INTRODUCTION
Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.1

Salient Features of Niosomes
• Niosomes can entrap solutes in a manner analogous to liposomes.
• Niosomes are osmotically active and stable.
• Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
• Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
• Niosomes can improve the performance of the drug molecules
  • Better availability to the particular site, just by protecting the drug from biological environment.
• Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.2

STRUCTURE OF NIOSOMES
Niosomes are lamellar structures that are microscopic in size. They constitute of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer. The figure in this article on Niosomes gives a better idea of the lamellar orientation of the surfactant molecules. Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures, however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. The schematic representation of drug loaded niosome is shown in Fig 1 below.

KEYWORDS: Niosomes, bioavailability, target site, vesicles, phospholipid bilayer.
ADVANTAGES OF NIOSOMES

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages:-

- The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.

- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.

- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics3,4.

METHOD OF PREPARATION

Ether injection method

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

Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Sonication

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

Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

Multiple membrane extrusion method

Polycarbonate membranes, which are placed in series for up to 8 passages. It is a good method for controlling niosome size. Mixture of surfactant, cholesterol and diethyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through5.

Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

Raja Naresh et al. have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed “Proniosomes”. The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. The formation of niosomes is shown below in figure 2.

Tm = mean phase transition temperature.

Blazek-Walsh A.I. et al have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water6.

CHARACTERISATION OF NIOSOMES

Niosomes are characterized chiefly for their size, morphology, charge, rigidity, homogeneity and drug loading capacity.

Vesicle size and morphology

Niosome size can range from around 20 nm to around 50 μm. Several techniques can be used to determine vesicle size and size distribution. Large niosomes, those with diameters over 1 μm, can be adequately measured by light microscopy and the Coulter counter. Light
microscopy offers the possibility of collecting information on particle shape, whereas the volume distribution of niosomes (>1 μm) in dispersions can be determined with Coulter counter. For vesicles in the submicron range, size can be assessed by electron microscopic analysis or by light scattering techniques. Electron microscopic analysis such as transmission electron microscopy or freeze-fracture techniques not only analyze niosome size, but also analyze number of bilayers. Further, scanning electron microscopy, atomic force microscopy and cryo transmission electron microscopy are also used to study the shape and surface characteristics of the niosomes.

**Vesicle charge**
The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vitro. In general, charged niosomes are more stable against aggregation and fusion than uncharged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by microelectrophoresis.

An alternative approach is the use of pH-sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

**Bilayer Rigidity and Homogeneity**
The biodistribution and biodegradation of niosomes are influenced by rigidity of the bilayer. In homogeneity can occur both within niosome structures themselves and between niosomes in dispersion and could be identified via. p-NMR, differential scanning calorimetry (DSC) and fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, fluorescence resonance energy transfer (FRET) was used to obtain deeper insight about the shape, size and structure of the niosomes 7,8,9.

**Niosomal drug loading and encapsulation efficiency**
To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorbed drug. The niosomal recovery was calculated as:

\[
\text{Niosome recovery(%) = } \frac{\text{Amount of niosomes recovered } \times 100}{\text{Amount of polymer + drug + excipient}}
\]

The entrapment efficiency (EE) was then calculated using formula:

\[
\text{Entrapment efficiency(%) = } \frac{\text{Amount of drug in Niosomes } \times 100}{\text{Amount of drug used}}
\]

The drug loading was calculated as:

\[
\text{Drug loading(%) = } \frac{\text{Amount of drug in Niosomes } \times 100}{\text{Amount of Niosomes recovered}}
\]

**Niosomal drug release**
Recently, FRET was used to monitor release of encapsulated matters in niosomes by using separate niosomal suspensions incorporating donor and acceptor. The simplest method to determine in vitro release kinetics of the loaded drug is by incubating a known quantity of drug loaded niosomes in a buffer of suitable pH at 37°C with continuous stirring, withdrawing samples periodically and analyzed the amount of drug by suitable analytical technique. Dialysis bags or dialysis membranes are commonly used to minimize interference10.

**NIOSONES AS NOVEL DRUG DELIVERY SYSTEM**
A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug.

- Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie et al investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production11.
- Carter et al reported that multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate12.
- Azmin et al reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution13.
• Chandraprakash et al reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice 14.
• Cable et al modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubicin in niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice 15.
• D’ Souza et al studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes 16.
• Namdeo et al reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in pawoedema bearing rats 17.
• Parthasarathi et al prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar prepared niosomes of Pentoxifylline and studied the in-vivo bronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs 18,19.
• Raja Naresh et al reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose 20.

Delivery by the transdermal route, however appears to show that the more fluid membranes appear to be more efficient. Vesicle size has not yet been fully characterised from a biological point of view and studies designed to systematically define the size requirements for certain pharmacodynamic objectives are sorely desired. At the present time the red blood cell may be used as the upper size limit for the intravenous route while larger vesicles are predicted to be better for ophthalmic delivery 21.

CONCLUSION
Over the years, there has been a great evolution in drug delivery technologies. Niosomal drug delivery systems are an example of one of the various drug delivery systems available. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments. The system is already in use for various cosmetic products. Niosomes represent a promising drug delivery technology and much research has to be inspired in this to juice out all the potential in this novel drug delivery system.

REFERENCES
16. Yoshiioka T, Sterberg B and Florence AT. Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). Int J Pharm. 105, 1994, 1-6.
### Table 1: Comparison of Niosomes with Liposomes

<table>
<thead>
<tr>
<th>Niosomes</th>
<th>Liposomes</th>
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<tbody>
<tr>
<td>1. Niosomes are now widely studied as an alternative to liposomes as</td>
<td>1. Liposomes exhibit certain disadvantages such as – they are expensive,</td>
</tr>
<tr>
<td>niosomes are promising vehicle for drug delivery and being non-ionic;</td>
<td>their ingredients like phospholipids are chemically unstable because of</td>
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<tr>
<td>it is less toxic and improves the therapeutic index of drug by</td>
<td>their predisposition to oxidative degradation, they require special storage</td>
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<td>restricting its action to target cells.</td>
<td>and handling and purity of natural phospholipids is variable.</td>
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<tr>
<td>2. Niosomes are prepared from uncharged single-chain surfactant and</td>
<td>2. Liposomes are prepared from double-chain phospholipids (neutral or</td>
</tr>
<tr>
<td>cholesterol.</td>
<td>charged).</td>
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<tr>
<td>3. Niosomes behave in-vivo like liposomes, prolonging the circulation</td>
<td>3. As with liposomes, the properties of niosomes depends both on the</td>
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<td>of entrapped drug and altering its organ distribution and metabolic</td>
<td>composition of the bilayer and on method of their production.</td>
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<td>stability.</td>
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![Fig 1: Schematic representation of drug loaded niosomes](image1)

![Fig 2: Formation of Niosomes by Proniosomes](image2)