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A Review on Novel Vesicular Drug Delivery System: Niosomes

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ABSTRACT:
Main aim of the present study is to enhance solubility and dissolution rate of poor soluble drugs. 40% of drugs are having poor aqueous solubility. Niosomes is a novel approach having a wide range of solubility and enhance dissolution rate of drugs and can be improved the therapeutic performance of drug molecules.
Nano chemistry field has shown a great progress in developing novel carriers such as immunoglobulins, liposomes, niosomes etc., as potential drug delivery systems. Niosomes are a novel vesicular drug delivery system, in which the medication is enclosed in a vesicle. Niosomes represent an emerging class of novel vesicular systems. Niosomes are non-ionic surfactant based unilamellar or multilamellar vesicles in which an aqueous solution of solute is enclosed by bilayered surfactant membrane. Niosomes can encapsulate both lipophilic and hydrophilic drugs sue to their unique structure. Niosomes composed of mainly two components surfactants and cholesterol. Most surface-active agents when immersed in water yields micellar structures however some surfactants yield bilayered vesicles which are niosomes. In recent years, it has been discovered that these vesicles can improve the bioavailability of drugs and may function as a new drug carrier for delivering several typical of therapeutic agents. Structurally, niosomes are similar to liposomes and hence they can represent alternative vesicular systems with respect to liposomes. The bilayer is made up of surface-active agents in niosomes rather than phospholipids as in case of liposomes. Niosomes are chemically stable during the formulation process and storage and economical compared to liposomes. In recent years a comprehensive research carried over niosomes as a drug carrier and they proved to be promising drug carrier which has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. The present review represents the structure, types of niosomes, different techniques used for preparation of niosomes such as hand shaking method, thin film hydration, sonication, ether injection method, reverse phase evaporation, proniosome technology, the bubble method etc., characterisation of niosomes such as vesicle size, morphology, size distribution, entrapment efficiency, invitro drug release study etc., and applications in various fields like gene delivery chemical drugs, targeted drug delivery etc.,

I. INTRODUCTION:

In the field of nanotechnology, niosomes are gaining increasing scientific interest as useful drug delivery systems for several therapeutic applications due to their unique features (Rita Muzzalupo et al**.,** 2019). Paul Ehrlich, in 1909 initiated the era of targeted drug delivery. Number of carriers were utilized to carry drug at target organ/tissue which include immunoglobulins, liposomes, niosomes, synthetic polymers etc., among them liposomes and niosomes are well documented drug delivery. It is one of technique used to obtain controlled release system.

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Niosomes are non-ionic surfactant based unilamellar or multilamellar vesicles in which an aqueous solution of solute is enclosed by bilayered surfactant membrane. Niosomes are microscopic lamellar structures of size range between 10 to 1000nm. The unique structure of niosomes make it capable of encapsulating both hydrophilic and lipophilic substances. Niosomes entrap the hydrophilic drug in the core cavity while the

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lipophilic drug can be entrapped in non-polar regions present within the bilayer (Lohumi Ashutosh et al**.,** 2012).

Niosomes have been one of the illustrious vesicles into all vesicular systems, being the focus of a great attention as potential drug delivery systems for different routes of administration, in recent years. Niosomes have the ability of entrapping various types of drugs, genes, proteins and vaccines.

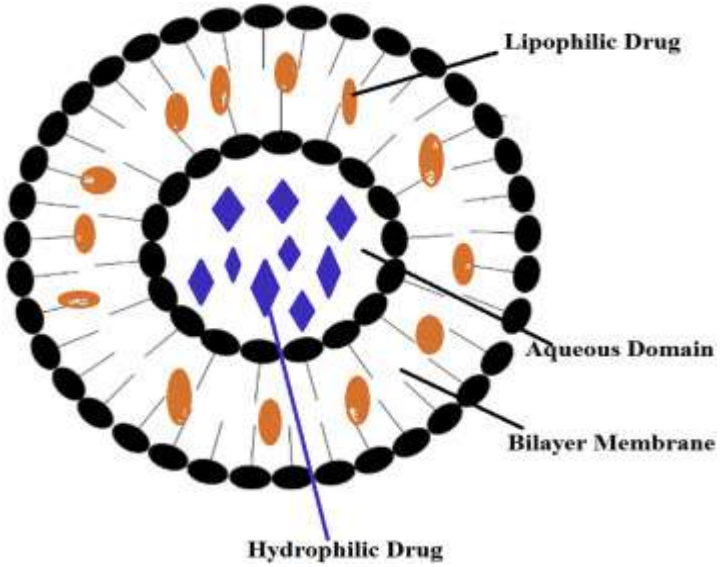

Fig no. 1 Structure of Niosome

Table no.1 Comparison of Liposomes and Niosomes

S NO	LIPOSOMES	NIOSOMES
1	Vesicles made up of concentric bilayer phospholipids	Vesicle made up of non-ionic surfactants with or without incorporation of cholesterol.
2	Their ingredients like phospholipids are chemically unstable because of susceptibility to oxidative degradation.	Niosomes are chemically stable.
3	They require special storage and handling	They do not require special storage and handling
4	Liposomes are prepared from double chain phospholipids	Niosomes are prepared from uncharged single-chain surfactant and cholesterol
5	Size ranges from 10-3000nm	Size ranges from 10-1000nm
6	They are expensive	They are economical.

1.1 ADVANTAGES OF NIOSOMES:

- Niosomes having a wide range of solubility as their infrastructure consists of hydrophilic and lipophilic part.
- Niosomes are osmatically active and stable.
- Niosomes provide better patient compliance than oily dosage forms because of water based suspension.
- Niosomes had flexible characteristic properties like vesicle composition, size, lamellarity, surface charge etc., by altering those characteristics desired concentration of niosomes can be obtained (Peryush Bhardwaj et al., 2020).
- Niosomes can be improved the therapeutic performance of drug molecules by improving oral bioavailability of poorly soluble drugs, by protecting the drug molecules from biological environment and by delaying clearance from circulation.
- Niosomal surfactants are biodegradable, biocompatible and non-immunogenic.

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- No requirement of special conditions for handling and storage of Niosomal product.
- The vesicle may act as a depot, releases the drug in a controlled manner.

1.2 DISADVANTAGES OF NIOSOMES:

- Due to fusion, aggregation, leaking of entrapped drugs and hydrolysis of encapsulated drugs, the aqueous suspension of niosomes have limited shelf-life.
- The method of preparation of multi-lamellar vesicles like sonication, extrusion is time consuming and require special conditions for processing.

II. COMPOSITION OF NIOSOMES:

Cholesterol and non-ionic surfactants are the two major components used for formulation of niosomes. Cholesterol provide rigidity and proper shape to niosomes. Non-ionic surfactants play an important role in the formation of Niosomes.

2.1. NON-IONIC SURFACTANTS:

Surfactants are amphiphilic molecules consists of hydrophilic region (water-soluble) and lipophilic region (organic-soluble). The lipophilic region is chains made up of alkanes, fluorocarbons, aromatic or other non-polar groups while hydrophilic regions involves functionalities such as sulfonates, carboxylates, phosphates and ammonium derivatives. Surfactants can be classified into cationic, anionic, non-ionic and amphoteric according to their functionality head group.

Non-ionic surfactants are one of the best polymeric nanocarrier having a wide role in sustained, controlled and continuous drug delivery (Saeid Moghassemi et al., 2014). Non-ionic surfactants have no charge groups in their hydrophilic heads. The most commonly used surfactants are spans (span 20,40,60,85,80) tweens (tween 20,40,60,80) and brijs (brij 30,35,52,58,72,76). Non-ionic amphiphiles used in niosome formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.
Surfactant selection is depending on Hydrophilic-Lipophilic balance (HLB) and Critical packing parameter (CPP) values.

Table no. 2 Different Types of Non-Ionic Surfactants

S NO	TYPES OF NON-IONIC SURFACTANTS	EXAMPLES
1	Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetosteryl alcohol, oleyl alcohol
2	Ethers	Brij, decyl glucoside, lauryl glucoside, octyl glucoside, triton X-100, nonoxynol-9
3	Esters	glyceryl laurate, polysorbates, spans
4	Block copolymers	Poloxamers

2.1.1 HYDROPHILIC-LIPOPHILIC BALANCE:

The relationship or balance between the hydrophilic portions of the non-ionic surfactant to the lipophilic portion. It was invented in 1954 by William C. Griffin. The HLB value is an indication of the solubility of the surfactant. HLB value range is from 0 to 20 for non-ionic surfactants. The lower HLB value (<9) indicates the lipophilic surfactant or oil soluble surfactant and the higher HLB value (>11) indicates the hydrophilic surfactant or water-soluble surfactant. Surfactant with HLB value 3-8 refer to water in oil emulsifier while the oil in water emulsifier exhibit the HLB value 8-18.

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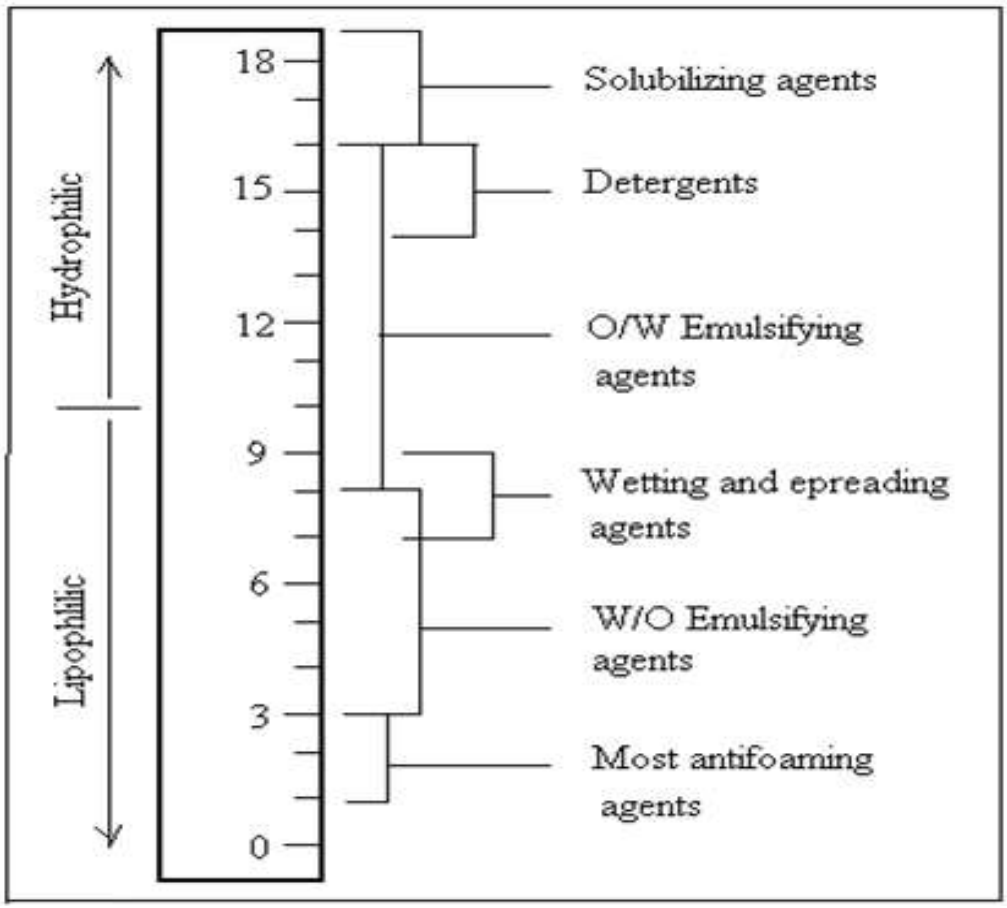

Fig no.2 Hydrophilic-lipophilic balance scale

2.1.2. CRITICAL PACKING PARAMETER:

In addition to HLB number, the other dimensionless parameter CPP is used to define the geometry of vesicle to be formed from surfactants which is affected by surfactants structure. Geometry of vesicles to be formed can be predicated on the basis of CPP of surfactants. It can be defined using following equation:

$$CPP = V / lc \times a_0$$

Where,
V= hydrophobic group volume
lc= the critical hydrophobic group length and
a_0= the area of hydrophilic head group

III. TYPES OF NIOSOMES:

The niosomes are classified as a function of number of bilayers or as a function of size or as a function of method of preparation (Saeid Moghassemi et al., 2014). They are majorly classified into three types:

1. Multilamellar vesicles (MLV)
2. Large unilamellar vesicles (LUV)
3. Small unilamellar vesicles (SUV)

3.1. MULTILAMELLAR VESICLES:

It consists of a number of bilayers surrounding the aqueous compartment separately. The approximate size of vesicle is 0.5-10 µm. It is simple to make and mechanically stable upon storage for longer periods. MLV are most commonly used niosomes.

3.2. LARGE UNILAMELLAR VESICLES:

LUV size ranges from 100-3000nm. Niosomes of this type have a high aqueous/lipid compartment

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ratio so that large volume of bio-active molecule can be entrapped.

3.3. SMALL UNILAMELLAR VESICLES:

SUV size ranges from 10-100nm. These are prepared from multilamellar vesicles by sonication method.

IV. METHOD OF PREPARATION:

Niosomes as drug delivery can be prepared by various methods as follows:

1. Ether injection
2. Hand shaking
3. Sonication
4. Reverse phase evaporation
5. Extrusion
6. Micro fluidisation
7. Heating
8. Freeze thraw technology

- **Advanced methods:**

1. Bubble method
2. Preparation of Niosomes from Pro-Niosomes

Fig no.3 Different Methods Of Preparation Of Niosome

3.4. PREPARATION OF SMALL UNILAMELLAR VESICLES:

3.4.1. SONICATION:

A typical method of production of the vesicles is by sonication of solution. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is probe sonicated at 60C for 3 minutes using a sonicator with a titanium probe to yield niosomes (Mahmoud Kamal et al., 2018). Multilamellar vesicles are obtained, SUV are obtained from MLV by subjecting to ultrasonic vibration. Vesicles obtained are unilamellar in shape.

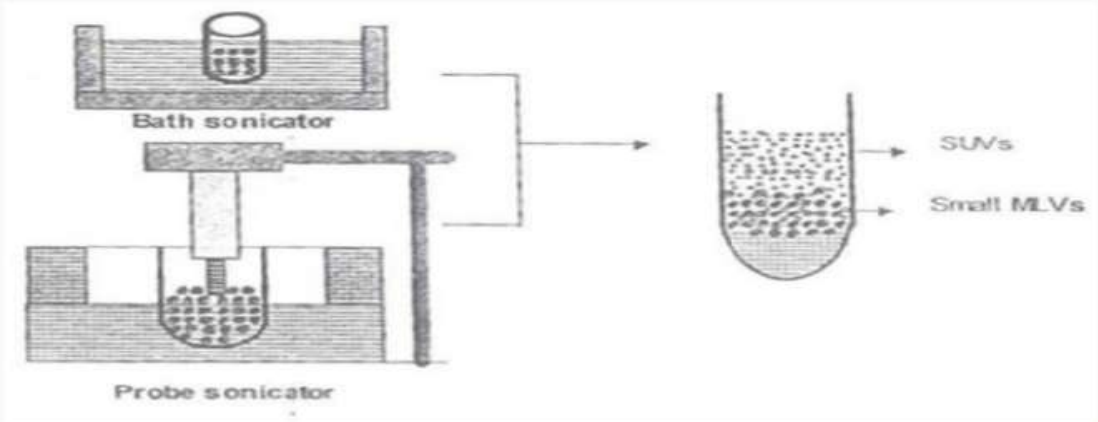

Fig no. 4 preparation of Niosomes by sonication

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3.5. PREPARATION OF MULTILAMELLAR VESICLES:

3.5.1. THIN FILM HYDRATION TECHNIQUE (HAND SHAKING METHOD):

Thin film hydration method is simple preparation method and is widely used. The mixture of vesicles forming ingredients like cholesterol and surfactants are dissolved in a volatile organic solvent such as diethyl ether or chloroform or methanol in a round bottom flask. The organic solvent is removed at room temperature (20C) using a rotary evaporator leaving a thin film of solid mixture deposited on the wall of flask. With gentle agitation, the dried surfactant film can be rehydrated with aqueous phase at 0-60C results in the formation of typical multilamellar vesicles (Kshitij b Makeshwar et al., 2013). This method has been used for preparing niosomes entrapping nimesulide. Minoxidil, diclofenac sodium, luteinizing hormone, doxorubicin, anti-oxidants etc.,

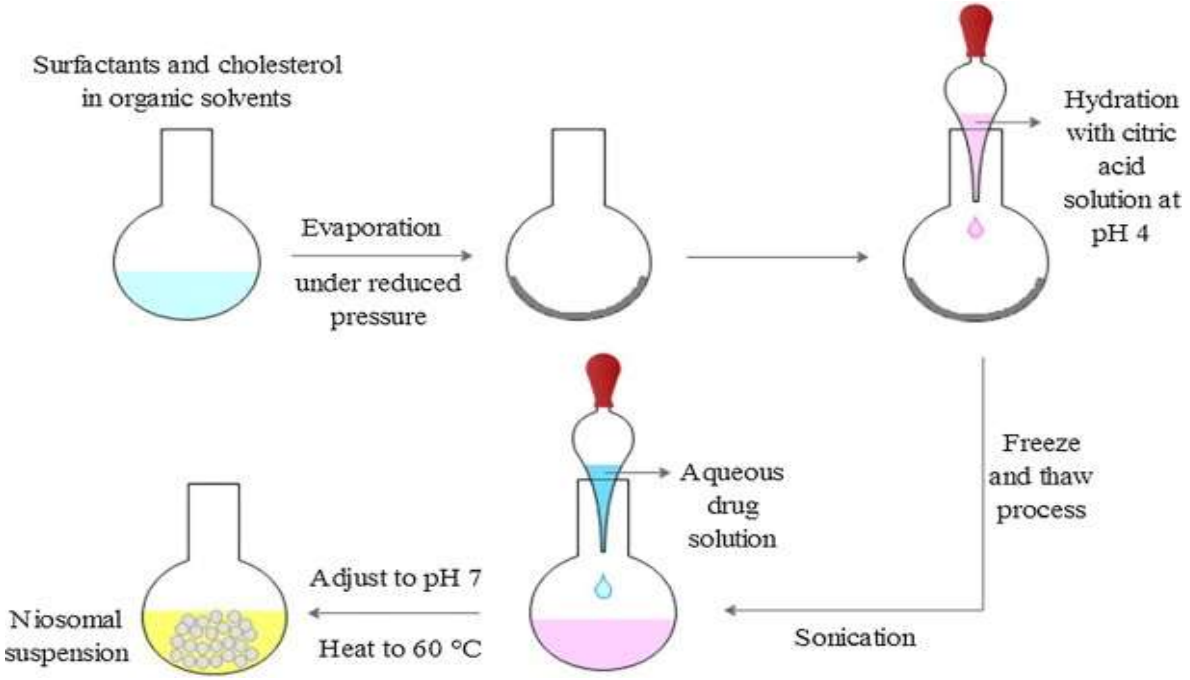

Fig no. 5 Formation of Niosomes by Thin Film Hydration Method

3.5.2. REMOTE LOADING (ACTIVE LOADING) BY USING TRANS-MEMBRANE PH GRADIENT TECHNIQUE (IN ACIDIC RANGE):

A mixture of surfactant and cholesterol are dissolved in chloroform in a round bottomed flask. A thin film is obtained on the wall of flask by evaporating chloroform under reduced pressure. The film is hydrated by vortex mixing with 300Mm citric acid. The MLV are frozen and thawed three times and then sonicated. Aqueous solution containing 10mg/ml is added to Niosomal suspension and vortexed. The PH of sample is raised to 7-7.2 by adding 1M disodium phosphate. The mixture is then heated at 60C for 10 minutes to obtain desired multilamellar vesicles.

3.6. PREPARATION OF LARGE UNILAMELLAR VESICLES:

3.6.1. ETHER INJECTION METHOD:

Firstly, a solution of surfactant mixture is prepared by dissolving it in diethyl ether and then slowly introduced into warm water and maintained at 60C. Using 14 gauge needle the surfactant mixture in ether is slowly introduced into aqueous solution of sample. Single layered vesicles are obtained by evaporating ether in solution. The size of obtained vesicles may range from 50-1000nm depending upon the conditions used (Saeid Moghassemi et al., 2014). The major disadvantage of this method is removal of ether because a small amount of ether is still present in a vesicle.

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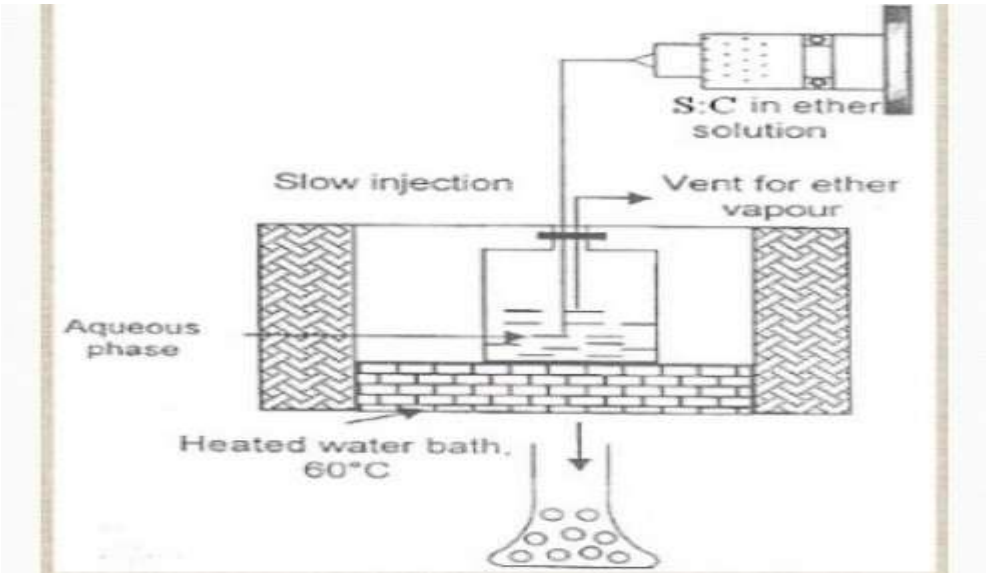

Fig no. 6 Ether Injection Method

3.7. ADVANCED METHODS:

3.7.1. BUBBLE METHOD:

It is a novel technique used for the one step preparation of niosomes and liposomes without the use of organic solvents. A round bottomed flask act as a bubbling unit consists of three necks positioned in a water bath to maintain the temperature. In first and second necks, water cooled reflux and thermometer are placed and the third neck is used for nitrogen supply. Surfactant and cholesterol are dispersed in buffer (PH 7.4) and mixed at 70C using high pressure homogeniser for 15 seconds. Immediately afterwards, bubbled at 70C using nitrogen gas to yield Niosomes.

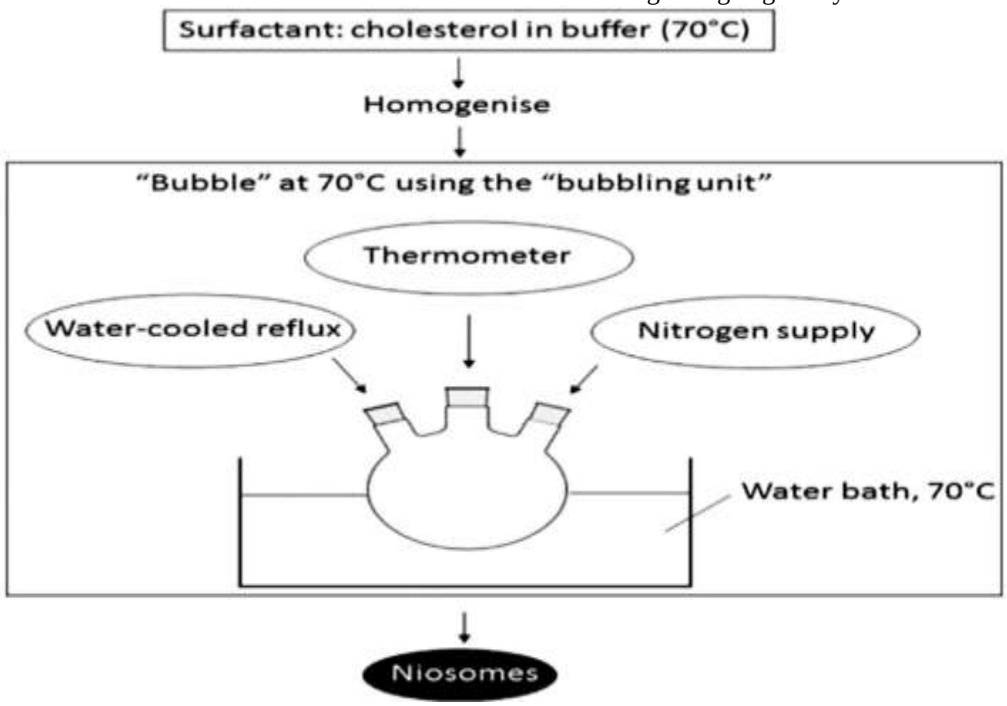

Fig no. 6 Bubbling Unit

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3.7.2. FORMATION OF NIOSOMES FROM PRONIOSOMES:

Proniosomes are dry formulation of surfactant coated carriers. To create Proniosomes, a water-soluble carrier such as sorbitol is first coated with the surfactant. The coating is done by preparing a solution of surfactant with cholesterol in a volatile organic solvent, which is sprayed onto the powder of sorbitol kept in a rotary evaporator. The evaporation of an organic solvent leaves a thin coat on sorbitol particles. The resulting coating is a dry formulation in which a water-soluble particle is coated with a thin film of dry surfactant. This preparation is termed as proniosome Venkata Ramesh yasam et al., 2013). Then proniosome powder is filled in a screw capped vial and mixed with water or saline at 80C by vortexing followed by agitation for 2 mins results in the formation of Niosomal suspension.

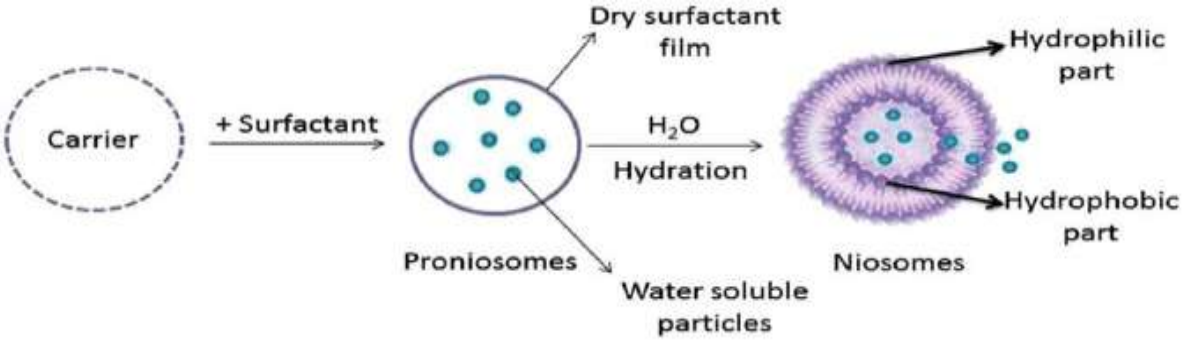

Fig no. 7 Conversion of Proniosomes to Niosomes

V. FACTORS AFFECTING NIOSOMAL FORMULATION:

3.8. NATURE OF ENCAPSULATED DRUG: The physico-chemical properties of encapsulated drug influence charge and rigidity of Niosomal bilayer. The encapsulated drug interacting with the surfactant head groups leading to increasing charge and creates mutual repulsion of surfactant bilayers and hence vesicle size increases.

3.9. NATURE OF SURFACTANT: The bilayers of niosomes can exist as a liquid state or in a gel state. It depends upon the temperature, type of surfactant and cholesterol. Entrapment efficiency is affected by the gel, liquid phase transition temperature of the surfactant. Entrapment efficiency is directly proportional to HLB value. Increase in HLB value increases the mean size of Niosomes.

3.10. HYDRATION TEMPERATURE: The size and shape of the niosome are influenced by the hydration temperature. Hydration temperature should ideally above the gel, liquid phase transition temperature. Assembly of surfactants into vesicles is influenced by change in temperature

3.11. CHOLESTEROL CONTENT: Incorporation of cholesterol increases the entrapment efficiency. It acts in two ways i.e., increases the chain order of liquid state bilayers and decreases the chain order of gel state bilayers. An increase in the cholesterol concentration leads to an increase in the rigidity of the bilayers and decreases the release rate of encapsulated drug.

3.12. RESISTANCE TO OSMOTIC STRESS: in hypertonic solution, vesicle diameter reduces. In hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by faster release due to osmotic stress.

VI. SEPARATION OF UNENTRAPPED DRUG:

The removal of unentrapped solute from vesicles can be accomplished by various techniques as follows:

3.13. DIALYSIS: The Niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or saline solution

3.14. GEL FILTRATION: The unentrapped drug is removed by gel filtration of Niosomal dispersion through a sephadex-G-50 column and elution with phosphate buffered saline.

3.15. CENTRIFUGATION: The Niosomal dispersion is centrifuged and supernatant is

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removed. The pellet is washed and then resuspended to obtain the Niosomal suspension free from unentrapped drug.

4. CHARACTERISATION OF NIOSOMES:

Physicochemical characterisation and analysis of niosomes include following parameters:

VII. VESICLE SIZE, MORPHOLOGY AND SIZE DISTRIBUTION:

Niosomes are assumed to be spherical in shape and their size can be determined using several techniques such as light microscopy, coulter counter method, scanning electron microscopy, transmission electron microscopy, light scattering techniques (Dynamic light scattering), zeta sizer, freeze fracture microscopy etc., Niosomes size distribution and polydispersity index can be determined by dynamic light scattering particle size analyser. Vesicle size can range from 20nm to 50µm.

4.1. CHARGE OF VESICLE AND ZETA POTENTIAL:

Zeta potential can play an important role in the behaviour of niosomes. Surface zeta potential can be determined by using zeta sizer, microelectrophoresis, PH sensitive fluorophores etc., charged niosome vesicles are more stable than uncharged niosome vesicles against aggregation and fusion.

4.2. ENTRAPMENT EFFICIENCY:

Entrapment efficiency play an important role in use of therapeutic vesicles in pharmaceutical application. For encapsulation of drug in niosomes, some parameters must be determined. Firstly, the amount of total drug in constant amount of suspension can be determined using spectrophotometric instrument, HPLC, ELISA etc., the concentration of drug in µg/ml can be determined using a standard curve of absorbance values. After one or more separation methods, the total concentration of drug can be determined (R Wasankar(2013). The concentration of loaded drug is obtained by determining drug concentration in completely destructed vesicles by adding 50% propane or 0.1% triton X 100 to Niosomal dispersion. Entrapment efficiency of drug can be determined now by following equation:

EE= WT-WF/WT X 100

{Or} EE= WL/WT X 100

Where,

WL= total amount of loaded drug in vesicles

WF= amount of free drug in suspension

WT= total amount of drug in suspension

VIII. INVITRO DRUG RELEASE STUDY:

The invitro drug release studies can be done by using following techniques:

a. **Dialysis:** A dialysis sac was washed and soaked in distilled water. The suspension of vesicle is pipetted out into bag made up of tubing and then sealed and placed in 200ml buffer solution in a beaker with constant stirring at 37C. The buffer was analysed for drug content at time intervals by using appropriate assay method (Kshitij b Makeshwar et al., 2013).

b. **Franz diffusion cell:** In Franz diffusion cell, the niosomes are dialyzed through cellophane membrane (dialysis membrane) against dissolution medium at room temperature. The samples are withdrawn at regular time intervals and analysed for drug content.

c. **Khesary diffusion cell:** Human cadaver skin (HCS) act as a dialysing membrane. The HCS were attached to Khesary cell which is filled with 100ml of PBS and add 10ml of Niosomal suspension on it. Finally, cell was immersed into receptor compartment. The dermal surface was just flush to surface of permeation fluid which was maintained at 37C and magnetically rotated at 50 rpm. Aliquots were withdrawn at intervals and replace the same volume with buffer and analysed for drug content using UV spectrophotometer.

IX. APPLICATIONS OF NIOSOMES:

Niosomes have been first used in cosmetic industry and then attention come in pharmaceutical companies. Niosomes can encapsulate various types of drugs and applied to various delivery routes.

DRUG TARGETING:

One of the most useful aspects of niosomes is ability to target drugs for organs/tissues. Niosomes can be used to target drugs to Reticulo-Endothelial System (RES) which is controlled by circulating serum factors called opsonins. These opsonins mark the niosomes for clearance. Such localisation of drugs used to treat tumours in animals and can also be used to treat parasitic infections of liver.

Niosomes can also be used for targeting drugs to organs other than RES (Rajesh Z Mujoria 2011) .

IN CANCER THERAPY:

- Rogerson et al studied distribution Niosomal doxorubicin. The cardio-toxicity effect was

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reduced by Niosomal formulation of doxorubicin.

- Azmin et al concluded in their research article that Niosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution.

ANTI-INFECTIVE AGENTS:

- Sodium stibogluconate is used for treatment of leishmaniasis. Niosomal or liposomal preparation of this drug exhibits higher levels of antimony as compared to free drug.

NIOSOMES AS DRUG CARRIERS:

Niosomes have been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging.

DELIVERY OF PEPTIDE DRUGS:

Oral peptide drug delivery has been faced problem that bypassing the enzymes which breakdown the peptide. In an invitro study of an oral delivery of vasopressin derivatives enclosed in niosomes found that entrapment of drug in niosomes increased the stability of niosomes (Kaur Dhanvir et al.,2018).

USE IN STUDYING IMMUNE RESPONSE:

From the study of adjuvant activity of non-ionic surfactant vesicles, niosomes have been reported as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

TRANSDERMAL DELIVERY OF DRUGS:

By incorporating transdermal delivery of drugs in niosomes, penetration rate has been increased. The topical delivery of erythromycin formulations including niosomes has studied, it was found that non-ionic vesicles could be formulated to target pilosebaceous glands.

OPTHALMIC DRUG DELIVERY:

Liposomal and Niosomal drug delivery can be used to achieve good availability in ocular drug delivery. Bio-adhesive coated Niosomal formulation of acetazolamide exhibits more tendencies for reduction of intra-ocular pressure than marketed formulation Dorzolamide.

Table no. 3 Drugs Used in Niosomal Delivery

S NO	ROUTE OF DRUG ADMINISTRATION	EXAMPLES OF DRUGS
1	Intravenous route	Doxorubicin, methotrexate, sodium stibogluconate, vincristine, diclofenac sodium, flurbiprofen, colchicine, rifampicin, zidovudine, insulin, amphotericin B, 5-flurouracil etc.,
2	Peroral route	DNA vaccines, proteins, peptides, ergot alkaloids, ciprofloxacin, norfloxacin, insulin
3	Transdermal route	Flurbiprofen, piroxicam, estradiol, nimesulide, ketorolac, ketoconazole
4	Ocular route	Timolol maleate, cyclopentolate
5	Nasal route	Sumatriptan, influenza viral vaccine
6	Inhalation	All trans retinoic acids

Table no. 4 Different surfactants used in Several Routes

Route	Examples of Surfactants
Intravenous	Span 60, 80 Span 60 Tween 60
Intramuscular	Span 85 Polysorbate 20
Transdermal	Brij-52,76 Tween-20,60,80

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Oral	Brij-52,72,76,92,97 Tween 60 Tween 20
Ocular	Span 60
Pulmonary	Polysorbate 20

X. CONCLUSION:

In the recent years, attentions have been attracted towards vesicular drug delivery systems such as liposomes and niosomes. Niosomal drug delivery system is one of the great evolutions in drug delivery technologies and is widely accepted by researchers. Niosomes are vesicles mainly composed of non-ionic surfactants and cholesterol or its derivatives. Structurally, they are similar to liposomes and having advantage over liposomes like cost, stability etc., niosomes are alternative system to liposomes. Niosome present a convenient, prolonged, targeted and effective drug delivery system with the ability of encapsulating both hydrophilic and lipophilic drugs. The potential of niosomes can be enhanced by novel methods and research has to bring out commercially available Niosomal preparations.

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