Niosomes are non-ionic surfactant vesicles of nanomaterials that are biodegradable, non-toxic, and more cost effective than liposomes (1). Niosomes enhance the therapeutic efficacy of drugs by limiting their effects to certain cells, which decreases drug clearance. They exhibit superior properties compared to greasy dosage forms. Major challenges like unfavorable pharmacokinetics, drug distribution, degradation of drugs in the blood by the reticuloendothelial system (RES), and low drug efficiency can be overcome by this drug delivery method. This review article primarily focuses on niosomes, their structure, preparation methods, current limitations and potential solutions to overcome these drawbacks. Stability issues, sterilization, toxicity, and other challenges are also discussed.

**KEYWORDS:** Nanomaterials, Niosomes, Drawbacks, Stability.

### I. INTRODUCTION

Nanotechnology is the most promising technology of the 21st century. This technology is used in various fields like medicine development, pharmaceuticals, cosmetics sciences, bioengineering. The rapid growth of nanotechnology in pharmaceutical development has made it possible to develop vesicular systems to transport therapeutic agents and ensuring their controlled release at targeted sites (2). Vesicular systems are advanced

colloidal carrier systems made of self-assembled amphiphilic molecules that form bilayer vesicles in aqueous environments. This system provides targeted or controlled release of drugs especially for drugs with poor solubility. This system reduced cost of medication by improving bioavailability.

The challenges faced by conventional drug delivery system such as poor bioavailability, lack of target specification, drug induced side effects can be overcome by use of vesicular drug delivery system. Encapsulation of drugs in vesicle can be prolonging the existence of drug in systemic circulation. Vesicular system include: Niosomes, Liposomes, Pharmacosomes, Ufasomes etc are being used (3).

### NIOSOMES

Niosomes are important vesicular system, that consist of micro-lamellar arrangement which can either be unilamellar or multilamellar. Niosomes are formed by self-assembling uncharged single surfactant with cholesterol with other materials based on formulation. Niosomes are combination of cholesterol with non-ionic surfactant of the alkyl or dialkyl polyglycerol ether (3,4). Due to the presence of hydrophilic, amphiphilic and lipophilic moieties, niosomes can entrap both hydrophilic and hydrophobic drug compounds. They show better stability than liposomes, due to this factor niosomes are widely used in pharmaceutical industry and in cosmetics (5). The presence of non-ionic surfactant with lipids, make better targeting drugs to the liver, brain and tumour (udupa & pillai, 1991). Niosomes minimize the side effects of some potent drugs by maximizing drug concentration at desired site, unlike systemic drugs that effects entire body after absorption.

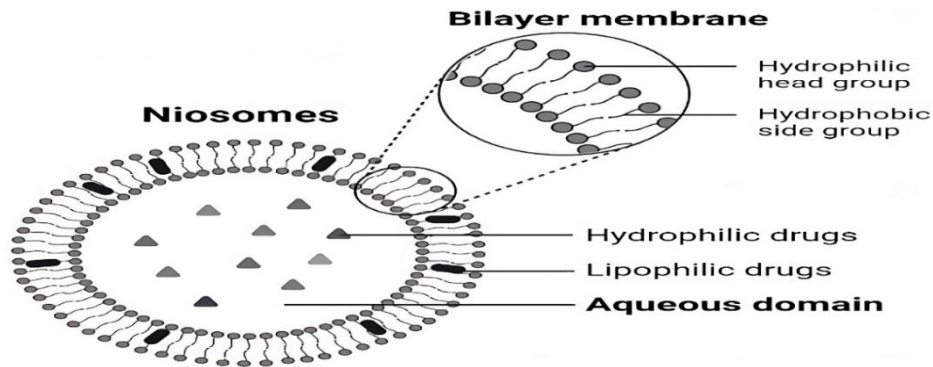


Figure 1: Structural composition of a single niosome showing entrapment zones for hydrophilic and lipophilic drugs.

### LIPOSOMES

Liposomes are artificial vesicles that are smaller in size and composed of at least one phospholipid layer. These are primarily used as drug carriers for pharmaceutical drugs, cosmetics, and nutrients. They transport drug molecules to the target site. Liposomes are similar in function to niosomes as they also trap hydrophilic as well as hydrophobic drugs because liposomes are amphiphilic in nature, which avoid degradation of the drug (3,4)

Compared to liposomes, niosomes are more stable, soluble, and cost-effective, which is why they are used more in the pharmaceutical industry. Niosomes are a promising drug delivery system because they can target specific cells, lowering toxicity, has greater bioavailability, and increase the therapeutic index. They are safer for a variety of purposes because they are made of lipids and non-ionic surfactants.

NIOSOMES	LIPOSOMES
Non-ionic surfactants are more stable	phospholipids are more prone to oxidation
Less expensive	More expensive
Drug entrapment efficiency is more	Drug entrapment efficiency is less
Easy to store	Require special storage conditions
Comparatively less toxic	More toxic

Figure 2: Comparative overview of niosomes versus traditional liposome carriers.

### STRUCTURE AND COMPOSITION

Niosomes are mainly composed of non-ionic surface-active agents, cholesterol (stabilizers), which are used in a proper ratio under certain temperatures to produce stable niosomes. The other components are charge-inducing molecules and hydrating medium (6).

### 1.SURFACTANTS

Surface-active agents or surfactants are amphiphilic compounds capable of reducing the interfacial tension between two liquids. Surfactants consist of a polar, hydrophilic (water-loving) head and non-polar, hydrophobic (water-fearing) tail exhibit amphiphilicity. Based on the nature of hydrophilic groups, surfactants are

classified as anionic, cationic, non-ionic and amphoteric. Non-ionic surfactants are commonly used in the formation of niosomes and enhance drug bioavailability. They have no electric charge in their hydrophilic heads. The commonly used non-ionic surfactants are terpenoids, spans, polysorbates, and alkyl oxyethylene (6,7).

## 2. CHOLESTEROL

Cholesterol is a white waxy steroid precursor that provide rigidity and proper shape to the niosomes. Cholesterol is stabilizer used mainly to increase stiffness and change the shape of niosomes, which are important for the activity (6). Some surfactants do not form vesicles; they require cholesterol to form vesicles. They are incorporated into the formation of a bilayer with non-ionic surfactants. Steroids reduce membrane permeability, which is a critical factor in determine the effectiveness of a drug delivery system. Membrane permeability determines how slow or quick a drug needs to be released, allowing controlled release at target site (7,8,9). Cholesterol is useful for preventing leakage of drug.

## 3. CHARGE INDUCING MOLECULES

As the name suggests, they provide charges such as positive and negative charges. Charge inducers are amphipathic substances added to niosomes and other vesicles to enhance their stability by providing positive or negative charges (8). The stability of niosomes is mainly due to the introduction of electrostatic repulsion between vesicles, which prevent them from fusing together (9). The most common negatively charged molecules are Dicylphosphate (DCP) and phosphatidic acid, the most common positively charged molecules are Cetylpyridinium chloride (CPC), stearyl amine (10).

## TYPES OF NIOSOMES

Niosomes are classified into three main categories based on size.

### 1. Small unilamellar vesicles (SUV)

These small unilamellar vesicles are mostly precursors of multilamellar vesicles prepared by ultrasonication, solvent dilution, and extrusion methods. It typically exhibits a particle size range of 10-100 nm.

### 2. Large unilamellar vesicles (LUV)

These large unilamellar vesicles contains an increased aqueous/lipid compartment ratio, and larger volumes of biologically active materials can be entrapped. It typically exhibits a particle size range of 100-300 nm.

### 3. Multi lamellar vesicles (MLV)

These multilamellar vesicles are the most commonly used niosomes. The estimated size of vesicles was 0.5–10  $\mu\text{m}$  in diameter. These were prepared by hand shaking method. As these are mechanically stable upon storage for long periods are used widely (11).

## METHOD OF PREPARATION

Niosomes are prepared by various methods according to the size and distribution of the vesicle, number of bilayers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane these parameters need to be checked for formulation.

### {Preparation of small unilamellar vesicles}

#### • Sonication technique:

The aqueous phase (buffer solution) containing the drug is combined with mixture of surfactant and cholesterol. The mixture is subjected to sonication for 3minutes. The vesicles formed are small and uniform in size (11,12,13,14). Quick size decreases and accurate temperature regulation are advantages, but heat generation could be the main disadvantage.

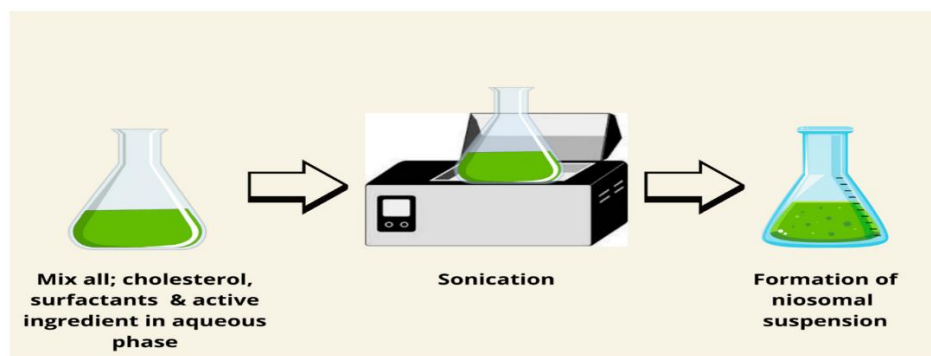


Figure 3: Schematic representation of the small unilamellar vesicle preparation via probe sonication technique.

- **Micro fluidisation:**

The two fluidised streams (aqueous phase and lipid dispersed phase) move and interact within the interaction chamber; this is responsible for mixing and creating homogenous pressure for achieving a narrow size niosomes (11,12,13). Greater uniform size and high aqueous phase encapsulations are advantages (15).

**{Preparation of multilamellar vesicles}**

- **Hand shaking method**

This method is same as the thin film hydration technique. In the handshaking method, the surfactant and cholesterol are mixed in a volatile organic solvent in round bottom flask, leaving a thin layer/film of solid mixture is deposited in walls of the flask after removing aqueous solution. This dried film is hydrated with aqueous solution with drug. By placing this hydrated film in water bath niosomes are prepared (11,12,13,14,15).

- **Transmembrane PH Gradient Technique**

The drug, surfactant, and cholesterol are dissolved in chloroform. The chloroform is removed to produce a thin film on the wall of flask, and the film is

hydrated with citric acid at pH 3-4. The suspension is subsequently frozen and thawed, followed by sonication. An aqueous solution containing the drug or natural molecule is then added to the suspension and mixed to produce niosomes (11,12,13,14,15). This method is similar to the hand shaking method.

**{Preparation of large unilamellar vesicles}**

- **Reverse phase evaporation technique.**

The cholesterol and surfactant are mixed in a combination of the ether and chloroform. Aqueous phase with drug is added to organic solvent. These solutions are sonicated. The resulting viscous niosomes interruption is mixed with the phosphate buffered saline and heated in a water bath for 10 minutes to produce niosomes (11,12,13,14,15).

- **Ether injection method**

The slow injection of the surfactants with other excipients through a 14-gauge needle at the rate of about 0.25 ml/min into aqueous solution with drug maintained at 60° c, evaporation of ether leads formation of niosomes (11,12,14,15). The drawback of this method is small amount of ether will be present in niosomes and it is difficult to remove it.

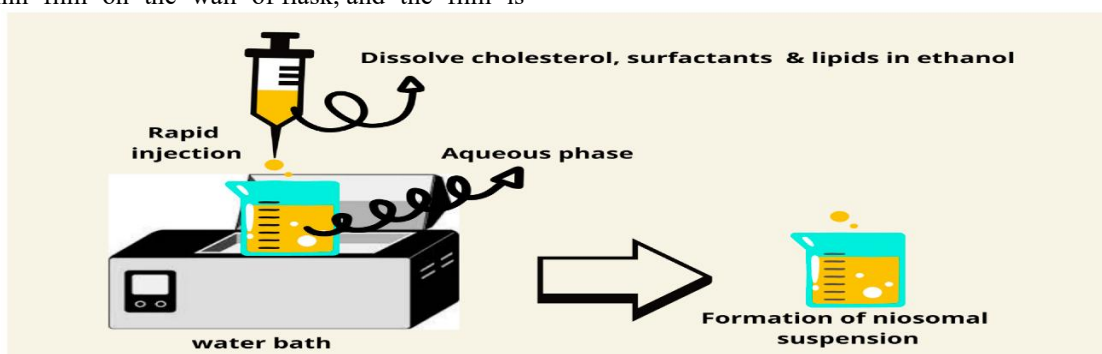


Figure 3: Schematic representation of the large unilamellar vesicle preparation via Ether injection technique.

**Miscellaneous**

- **Multiple membrane extrusion method**

The combination of surfactant, cholesterol, and diacetyl phosphate in chloroform is created into slight firm by evaporation. Film is hydrated by aqueous drug solution. This method is used mainly for controlling size of niosomes.

- **Emulsion method**

Simple method for preparation of niosomes through emulsification. The surfactant, cholesterol mixed in an aqueous drug solution then heated and emulsified to form niosomes (11,14).

- **Noisome preparation using micelle**

The niosomes also be created from a combination of micellar solution using the enzyme. The

combination of micellar solution of C16 G2, dicalcium hydrogen phosphate, polyoxyethylene cholesteryl sebacetate diester transformed to a noisome distribution when they incubated with esterases. The (PSCP) is split by the esterases to Yield of the polyoxymethylene, sebacic Acid and cholesterol. The C16 G2 niosomes are produced by cholesterol with use of enzymes (11).

**Limitations**

Niosomes serve as drug carriers in vesicular system for drug delivery, due to their numerous benefits like enhanced bioavailability, biodegradable, higher rate of drug release at target site, encapsule larger drug molecules, non-immunogenic to the body. Niosomes are more stable when compared to

liposomes but due to various parameters it also has certain drawbacks that need to be considered during manufacturing, and storage condition are mentioned below (1,16).

### 1.physical instability:

Stability of niosomes is the crucial parameter that need to be maintained. Various factors like temperature, pH, value of HLB, concentration of surfactants and cholesterol, high ionic strength cause fusion of vesicle, medicament leakage, chemical degradation.

- **Aggregation and fusion**

Due to presence of non-ionic surfactant in niosomes, they lack strong electric repulsions between the particles in aqueous suspension as these non-ionic surfactants has no charge, without the sufficient electric charge, there is less repulsion between vesicles leading to vesicle fusion or cluster formation which can be an issue in stability of niosomes (17,18).

- **Drug leakage**

A Finished product needs to be stored under certain temperature and pH conditions. During storage of drugs, niosomes tend to leak medicament. Temperature and pH changes cause for leakage, increased temperature lead to increase of fluidity and promote drug leakage and other factors like aggregation of vesicles and improper ratio of cholesterol in niosomes during preparation can also lead to leakage. If cholesterol level is too low than required, it make bilayer too fluid, resulting in higher permeability and leakage of drug (17,18,19).

- **Chemical instability**

undergoes hydrolyses and oxidation degradation promote to drug leakage. Surfactants and Niosomes ester bond like span20/40/60 and tween 20/60/80 are more likely to undergo hydrolysis at acidic or alkaline pH, causing low rigidity of bilayer (20). Preparation methods like sonication lead to reduction in chemical stability in niosomes by generating free radical and local heat.

### 2. Sterilization

During the preparation, sterilization is critical for any dosage form, but it is the main problem for niosomes as they are thermodynamically unstable. Heat sensitive or autoclave sterilization uses excess temperature (121° c) which exceed the phase transition temperature of surfactants, due to this the niosomal membrane become unstable, leading to leakage of entrapped drug (1). Membrane filtration can also be issue for niosomes of size 220nm as they get trapped on the filter surface or surfactants get

adhere to membrane surface, causing loss of active pharmaceutical ingredient.

### 3.Scale- up

Niosomes which are developed in laboratory must be produced in industrial scale, which can be challenging task. Preparation method like thin film hydration and reverse phase evaporation, are facing problem in maintaining smaller particle size and high encapsulation efficiency. Other problems like aggregation, difficulty in maintaining uniform sonication are other drawbacks.

### 4. Low encapsulation efficiency

Encapsulation efficiency (EE%) measures the percentage of active material (drug) entrapped within a carrier compared to initial amount added. The physical properties of the drug can also be a drawback, if a drug does not interact well with the surfactant and cholesterol used, make it difficult for the niosome to entrap drug properly.

### 5. Toxicity

Small particle size of niosomes can lead to drug leakage, which may result in localized toxicity. While Smaller vesicles improve penetration across biological barriers this increased uptake can causes cytotoxicity (9). Toxicity also depends on the type of surfactant to be used. For example, Tween 20 surfactants produce less toxicity than Tween 61.

### 6. Method specific issues

- **Sonication method**

Titanium shredding may occur due to high power and temperature during preparation method of niosomes, cause metal contamination and this method is time consuming and require specialized equipment.

- **Thin layer hydration**

It is one of the common methods for niosomes preparation. The major disadvantage is lower drug entrapment efficiency, to produce smaller, uniform vesicles other methods like sonication is required which can take a lot of time and can cause drug leakage.

### Solutions

#### Toxicity

Niosomes show cellular toxicity depending on the type of surfactant utilized, however they are less toxic compared to liposomes.

- **Non-ionic surfactants use**

as they have no charge in their hydrophilic head, which makes them more biocompatible and non-immunogenic, non-ionic surfactants like span and tween exhibit less toxicity than anionic, amphoteric, or cationic surfactants.

- **Modification of the Surface**

PEGylating, which includes attaching polyethylene glycol to niosomes and forming a dense, hydrated "cloud" around vesicles to prevent it from being cleared by RES, can prevent niosomes from being broken down by the reticuloendothelial system and eliminated from the bloodstream.

#### Improving stability:

There are various approaches to improve physical stability of niosomes. Those include choosing the proper surfactants help in maintaining fluidity of the bilayer membrane. Incorporation of cholesterol in niosomes improve their physical stability by inserting itself between surfactant molecules to enhance rigidity of bilayer. use of charge inducers like -diethyl phosphate or stearyl amine prevents aggregation through electrostatic repulsion (1), HLB value need to be between 4-8 which produce stable niosomes. Other methods like lyophilization process convert niosomes into a dry powder enhancing their shelf-life, it also reduces oxidative degradation (21). Niosomes of size 1-10um are more stable. Considering all these parameters result in developing stable dosage forms (18).

#### Sterilization

Heat sterilization affects the niosomes preparations by melting bilayer and causing drug leakage, so membrane filtration is mostly used, effective and suitable method for niosomes of size less than 0.22um. it is suitable for small-lamellar vesicles (SLV) as they can retain on the filters like polycarbonate membranes or specific units like minisart, aseptic method is employed for other vesicles. Other methods include gas and gamma-irradiation, which has strong penetration while making it ideal for drug carriers that are sensitive to heat, this sterilization could produce stable and sterile niosomes (16).

## II. CONCLUSION

The meticulous modification of niosomes structural components is essential to their potential as superior drug carriers. To address the limitations, a closer examination of the synergistic effects of surfactant-to-cholesterol ratios and surface modification like PEGylation needs to be done to solve the fundamental issues of drug leakage and low encapsulation efficiency. Niosomes are positioned to overcome present delivery challenges as research progresses toward more sophisticated multi-component systems, providing a stable platform for both hydrophilic and hydrophobic components in a variety of medical and cosmetic application. A shift from laboratory trail-and-error to large-scale, standardized production will guarantee that niosomal

system provide the high-efficiency, reliable administration needed for next generation therapies.

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