**Review on niosomal structure Through nasal Route**

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**Abstract:** Nanotechnology has created one of the most dynamic science and technology domains at the confluence of physical sciences, molecular engineering, biology, biotechnology and medicine. There has been a considerable research interest in the area of developing drug delivery using nanoparticles (NP’s) as carriers for small and large molecules. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of drug delivery system especially brain. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to this site of action. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Various polymers have been used in the formulation of niosomes for drug delivery research to increase therapeutic benefit, while minimizing the side-effects. It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antifungal agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. Niosomes represent a promising drug delivery module. Niosomes are thought to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical and parenteral.

**Key Words:** Nanotechnology, niosomes, nasal route, targeting.

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**I. Introduction**

The drug delivery by nasal route generated the interest of the widespread among the community of the scientists as a good alternative route of administration that can avoid the first pass effects of some drugs that are susceptible for the enzymatic degradation of drugs. Intranasal route also allows better absorption of the drug through the vascularity and permeability of the nasal mucosa. The barriers that face the drug through the intranasal route is the enzymatic that located in the nasal mucus lining. Despite that, large numbers of the drug at the include peptides, protein, vaccines and hormones can be delivered into the epithelium through the nasal route. Intranasal route of administration has several advantages and disadvantages as shown in Table (1).

**Table (1): The advantages and limitations of intranasal route (1).**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
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<tr>
<td>1. Avoid the enzymatic degradation in GIT.</td>
<td>1. Therapeutic volume of the drug is 20-200 mL.</td>
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<tr>
<td>2. Avoid first pass effects.</td>
<td>2. The components that have high molecular weight cannot be delivered.</td>
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<tr>
<td>4. Use lower doses because of higher bioavailability.</td>
<td>4. Nasal irritation.</td>
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<td>5. Therapeutic route is non-invasive.</td>
<td>5. Limitation in the understanding.</td>
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<tr>
<td>7. Transport the medication directly to the systemic circulation and the brain.</td>
<td>7. Side effects by pathological activities.</td>
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<tr>
<td>8. Avoid over-doses.</td>
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To overcome some limitations of the intranasal route, we can formulate the drug into niosomes, proliposomes and filmshates. Nanocarrier drug permeability that is shown to be better than suspensions, solutions, sprays, emulsions, snuffs and ointments. The cause is that niosomes, proliposomes and films allows prolonged contact with the mucous membrane (1).

**Nasal cavity functional feature:**

The nasal mucosa is supplied with the blood to achieve the functions of the cavity of the nose that include mucification, heating, mucociliary clearance, olfaction and immunological functions. The surface area of the cavity is about 150160 cm²; that is the result of presence about 400 microvilli/cell. The volume of these secretions of the nose is about 15 mL/day.
Allofthese conditions favor the large permeability of the drug through the nose. (1)

**Drug permeation mechanism** (2):

![Diagram showing different pathways](image_url)

*Figure (1)*: show different pathways as (A) show the drug pass through epithelium, (B) paracellular transport, (C) transcellular transport, (D) carrier mediated transport and (E) intracellular tight junction. The permeation through the nasal cavity while administration of the drug can be carried out by either paracellular pathway as shown in figure 1 passively or actively and passively via transcellular pathway. In which it depends mainly on the lipophilicity of the drug. (1)

### II. Factors That Affect The Drug Permeability Through Nasal Route

**Mucociliary Clearance:**

It involves the combined actions of the mucus layer and the cilia and is an important factor in the physiological defense of the respiratory tract against inhaled hazardous particles. The composition, function and clinical aspects of nasal mucus have been widely reviewed. It is assumed that the speed of mucociliary clearance in healthy humans is about 5 mm/min; although this is easily influenced by pharmaceutical excipients, airborne irritants or diseases. The tips of the cilia are in contact with and transport the superficial viscoelastic mucus layer towards the nasopharynx, while the less viscous lower layer of the mucus is relatively stationary. Several workers, using various in vitro or in vivo methods, have investigated ciliary beat frequency in order to evaluate the effects of drugs or formulation additives or of infections in the upper airways on the mucociliary system. The cilia beat in a coordinated fashion, with a frequency of approximately 10 Hz, when measured in in-vitro studies on human nasal cilia (2).

**Enzymes:**

While nasal administration of drugs does avoid first pass hepatic metabolism, there is a broad range of metabolic enzymes situated in the nasal mucosa which can limit the bioavailability of some drugs, especially those containing peptides or proteins. Among the enzymes present are the oxidative phase I enzymes (e.g. cytochrome P-450 enzymes), non-oxidative enzymes, conjugative phase II enzymes and proteolytic enzymes such as endo- and exo-peptidases. The nasal enzyme population and/or activities vary extensively among different species. However, the level of activity seems to be lower for nasal enzymes than for those in the gastrointestinal tract or liver, on the basis of the amount of tissue involved. (3)

**Nasal pathophysiology various pathophysiological changes:**

Such as the common cold, seasonal rhinitis, nasal polyps and cancer, may also alter absorption from the nasal cavity in different ways, although this has not yet been thoroughly investigated; while it has been demonstrated that a rhinovirus infection in vitro causes sloughing of epithelial cells and destruction of the epithelial layer, microscopy studies of mucosal biopsies from otherwise healthy patients with colds didn’t show any abnormalities in ciliated cells. (2)

**Physico-chemical characteristics of the substance:**

The physicochemical characteristics of the administered drug, which can influence nasal absorption, include molecular weight, solubility, dissolution rate, charge, partition coefficient, pH, particle size and the presence of polymorphism. (4)

**Solubility of the drug in nasal secretion:**

As the drug needs to be solubilized in the nasal secretion before its permeation. Diurnal variation as diurnal rhythm affects the nasal secretions. As the secretion and clearance rates are reduced at night which affects the drug permeation.
Ph Of The Nasal Cavity:
As it is varied from 5.5 to 6.5 in adults and from 5 to 7 in infants. Usually drug permeation increased when the nasal pH is lower than the drug pKa because under this condition the drug molecules present as unionized species. Change in nasal pH affects the ionization of the drug molecules that affect the drug permeation.(1)

Molecular weight:
An inverse relationship between molecular weight and percent absorption has been reported; data are supported by the results of rat studies compiled with literature data, which indicate good bioavailability for compounds with molecular weights up to 1000 kDa in formulations without adjuvants. (10) However, contrary to the findings of Donovan et al. (1990) no difference in absorption characteristics between gastrointestinal and nasal mucosae was found in rats (6) Accordingly, mechanisms other than the suggested aqueous pores between cells of the nasal mucosa) might be involved in the absorption of large molecules. Other studies have demonstrated that hydrophobicity is an important factor in nasal drug delivery in contrast to studies on quaternary ammonium compounds where a decrease in absorption was found with increased lipophilicity and molecular weight.(3)

The drug administered through nasal route taken by different methods:

Figure (2): show the drug deposition two minutes after drug delivery using (A) traditional liquid spray, (B) breath powered Bi-directional powder device and (C) breath powered Bi-directional liquid device incorporating spray pump

Devices for liquid formulations:
Liquid formulations include emulsion, aqueous solutions and suspensions. Liquid formulation considered to be good method as it does humidification in which counteract the dryness of the nose that usually accompany the chronic diseases of nose. The devices used with liquid formulations mainly spray pump systems as showed in figure (2) usually require preservatives which is mainly benzalkonium chloride that may cause reduction in ciliary movement and irritation also recent studies proved that the use of benzalkonium chloride in long term use is well tolerated and safe for the long-term use.(11)

Drops delivered with pipette:
It is the oldest method for the nasal delivery in which the breast milk has been dripped for the treatment of nasal congestion in infants, methanol vapors have been used to wake fainted people and both vapors and drops are still present in the market till now. Drops are administrated by liquid sucking into glass dropper; the dropper is inserted into the nostril with extended neck then squeezing the rubber top to allow the drops to be emitted. For the purposes of multiple use drops have been replaced by metered dose spray pump.(11)

Liquid delivery by rhinyle catheter and squirt tube:
It is a simple way in which physicians used to insert the drug into the nose by inserting a tip of catheter to the required area under visual control then squirt the required drug to the desirable location. This method mainly used in the studies that include the use of animals. But this method has a dangerous disadvantage that it cannot be used for self-medication.(12)
in which the drug is ionized while delivering from a jet outlet. The size and particles of the dose varied according the applied force. While releasing the pressure the nasal secretions and micro-organisms are sucked into the bottle so the use of the squeeze bottles is not recommended for children.(11)

**Spray pumps metered dose:**
Which offers high reproducibility of the dose that emitted and plume geometry in tests applied in vitro. The size of the particles and the plume geometry varied within limits and depend on the pump properties, the orifice of the actuator, formulation and the force applied. In the traditional spray pump the air is replaced by emitted liquid so preservatives are required to prevent contamination. Pump manufacturers are developing other methods to avoid the use of preservatives.(11)

**Single and due dose spray devices:**
It is preferred to be used for narrow index drugs and used also for vaccines and other drugs that need single accurate dose.(11,13)

**Nasal pressurized metered dose inhalers:**
Most of the drugs used for the local action delivered using spray pumps but some other drugs as nasal aerosols taken by inhalers (11,12)

**Devices for powder formulations:**
Powder sprayers with compressible compartment to supply pressure in which when it is released it make a plume of powder particles which is like that produced by liquid spray.(11)Breath actuated inhalers in which the human use his own breath for the powder inhalation into the nostril from a capsule or blister.(11)Nasal insufflator describes the devices that contain nosepiece and mouthpiece which are connected. The drug delivery carried out while exhalation of the drug into the mouthpiece to close the velum, then the airflows carries the particles of powder into nose through the nosepiece of the device.(11)

**Nasalphysiologythataffect the drugdelivery**

![Nasal anatomy](image)

**Figure (3): Nasal anatomy**

**Aerodynamic andnasalvalve:**
The dynamic segment of narrow anterior triangular of thenasal anatomy called nasal valve which is the limiting segment primary flow and extends anterior and posterior to the inferior turbinate head approximately 23 cm from the opening of the nose. The narrow triangular slit plays a role of dynamic valve for the modification of the rate and the direction of the airflow during the respiration.(12)

**Thenasal mucosal clearance and filtration:**
The anterior region of the valve is called vestibule which is lined by nonciliated squamous epithelium then the valve is gradually converted into ciliated epithelium which is typical of ciliated respiratory epithelium posterior to the region of the valve. Behind the valve of the nose, the turbinates of the nose divided the nasal cavity into slit-like passages with larger surface area and cross-sectional area. The speed of the laminar airflow is slowed down to 23 m/s and disrupt with debris that promotes deposition of the particles that are carried with air and behind the region of the valve. The ciliated respiratory mucosa which is posterior to the nasal valve, covered by a blanket designed protective mucosa that traps particles and micro-organisms.(11)
Thenasalcycle:
Thephysiologyofthealternationbetweencongestionanddecongestionobservedhasbeenasobservedinabout80
%of thehumansthatarehealthyiscalledthenasalcycle. Theautonomiccycleschangedduringairflowresistancewhichmainlydependsonbloodcontentofsubmucosalcapacitanceveassesthatconstitutetherecipientatsiteswhichare
critical, notably the region of the nasal valve. The airway is a complex network of channels that connect the nares to
the larynx. The airway is divided into two main parts: the nasal cavity and the nasopharynx. The nasal cavity is
further divided into the nostril, the nasal septum, and the turbinates.

Nasal sinus vasculature and lymphatic system:
The nasal cavity is connected to the paranasal sinuses, which are air-filled cavities located in the bones of the
face. The maxillary, ethmoid, sphenoid, and frontal sinuses are the most important paranasal sinuses. The
paranasal sinuses are lined with mucus-secreting epithelial cells that produce mucus, which helps to keep the
airway moist and clean. The mucus is transported from the nasal cavity to the throat by cilia, which are small
hair-like structures that move in a coordinated fashion to move mucus and trapped particles out of the nose.

Targetednasaldelivery:
Inmostcases,theseactiveconstituentsofthedarugonthesurfaceoftheepitheliumaregood
or the drug is not absorbed through the nasal mucosa. The drug is then absorbed into the bloodstream and transported
to the systemic circulation. However, the absorption of drugs through the nasal mucosa is limited by the presence
of nasal valve closure, which can reduce the absorption of drugs. The absorption of drugs through the nasal mucosa
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Brain targeting through nasal route:
When the drug passes through the barrier of the nasal epithelium and enters the nasal mucous space, the drug
molecule diffuses across the mucosal membrane. The drug then enters the systemic circulation and is distributed through
the body. The brain is one of the most important target organs for drug delivery, and the nasal route is a promising
method for drug delivery to the brain. The nasal route offers several advantages, such as a low profile, ease of
administration, and a rapid onset of action. However, the nasal route also has some limitations, such as a low
absorption rate and a lack of targeting capability.
III. Types of Nanotechnology-Based Drug Delivery Systems

Polymeric Nanoparticles (NPs)

Nanoparticles are defined as particulated dispersions or solid particles with diameters ranging from 1 to 100 nm. By using several methods, nanoparticles have been prepared, such as methods including ionic gelation, coacervation, polymerization, and emulsion solvent evaporation (24), solvent evaporation or spontaneous emulsification, supercritical fluid technique, spray drying, and precipitation techniques (10). The mechanisms by which nanoparticles can pass the BBB can be explained by improved adsorption of the nanoparticles to the capillary walls due to increased retention of the nanoparticles in the brain blood capillaries. This results in enhanced drug transport across the BBB, which can open between the endothelial cells of the brain blood vessels. An alternative method is to facilitate the transport of drug nanoparticles coated with cationic lipids through the tight junctions of the BBB, which allows permeation of the nanoparticles across the BBB (2). Other methods to improve drug delivery include the use of mucoadhesive polymers, coating nanoparticles with polyethylene glycol, and increasing the retention time of nanoparticles delivered through the nasal route (17, 18).

Surfactant-based systems:

Drug delivery systems in which molecules of surfactants are self-aggregated which takes place in the presence of water and to form to the nanoparticles. These systems are called surfactant-based drug delivery systems. These systems are more organized even when other components such as oils or other surfactants are added to the system of surfactant and water. Thus, microemulsions (MEs) and nanoemulsions (NEs) are produced. Microemulsions are usually thermodynamically stable isotropic liquid mixtures formed by mixing oil, water, and surfactants all together. In contrast, nanoemulsions are conventional emulsions that contain very small particles. The size of droplets of microemulsions ranges between 100 and 140 nm, which leads to fast formation of the system that are opaque to light and thermodynamically stable. Nanoemulsions are not transparent with a diameter ranging up to 140 nm, so they are less thermodynamically stable than microemulsions (29). The two systems are very different because MEs are formed by self-assembly and NEs are formed by mechanical shearing. Other parameters of the systems include:

- Core-to-surfactant mass ratio
- Concentration of surfactant
- Type of surfactant
- Type of oil
- Type of water
- **Solid lipid carriers**

Solid lipid nanoparticles (SLNs) as shown in Figure 10 are typically spherical particles, with an average diameter between 100 and 1,000 nm when dispersed in water. SLNs have a core of a solid lipid that is insoluble in lipophilic molecules (Müller et al., 2002). The lipid core typically consists of free fatty acids (e.g., cholesterol), mono- or diglycerides (e.g., glyceryl behenate), triglycerides (e.g., tristearin), waxes (e.g., cetyl palmitate) or surfactants (e.g., stearyl alcohol), which are stabilized by surfactants and prevent aggregation. The hybridization process helps in improving the adhesiveness of the SLNs, which can be used to deliver drugs across the BBB.

**Figure (4):** Structure of solid lipid nanoparticles (32)

Solid lipid nanoparticles are typically spherical particles with an average diameter between 100 and 1,000 nm when dispersed in water. The SLNs have a core of a solid lipid that is insoluble in lipophilic molecules (Müller et al., 2002). The lipid core typically consists of free fatty acids (e.g., cholesterol), mono- or diglycerides (e.g., glyceryl behenate), triglycerides (e.g., tristearin), waxes (e.g., cetyl palmitate) or surfactants (e.g., stearyl alcohol), which are stabilized by surfactants and prevent aggregation. The hybridization process helps in improving the adhesiveness of the SLNs, which can be used to deliver drugs across the BBB.

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guish MEs from NEs: MEsaremorestableinlong-term storage than NEs; MEs can be agitated, cooled, or heated and then returned to their original condition, whereas NEs cannot return to their original conditions. Microemulsion resulted from spontaneous mixtures of water, oils, and surfactants, however, can be transformed to facilitate the formation of microemulsion. It is recommended to apply heating or stirring because of the kinetic energy barrier that must be overcome. Nanoemulsions can be formed ed by using some external energy provided by microfluidizers, high pressure homogenization, and sonication methods to convert the mixture into a colloidal dispersion or phase inversion. Nanoemulsion formed from curcumin under a developer that can deliver drug through intranasal route, and the results from the demonstration experiments showed improved learning and memory in the group treated with curcumin-loaded nanoemulsion compared with the group treated with the pure drug.

Vesicular drug delivery system:

Systems that have been presented as carriers for delivery of drugs for many years are called vesicular drug delivery systems. They were supposed to achieve many goals, which included enhancement of the transport of drug through different biological membranes, targeted delivery, and controlling the release of drugs as well as prolonging the release if needed. These systems include liposomes, transfersomes, niosomes, vesosomes, ethosomes, and colloidosomes. Only vesicles are employed in the nasal drug delivery will be discussed such as

Liposomes

Liposomes as shown in figure 1 are microscopic vesicles spherically shaped composed of one or more bilayers of lipids, arranged around a central core aqueous in nature (21). They are made of nontoxic, biodegradable, and natural constituents such as phospholipids. Liposomes may include the composition membrane stabilizers, cholesterol, and lipids. The stability of liposomes is achieved by encapsulating drugs with wide distribution of the lipophilic portion of drugs being located in the bilayer of lipids and the portion on which hydrophilic is located in the central aqueous layer. Liposomes can change the pharmacodynamics and pharmacokinetics of the entrapped drugs and, thus, are considered to be efficient drug delivery systems. The activity of liposomes as carriers for drug delivery depends on the factors such as release rates, stability, and efficiency of encapsulation, distribution in the body after administration, rigidities and sizes of surface charge. Liposomes can be used as carriers and dispersed by changing the preparation methods and using different types of lipids. The stability of liposomes is considered the main problem in the research of liposomes, and this problem resulted from the chemical degradation of components of liposomes in parallel with the problems of physical stability (28). That can include the size change upon storage and the loss of entrapped drug. Increasing the rigidity of the bilayer and decreasing the loss of entrapped material membrane reducing the water content of liposome formulations producing the so-called proliposomes can help in improving the physical stability of liposomes

Proliposomes:
Proliposomes are free flowing, dry particle that upon addition of water form vesicular dispersions instantly. They freeze-flush particle properties allow the fabrication of these nanoaggregates into solid dosage forms, which then isocylindrical liposomes on contact with water or biological fluids. Proliposomes are prepared by penetrating gas solution of drug and phospholipids in volatile or organic solvents into the microporous matrix of watersoluble carrier particles, then evaporating the volatile organic solvents and placing the drug and the drug on the microporous structure of the carrier material, thus, keeping the free flowing surface characteristics of the carrier material. Proliposomes have some advantage which include decreasing the problem of physical instability such as leakage, fusion, and aggregation. In addition, proliposomes are characterized by ease of storage, distribution, transportation, and dosage (29).
Niosomes
Niosomes are multilamellervesicular structure of nonionic surfactants as shown in figure 12, similar to liposomes however instead of phospholipids that are component of liposomes they are composed of non-ionic surfactants. (22)

Figure (6): structure of niosomes (26)

Advantages of Niosomes (11)
- Niosomes have the ability to entrap lipophilic, hydrophilic and amphiphilic drugs so they can be used to deliver a wide range of drugs with different properties.
- Niosomes have a better therapeutic effect when compared to other conventional oily formulations and better patient compliance.
- Composition, size, shape and fluidity of niosomes can be controlled.
- Niosomes due to depot formation can provide controlled and sustained release of drugs.
- Niosomes can be administered through different routes such as topical, oral, parenteral and intranasal.
- Niosomes have the ability of increasing the permeation of drugs through the skin.
- Niosomes protect the active constituent from acid and biological enzymes that lead to increased stability of the active constituent.
- Niosomes are stable as they are composed of nonionic surfactants (more than liposomes that composed of phospholipids).
- Transportation, handling, and storage of niosomes are easy.
- Niosomes can improve oral bioavailability of the drug.
- Niosomes are non-immunogenic (safe) to the body, biodegradable and biocompatible. (10)

IV. Factors affecting the physiological properties of niosomes

Membrane Additives:
The number of additives added to the formulation of niosomes besides the nonionic surfactant and the drug can influence the stability of niosomes, also permeability and morphology of vesicles are influenced by the number of additives such as increasing the rigidity and stability of niosomes by adding cholesterol to the formulation. (10)

Temperature of Hydration:
Hydration temperature has a great influence on size, shape, and stability of niosomes. Composition of vesicles of niosomes is affected by the change in temperature of the system of niosome. The change in temperature can also cause transformation invesicle shape. At temperature of 25°C Polyhydralvesicles of C16G2 solulan C24 (91:9) is formed, however, at temperature of 45°C is converted into vesicles of spherical shape. (39)

Properties of Drugs:
The entrapment efficiency of drugs in niosomes is affected by lipophilicity, chemical structure, hydrophilicity, molecular weight and the hydrophilic-lipophilic balance (HLB) of the drug. Charge on polymer may be increased as it is affected by interaction between drug particles and the head group of the non-ionic surfactant which in turn causes repulsion of the surfactant bilayer that finally leads to an increase in the size of vesicles. (26)
Amount and Type of Surfactant:
The mean size of niosomes can increase with the increase of HLB value of surfactants (like span 20 (HLB 8.6) to span 85 (HLB 18)) indirectly proportional to the free energy of the surfactant. The structure of bilayered disordering in the liquid phase transition temperature, followed by the increase in the area of niosomal bilayer, which increases the entrapment efficiency. The rigidity of the bilayer increases with the increase in the HLB value of surfactants, thereby increasing the efficiency and decreasing the size of niosomes (28).

Cholesterol Content and Charge on the Surfactant:
The presence of cholesterol in niosomal bilayer can increase the entrapment efficiency and the diameter of niosomes. Cholesterol can act by two ways: either by decreasing the chain order of the gel state bilayer or increasing the chain order of liquid-disk bilayer. It has been found that rigidity of bilayer increases and the drug release is delayed because of the high concentration of cholesterol (28).

Method of Preparation of Niosomes:
Method of preparations can also affect the properties of niosomes. For example, Reverse phase evaporation as well as microfluidization methods can be used to produce vesicles that are smaller in size and with greater stability (32).

Hand Shaking Method:
Initially, surfactant and cholesterol are dissolved in some organic solvent such as benzene, chloroform, and ether. Then, the solvent is evaporated under decreased pressure in a rotary evaporator in a round bottom flask that leaves the mixture of cholesterol and solid surfactant on the walls of round bottom flask. Then, aqueous solution containing drug with continuous shaking, this layer was then rehydrated which cause swelling of the surfactant layer. Swollen amphiphiles eventually folds and form vesicles which entrap the drugs (26).

Ether Injection Method:
A slowly injection of a solution containing a certain ratio of surfactant and cholesterol in ether into aqueous solution of the drug that is preheated and maintained at 60 °C through the specified gauze needle. Formation of unilamellar vesicles of the surfactants containing the drug takes place due to vaporization of ether. Ether cannot be used in case of thermolabile drugs so in this case, fluorinated hydrocarbons have been used as an alternative, because their vaporization takes place at a much lower temperature. The size of niosomes that result from this method ranges from 50 to 1000 mm, which mainly depend on the experimental conditions and formulation variables (36).

Sonication Method:
In this method, initially in the aqueous phase, the cholesterol-surfactant mixture is dispersed, then at 60 °C this dispersion is probe sonicated for 10 minutes that leads to the formation of multilamellar vesicles (MLV). Which are further ultrasonicated either by bath sonicator or probe sonicator, which finally resulted in the formation of unilamellervesicules (26).

Reverse Phase Evaporation Method:
The solution of cholesterol and surfactant is prepared in a mixture of chloroform and ether (1:1). Then, the solution of drug is added and at temperature four and five °C sonication occurred. Phosphate buffer saline (PBS) is added to the solution obtained from sonication and the solution is subjected to further sonication which leads to the formation of gel. Thereafter, pressure is reduced and temperature is raised to 40 °C for the solvent removal. For ten min, the PBS is added again and heated on water bath at 60 °C to produce niosomes. (39)

Microfluidization Method:
Two fluidized streams (one containing the surfactant and the other one containing drug) interact at ultra high speed, in certain micro channels within the chamber of interaction in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It leads to reproducibility in the formulation of niosomes, smaller size of niosomes and better uniformity (29).

Extrusion Method:
A mixture of diacetyl phosphate and cholesterol is prepared by the use of rotary vacuum evaporator the solvent is evaporated leaving a thin film. The thin film is then hydrated with aqueous drug solution and the
suspension thus obtained is extruded through the polycarbonate membrane which has mean pore size of 0.1mm and then placed in series up to eight passages that lead to formation of uniform size niosomes.(38)

V. Components Of Niosomes

Non-ionic Surfactants:
In bilayer lattice, non-ionic surfactants place themselves where the hydrophilic heads face the aqueous region while the lipophilic head orient themselves in such a way that the interaction with the aqueous media would be minimized (face the lipid bilayer). Every bilayer folds over itself as continuous membrane in order to achieve thermodynamic stability. Types of non-ionic surfactant include: Alkyl Esters such as Sorbitan esters which are the most preferred Surfactant used for the preparation of niosomes in this category, Alkyl Ethers such as monoalkyl glycerol ether, Fatty Acid and Amino Acid Compounds and Alkyl Amides such as glucosides have also been used to produce niosomal vesicles.(15)

Cholesterol:
Cholesterol is mainly used for the formulation of niosomes and it is a steroid derivative that is essential component of cell membrane and affects the permeability as well as fluidity of bilayer (10). Properties of niosomes such as encapsulation efficiency, rigidity, membrane permeability, ease of rehydration of freeze dried niosomes and their toxicity are affected by incorporation of cholesterol. Cholesterol prevents the vesicle aggregation by electrostatic forces or repulsive steric that leads to the conversion from the gel to the liquid phase in the system of niosome; hence the niosome becomes less leaky in nature.

Charged Molecule:
In order to increase the stability of niosomes, some charged molecules are added to niosomes which prevents aggregation of niosomes by electrostatic repulsion. The negatively charged molecules that are used include phosphatidic acid and diacetyl phosphate (DCP). Similarly, stearyl pyridinium chloride and stearylamine (STR) are the well-known positively charged molecules used in niosomal preparations.(1,16) Only 2.5—5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.(39)

VI. Types of Niosomes

Proniosomes:
This type of niosomes containing surfactant and carrier that requires to be hydrated before its usage, this hydration leads to the formation of dispersion of aqueous niosome. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation.

Bola Surfactant Containing Niosomes:
The surfactants that are made of omega-hexadecyl-bis-(1-aza-18 crown-6) (bola surfactant): span-80/cholesterol in 2: 3: 1 molar ratio.

Niosomes in Carbopol Gel:
In this type, niosomes prepared from cholesterol, drug and spans are then incorporated in carbopol-934 gel (1% w/w) base containing glycerol (30% w/w) and propylene glycol (10% w/w).

Aspasomes:
This type formed by Combination of highly charged lipid diacetyl phosphate, cholesterol and acorbyl palmitate.

Vesicles in Water and Oil System (v/w/o):
This type of niosomes can be created by. Adding of niosomes suspension that is formed from mixture of solulan C24, cholesterol and sorbitol monostearate to oil phase at temperature 60 °C that leads to the formation of vesicle in water in oil (v/w/o) emulsion which can be converted to vesicle in water in oil gel (v/w/o gel) by cooling to room temperature, This gel has the ability to provide controlled release as well as entrap /proteinous drugs and proteins also protect it from enzymatic degradation after oral administration.

Niosomes of Hydroxyl Propyl Methyl Cellulose
It the type of niosomes in which, a base including 10% glycerin of hydroxy propyl methyl cellulose was initially developed and then niosomes were incorporated in it.
Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. This review article focuses on the advantages, disadvantages, preparation methods, factors affecting, characterizations, invitro methods, drug release kinetics, and applications of niosome.

**Table (2):** variation between niosomes and liposomes (Manda et al., 2014) on between niosomes and liposomes (28).

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<th>Liposomes</th>
<th>Niosomes</th>
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<tbody>
<tr>
<td>Required/special methodforstorage, handling and purification of osphopolips</td>
<td>No special methods are required for such formulations comparatively</td>
</tr>
<tr>
<td>Phospholipids are prone to degradation</td>
<td>Non-ionic surfactants are stable (Mahaleet)</td>
</tr>
<tr>
<td>More expensive</td>
<td>Less expensive</td>
</tr>
</tbody>
</table>

**References**

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