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NIOSOMES: A NOVEL APPROACH FOR TOPICAL DELIVERY OF DRUGS

Srivastava NS*, Thakur S, Kaur J.
PCTE Groups of Institutes, Faculty of Pharmaceutical Sciences, Baddowal cantt, Ludhiana.
Email neha@pcte.edu.in

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Abstract

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a lipid vesicles. These are novel vesicular drug delivery system similar to liposomes used to deliver amphiphilic and lipophillic drugs. Niosomes are more stable, less susceptible to oxidation and can effectively deliver the drug for longer period of time. It serve as drug depots in the body which release the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug. The therapeutic efficacy of the drugs is improved by reducing the clearance rate, targeting to the specific site and by protecting the encapsulated drug. They also improve the therapeutic performance of the drug molecules by protecting the drug from biological environment and restricting effects to target cells. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. Many factors affect noisome formation such as the method of manufacture, nature of surfactant and encapsulated drug, temperature at which the lipids are hydrated and the critical packing parameter. This review article encloses different methods of preparation of niosomes, factor affecting the formulation of niosomes and characterization of niosomes. It also highlights the different application of niosomes.

Keywords: Niosomes, vesicles, topical delivery, lipid particulate delivery.

Introduction

Topical drug delivery is one of efficient route for local and systemic treatment [1]. A topical delivery system or vehicle is the mean of delivering the drug on the surface or across the different layers of skin. The transportation of medicament across the skin barrier is the major challenge faced by the scientists. Penetration across the skin is highly variable due to the lipophilicity and partitioning of the drug as well as excipient used in the vehicle [2]. A topical medication are designed to act locally at the site of administration and produce local therapeutic effects. Absorption of the drug is the rate

limiting step affecting the bioavailability of the applied drug. The delivery system is effective for drugs which are required in very small concentration for action. Improper technique or overuse of topical drugs can increase the risk of side effects as well as alter drug efficacy [3,4]. Most of the new chemical entities belong to class IV category indicates poor solubility and poor permeability. This category pose the major challenge for the formulation scientists with respect to solubility and bioavailability, which cannot be overcome by traditional topical delivery. Lipid-based drug delivery systems (LBDDS) can be modified in various ways to meet a wide range of product requirements as per the disease conditions, route of administrations, and also cost product stability, toxicity, and efficacy. Lipid base delivery system is the novel and effective way to deliver the drugs, gene, vaccines across the dermal layers [4].

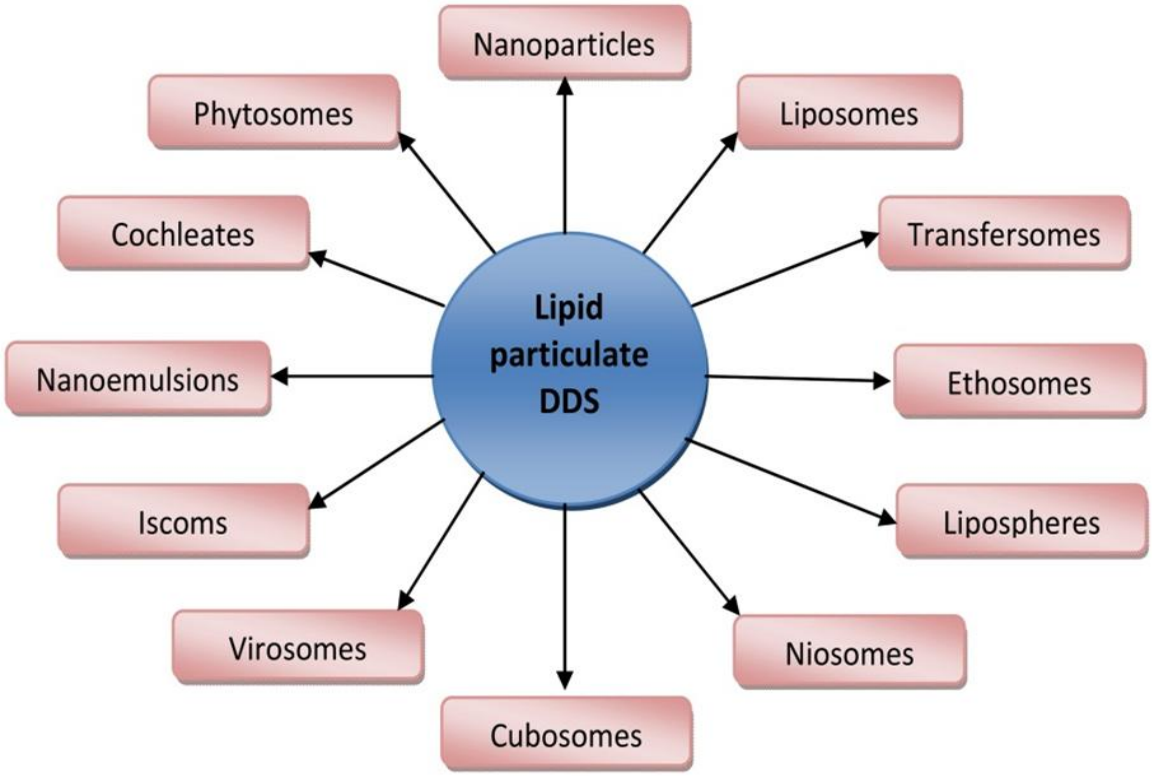

Fig 1: Different Lipid Particulate Drug Delivery System.

Niosomes

Niosomes are the non-ionic surfactant vesicles with microscopic lamellar structures formulated by admixture of cholesterol and non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class and followed by subsequent hydration in aqueous media [5,6]. These are the type of lipid vesicular systems similar to liposomes which can act as carriers of amphiphilic and lipophilic drugs. Niosomes are nano ranged particles with lamellar structures of size range between 10 to1000 nm [7]. Niosomes are formulated with surfactant and cholesterol followed by hydration of lipid film [8].

Niosomes are the promising carrier for topical delivery of drugs and has potential to improve therapeutic effect of drugs while reducing it side effects [9]. Non ionic surfactant is the major component of niosomes which make it more stable as compared to liposomes. These niosomes are less susceptible to oxidation, less costlier and less susceptible to the quality of material influencing the shape and size [10]. Niosomes might be produced by various types of nonionic surfactants including polyglycerol alkyl ethers, crown ethers, ester-linked surfactants, glucosyldialkyl ethers, polyoxyethylene alkyl ethers, Brij, Tweens and Spans [11].

Niosomes are designed to deliver the drugs in controlled manner for prolonged period of time through its bilayer structures by encapsulating drugs in its structure. It is one of the emerging approach for targeting the drugs by surface modification. Thereby reducing the dose required to be administered to achieve the desired effect [12]. The therapeutic efficacy of the drugs is improved by protecting the drug by encapsulation, reducing the clearance rate and targeting to the specific site. Drug targeting helps to localized the drug and produces therapeutic effect at low dose concentration with lesser side effects [10]. These may act as a depot, releasing the drug in a controlled manner restricting effects to target cells [11, 12].

Niosomes exhibit good chemical stability but they are physically less stable [13]. Different forces are responsible for the stability of niosomes which includes repulsive forces emerging from the electrostatic interactions between charged groups of surfactant molecules, vanderwaals forces among surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These are the forces which helps to maintain the vesicular structure of noisome [14, 15].

Skin is the most stringent barrier for the penetration of drugs. Stratum corneum, the uppermost layer of skin, is a rate limiting step for percutaneous absorption of drug. The physiochemical properties of the drugs plays the key role in penetration and diffusion across the bilayer structure of skin. Stratum corneum facilitates three major routes for the transportation of drugs.

The routes are intercellular, transcellular (paracellular), and transappendageal. The drug have to travel through different layer of skin to enter in to systemic circulation or to be transported to various tissues. The penetration of the drug molecules are largely dependent on its physicochemical characteristics such as partitioning of drug and diffusion coefficients across the different membranes [11].

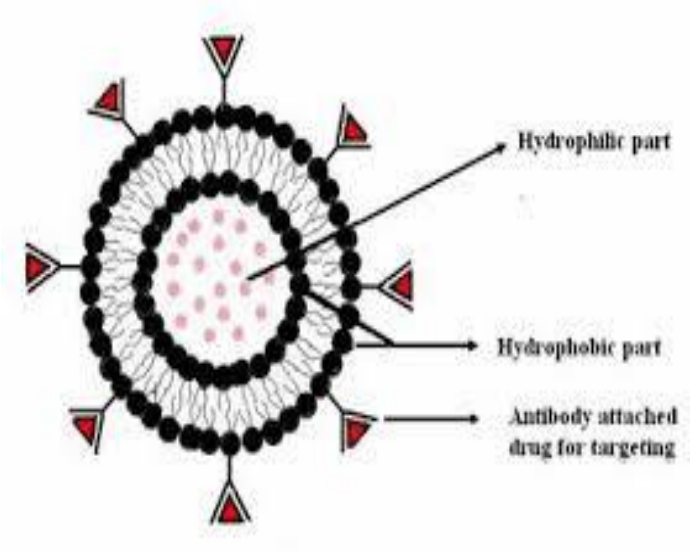

Fig 2: Structure of niosomes.

Advantages of niosomes

- ✓ Niosomes are stable and osmotically active and also increase the stability of the entrapped drug [16].
- ✓ The surfactants used and the prepared niosomes are biodegradable, biocompatible and non-immunogenic.
- ✓ No special conditions is required for handling and storage of surfactants.
- ✓ The performance and the characteristics of the prepared niosomes can be controlled by, concentration of various additives, altering the composition, lamellarity, size and surface charge of vesicles [17].
- ✓ Patient compliance is very high as compared with oily dosage forms.
- ✓ Niosomes enhances the bioavailability of poorly soluble drugs and improves skin penetration of drugs.
- ✓ Niosomes constitute of lipophilic, hydrophilic and amphiphilic and moieties together in one structure.
- ✓ The characteristics of the vesicle formulation are variable and controllable [18].

Classification of Niosomes

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size (e.g. LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below [7].

i) Multi lamellar vesicles (MLV)

ii) Large unilamellar vesicles (LUV)

iii) Small unilamellar vesicles (SUV) [19]

1. **Multilamellar vesicles:** It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. These vesicles are highly suited as drug carrier for lipophilic compounds.
2. **Large unilamellar vesicles:** Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.
3. **Small unilamellar vesicles:** These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method [19].

Factors Influencing Niosomes Formation:

Various factors which effect the niosomes formulation are following:

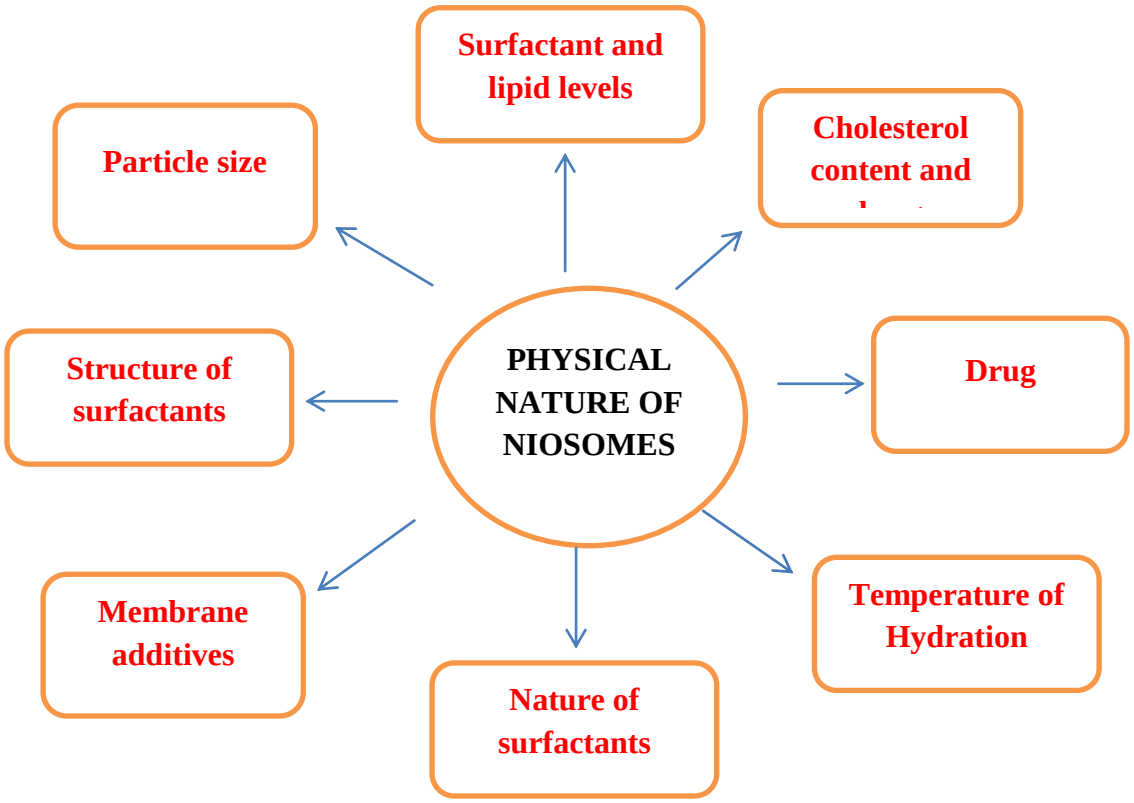

Fig 3: Factors affecting formulation of niosomes.

Nature of surfactants:

Non ionic surfactant is the material of choice for the formulation of niosomes. Different non ionic surfactants alone and in combinations has been reported which can accommodate large variety of drugs [20, 21]. A surfactant used for preparation of niosomes must have a hydrophobic tail and hydrophilic head which can entrap both hydrophobic as well as hydrophilic

drugs. There are different categories of surfactants have different effect on property of the niosomes. The hydrophobic tail comprised of hydrocarbon chain that can be branched linear or aromatic. The clustering of this chain renders the hydrophobic environment [22].

Sorbitan fatty acid ester is the most commonly used nonionic surfactant. Different grades can be employed such as Span 20, 40, 60, 80 for the effective formulation of niosomes. Long chain fatty acid esters more than 18 alkyl groups are hydrophobic in nature [23]. Solubility in water can be increases by addition of poly oxythylene groups to the surfactant structure. Ethoxylated derivative of sorbitan fatty acid esters are more water soluble (Tween 20, 40, 60 and 80). Kandasamy Ruckmani and *et al* prepared the niosomes of zudovudine using tween 20, 40,60 and 80 as well as span 20, 40, 60 and 80. The length of the alkyl chain affects the hydrophilic-lipophilic balance (HLB) value of the surfactant and the lower the HLB value of the surfactant, the lower will be the entrapment efficiency The study reveals that tween 20 and span 60 showed highest entrapment efficiency. The higher entrapment was due to the high-phase transition temperature, solid nature, hydrophobicity of the surfactant [24].

Bola form amphiphiles are the new surfactant used in preparation of niosomes. These are the surfactant containing two hydrophillic molecules connected with hydrophobic bonds [25]. Rita Muzzalupo *et al*, formulated used bola form surfactant (4, 7, 10,13-pentaoxa-16-aza-cyclooctadecane)-hexadecanedioc acid diamide (BD -16) and α, ω-(4, 7, 10, 13-pentaoxa-16-aza-cyclooctadecane)-hexadecane (BC-16) in the formulation of niosomes. Niosomes with combination of cholesterol and BD 16 was prepared hydration of film. Niosomes were evaluated for particle size, entrapment and morphology. The results obtained in this study show a high encapsulation capacity and uniform size [26].

Sucrose based surfactants consist of fatty acids as lipophilic tail and sucrose as the hydrophilic head group. These natural surfactants have been reported with vesicle formation capabilities and are used to formulate drug delivery systems [25]. Abd-Elbary A and *et al* formulated sucrose starate based proniosomes of cromolyn sodium. Formulated niosomes showed higher drug release and good stability and minimize the problems associated with traditional niosomes such as aggregation, fusion or sedimentation [27].

Brij are the polyoxyethylene alkyl ethers considered to be more hydrophillic and more stable [20]. These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties which are linked with ether linkage. The general formula of this group is (CnEOm), where n can be 12-18 and m can be 3-7. Surfactants with polyhydroxyl head

and ethylene oxide units are also reported to be used in niosomes formation. The different grades of Brij used for vesicle formation are Brij 30, 35, 52, 58, 72, 76, 92, and 97. Different studies have been reported in literature using these surfactants [28]. Brij 30 has an HLB value of 9.7 and a phase transition temperature less than 10. It forms large unilamellar vesicles when combined with cholesterol [29].

Manconi et al. prepared niosomes of tretinion using polyoxythelene 4 lauryl ether and reported that it formed large unilamellar vesicles with high entrapment efficiency. [30]. Brij 52, 56 and 58 are cetyl derivatives of polyoxyethylene which have the vesicle forming ability. Brij 58 has have inverted vesicle forming capacity, which are useful for studying ion-pumping activity at the plasma membrane. The HLB value of Brij 58 is 15[31].

Brij 72 and 76 are stearyl derivatives of polyoxyethylene ether and posses good vesicle forming capability. Brij 72 forms multilamellar vesicles with high encapsulation efficiency. Thus, vesicles made of Brij 72 encapsulated more finasteride than those formulated using Brij 76. This is probably because of its low HLB value of 4.9 compared to that of Brij 76 of 12.44 [32].

Phase transition temperature: Phase transition temperature of surfactant play the key role in formulation of the vesicles. It affects the fluidity, stability, vesicle size and entrapment of the drugs. The surfactants with higher phase transition temperature are suitable for the formulation of niosomes. Longer the alkyl chain of surfactant higher the phase transition temperature, this is due to higher interaction of the adjacent molecules.

Span 20 has lower phase transition temperature and is liquid at room temperature while span 40 posses phase transition temperature is 46-47^{0}C and span 60 has 55-58^{0}C. This reflects that span 20 produces leaky vesicles compared to span 40 or 60.

Encapsulation efficiency is an important aspect of phase transition. Higher the gel to sol transition temperature greater the encapsulation of the drugs [20, 33]. Pratap S. Jadon formulated niosomes of griseofulvin, the result reflects highest entrapment by span 60 (76.8%). Span 20 shows the lowest entrapment [34].

Same trend is observed with tweens, Tween 80 with lowest carbon chain has lowest entrapment followed by tween 20, tween 40 and tween 60 [20]. A. Abdul Hasan Sathali formulated niosomes of terbinafine hydrochloride formulated niosomes using tween 20, tween 40, tween 60 and tween 80. Highest encapsulation is seen with span 60 (84%) indicates higher the chain length higher will be the encapsulation [35].

Temperature of Hydration: The temperature of hydration is one of the factor affecting the size and shape of the noisome. The temperatures of hydrating liquids used to make niosomes should usually be above the gel to liquid phase transition temperature of the system [36]. Apart from this volume of hydration liquid and time of hydration also affect the quality of niosomal structure or leaky niosomes. Kandasamy formulated niosomes containing Tween 80 was hydrated with phosphate buffered saline, pH 7.4 (6 ml), resulted in formation of stable vesicles. By increasing the volume of hydration medium leads to leakage of drug from vesicles. The time of hydration also affects the vesicle formation, increase in the hydration time of the film from 20 to 45 min resulted in a higher percentage of drug entrapment [24].

Drug: The encapsulated drug governs various factors of niosomes including its characteristics and stability. Drugs are basically classified depending on their affinity for water, i.e hydrophobic (water insoluble) and hydrophillic (water soluble). Niosomes encapsulating hydrophillic drugs are less stable compared to niosomes encapsulating hydrophobic drugs.[20, 37, 38]. Increase in concentration of drug increase in encapsulation due to saturation in hydration medium. Hoa *et al.* have reported that increasing the Colchicine drug load from 3 to 7 mg led to significant increase in EE%. The entrapment of drug inside the niosomes affects the vesicle size, due to interaction of solute with surfactant, increasing the charge and repulsion of the surfactant bilayers, leads to increase in vesicle size. The HLB of the drug affects degree of entrapment [39].

Cholesterol content and charge: Increase the cholesterol content in niosomes with increases its diameter and entrapment efficiency. Cholesterol is the major component of niosomes, higher the cholesterol content increases the stability and entrapment efficiency of the niosomes. It serves as dual function, cholesterol increases the chain order of liquid-state bilayers at the same concentration cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid- ordered phase [40].

The increase in the cholesterol content decrease the bilayer fluidity and provide rigidity to the membrane. It also helps to retail the drug for longer period of time [37, 40].

Charge inducing agents imparts charges which tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and also increases the volume of entrapment. The incorporation of cholesterol in lipid bilayers is to control their cohesion and mechanical property and their water permeability. Through the addition of cholesterol, the fluidity of niosomes is changed considerably [41].

Table no: 1: Nature of drug and its effect on stability.

Nature of the drug	**Leakage from the vesicles**	**Stability**	**Other properties**
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophobic drug	Increased	Decreased	-
Amphiphilic drug	Decreased	-	Increased encapsulation, Altered elecrophoretic mobility
Macromolecules	Decreased	Increased	-

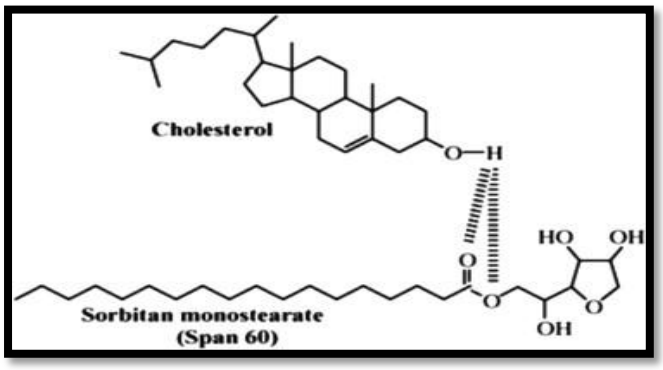

Fig 4: Chemical bonding of cholesterol and span 60.

Membrane additives: Various additives can be added to the formulation which affects the quality and stability of niosomes. The membrane stability, morphology and permeability of vesicles are affected by numbers of additives e.g. addition of cholesterol in niosomal system increases the rigidity and decreases the drugs permeability through the membrane [42]. Charge inducing agents (positive, negative or non ionic) influences various parameters such as vesicle size, entrapment of drug etc. Varaporn Buraphacheep Junyaprasert studied the effects of charge inducing agents on physiochemical properties and membrane stability of niosomes. The results reveals that charge inducing agents affects the particle size and zeta potential. Entrapment of drug depends on type of drug and charge of the charge inducing agents [43].

Mechanisms of niosomes penetration through skin delivery

Niosomes are the challenging tool for dermatological disorders. Niosomes have also been used in cosmetic and for delivery of peptide drugs. Topically applied niosomes can increase the residence time of the drug in the SC and epidermis

while reducing the systemic absorption of drugs. They are thought to improve the horny layer properties both by reducing transepidermal water loss and by improving smoothness, reconstituting lost skin lipid. Thus niosomes act as penetration enhancers [11].

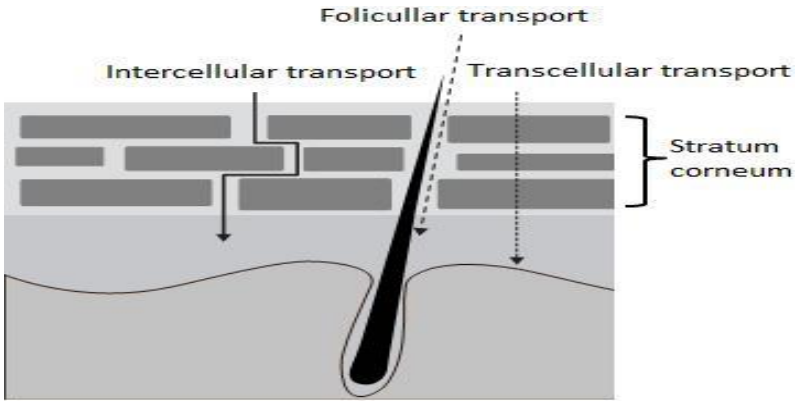

Fig 5: Skin transport pathways.

Method of Preparation

Thin film hydration technique/Hand shaking method:

Surfactant and cholesterol are dissolved in a volatile organic in a round bottom flask. The organic solvent is removed at room temperature at 20^{o}C using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. Surfactant film can be rehydrated with aqueous phase at 0-60^{o}C with gentle agitation. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication [41].

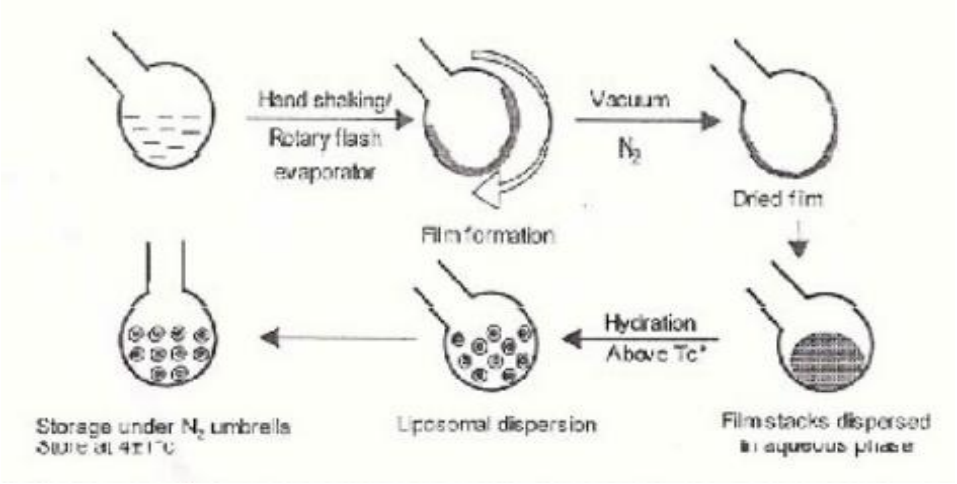

Fig 6: Hand Shaking Methods.

Ether injection method:

Formation of 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 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 [18].

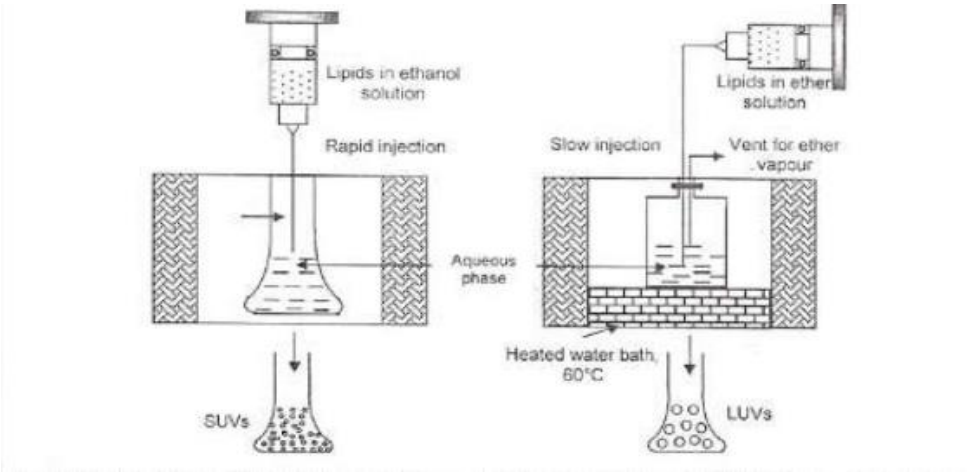

Fig 7: Ether Injection Method.

Reverse phase evaporation technique:

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and 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. Viscous niosomes suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes [44].

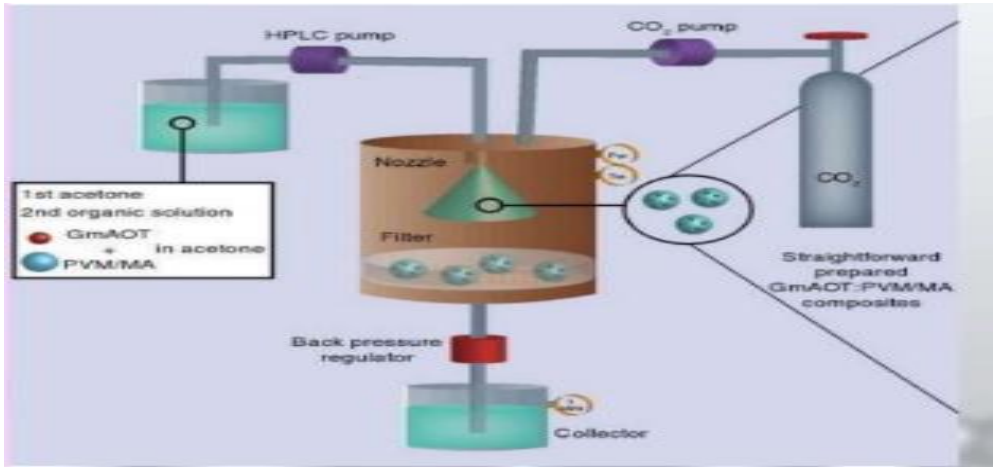

Fig 8: Reverse Phase Evaporation Technique.

Sonication

The aqueous phase is added into the mixture of surfactant and cholesterol in a scintillation vial. Then, it is homogenized using a sonic probe. The resultant vesicles are of small unilamellar type Niosomes. It is possible to obtain SUV Niosomes by sonication [45, 46].

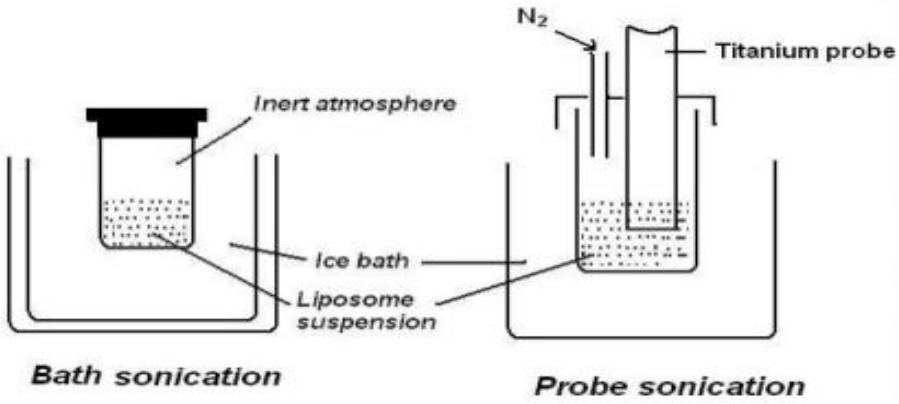

Fig 9: Sonication.

The "Bubble" Method:

The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in the buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas [47].

Microfluidization:

A solution of surfactants and drug is pumped under pressure from a reservoir through an interaction chamber packed in ice at a rate of 100 mL/min. From the interaction chamber, the solution is passed through a cooling loop to remove the heat produced during microfluidization and returned to the reservoir for recirculation or allowed to exit the system. The process is repeated until a vesicle of the desired size is produced [31].

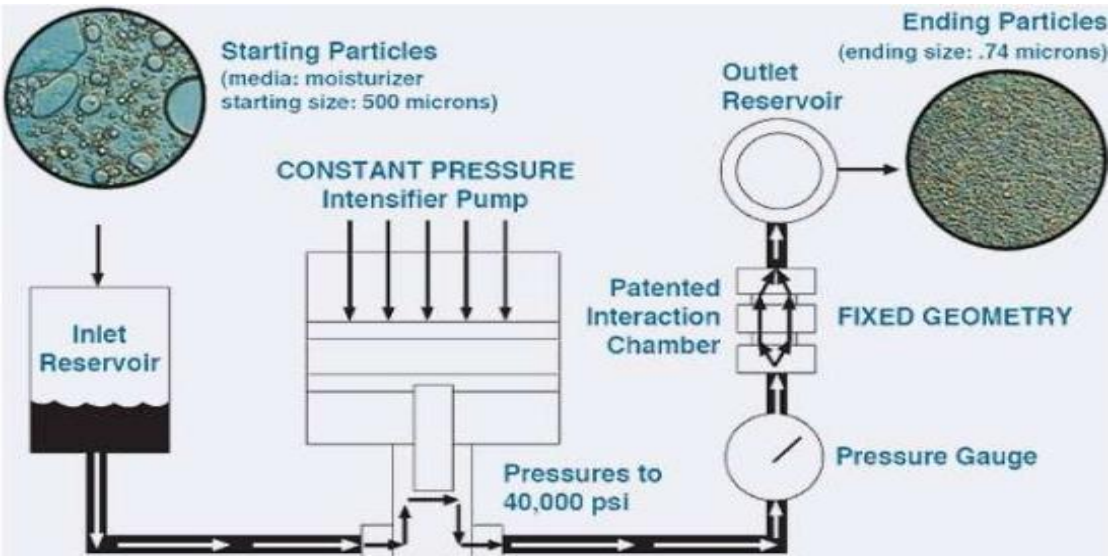

Fig 10: Microfluidization

Separation of Un-entrapped Drug

The removal of un-entrapped solute from the vesicles can be accomplished by various techniques, which include:

(i) Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

(ii) Gel Filtration: The un-entrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

(iii) Centrifugation: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then re-suspended to obtain a niosomal suspension free from un-entrapped drug.[6]

Characterization of Niosomes

Vesicle diameter:

Niosomes are spherical shape and their diameter can be determined by light microscopy, photon correlation microscopy and freeze fracture electron microscopy.[9]

Entrapment efficiency:

After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug [40].

Where, % Entrapment efficiency (% EF)

Entrapment Efficiency = (Amount of drug entrapped/ total amount of drug) x 100

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 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 [48].

Stability study:

All niosomal formulations were subjected to stability studies by storing at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations were checked by entrapped efficiency parameter [49].

***In-vitro* drug release study**

The In-vitro diffusion study was performed by a modified Franz diffusion cell of capacity 15 ml using cellophane membrane. The cellophane membrane was activated by keeping it in the mixture of phosphate buffer 7.4 and ethanol for over-night. A section of membrane was cut, measured, and placed on the receiver compartment. The donor compartment was filled with niosomal formulation. A 15 ml of aliquot of 4:6 (v/v) Ethanol: pH7.4 phosphate buffer was used as receptor medium. The receptor medium was maintained at 37^0C and stirred by a magnetic bar at 300 rpm. Aliquots of 0.5 ml of the receptor medium were withdrawn and immediately replaced by equal volume of fresh receptor solution at appropriate interval of an hour up to 12 h. The 0.5 ml sample is diluted to 10 ml receptor medium and observed spectrophotometrically [50].

Scanning electron microscopy: The niosomes were observed under a scanning electron microscopy (SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmHg. Photographs were taken at suitable magnification [50, 51].

Applications of Niosomes:

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

1) Targeting of bioactive agents

a) To reticulo-endothelial system (RES) - The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver [52].

b) To organs other than RES - It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies. immunoglobulin's seen to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.

Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells [53].

2) Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes [54].

3) Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in-vitro study conducted by Yoshida et al, oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide [5].

4) Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants following parenteral administration with a number of different antigens and peptides [36].

5) Cosmetic delivery

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Niosomes were developed and patented by L'Oréal in the 1970s and 80s. The first product 'Niosome' was introduced in 1987 by Lancôme.

The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration [55].

6) Neoplasia

The anthracyclic antibiotic Doxorubicin, with broad spectrum anti tumour activity, shows a dose dependant irreversible cardio toxic effect. The half-life of the drug increased by its niosomal entrapment of the drug and also prolonged its circulation and its metabolism altered.

If the mice bearing S-180 tumour is treated with niosomal delivery of this drug it was observed that their life span increased and the rate of proliferation of sarcoma decreased38. Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in total regression of tumour and also higher plasma level and slower elimination [56].

7) Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment [57].

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Corresponding Author:
Neha Srivastava*,
Email: *neha@pcte.edu.in*