

THE NOVEL TECHNIQUES FOR ENHANCING POORLY SOLUBLE DRUGS – NANOSUSPENSION, VESICULAR DRUG DELIVERY SYSTEM (TRANSFERSOMES, INVASOMES & NIOSOMES)

Abstract

The conventional drug delivery system has several limitations, like poor solubility and the inability to achieve sustained and prolonged drug release. To overcome these limitations of conventional drug delivery systems, novel techniques have come into the existence. Solubility is the major issue seen in poorly soluble drugs, which leads to low efficiency. This book chapter explains the various solubility enhancement techniques, including nanosuspension and vesicular drug delivery systems (Transferosomes, Invasomes, and niosomes).

Keywords: Nanosuspension, drug content. Transferosomes, Invasomes, entrapment efficiency.

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I. CONVENTIONAL DRUG DELIVERY SYSTEM

Conventional drug delivery system as various limitation such as poor bioavailability and these cannot achieve sustained and prolonged release of drug. In conventional dosage form only small amount of drug reaches to target site and rest will distribute throughout body and effect the healthy tissues⁽⁴⁰⁾. These conventional dosage form have many limitations such as:

- Lacking target specificity.
- Low Bioavailability of drug.
- Drugs with a short half-life has a greater probability of missing the dosage.

Therefore, to reduce this limitation and increase pharmaceutical activity and decrease the toxicity a drug delivery system should be developed

1. Controlled Drug Delivery System^(41, 42): Controlled drug delivery systems can maintain drug levels within a particular range, require fewer administrations, use the drug in issue as effectively as possible, and promote patient compliance.

Controlled drug delivery system has several advantages compared to conventional drug delivery system they are:

- Release the drug in a sustained and controlled manner at a specific site and reduce patient compliance.
- It is convenient to the patient and decreases the frequency of dosing.
- Overdosing or Under dosing can be reduced and decrease in side effects.
- A steady amount of drug remains in the blood and tissue over an extended duration of time with this drug delivery method.
- For some drugs improves its bioavailability.
- Reduction in the cost of healthcare through better therapy, a shorter course of treatment, and less time spent by the patient's provider dispensing, administering, and monitoring medication.

2. Disadvantages

- A delay in the drug's action
- If a formulation technique is unacceptable there may be a chance of dosage dumping.
- Enhanced potential for first pass metabolism.
- Greater dependence on GI residence duration and dosage form.
- In some circumstances, it's possible to alter the dose less accurately.
- When compared with conventional dosages, the cost per unit dose is greater.

II. THESE ARE SOME NOVEL TECHNIQUES FOR ENHANCING SOLUBILITY FOR POOR SOLUBLE DRUGS

1. Nanosuspension: The drug discovery process by technology such as screening, computer-aided drug design, and combinatorial chemistry is leading to a vast number of

drug candidates that have good efficacy, but unfortunately, many of these drugs will exhibit poor aqueous and non-aqueous solubility, hence the need to develop an innovative formulation. Also, poorly soluble drugs are challenging as they cannot achieve dissolution; hence, they have difficulty passing through the dissolving fluid to absorb through the mucosa or to be completely absorbed if the dissolution process is slow due to the formulation factor and physiochemical property of drug, which is the rate-limiting step in absorption. And it will also influence bioavailability. In the case of BCS class 2 and 4 drugs. For these drugs an alternative approach is required for better efficacy. The nanosuspension consists of the stabilizing agent and a liquid dispersion medium. The major merit of the nanosuspension is that it is applicable to the majority of the drug and it will not only increase the solubility of the drug but also alter the pharmacokinetics of the drug and hence improve its safety and efficacy. The low bioavailability of the drug can be rescued by formulating it into a nanosuspension. The main aim is to maximize bioavailability and boost dissolution rates. The formulation of poorly water-soluble drugs has become a challenging problem that is faced by pharmaceutical scientists. The problem became more intense when it came to class 2 and class 4 drugs. Nanosuspension is the nanosized, heterogeneous dispersion of insoluble drug particles that is stabilized by surfactant. The size ranges from 200-600nm. There are various methods for the preparation of nanosuspension, but the most commonly used are bottom-up and bottom-down methods..⁽¹⁻⁶⁾

2. Merit

- Nanosuspension is applicable for poorly water soluble as well as poorly lipid soluble.
- It will increase the bioavailability.
- It cause increase in the saturation solubility due to larger surface area.
- It will increase dissolution rate.
- It can be given in various route of administration.
- Useful in passive targeting.
- Nanosuspension will decrease the dose.
- It is Suitable for hydrophilic drugs.
- High drug loading capacity can be achieved by nanuspension.
- It will Enhance the physical and chemical stability of drugs.
- It will Provides a passive drug targeting.⁽¹⁻³⁾

3. Demerit

- Sedimentation may lead due to the smaller particle size.
- Stability issues can be seen freeze and spray drying
- Dose accuracy can be a challenging part.
- Sufficient care must be taken while handling
- Smaller particle and lager surface area leads to the particle aggregation.
- Toxic metabolic may form.⁽¹⁻⁵⁾



Figuer 1: Different types of formulation for Nanosuspension

- 4. Need of Nanosuspension:** More than 40 percent of drug are poorly soluble in water, so they may show problem in formulating them into conventional dosage form and also for the class 2 drugs which is poorly soluble in aqueous and organic media the situation is worse. Preparation of nanosuspension is more preferred for these compounds which is insoluble in water. Nanosuspension is the one of the unique techniques for enhancing solubility and bioavailability for the poorly soluble drug in aqueous and organic media. There is need to develop a nanosuspension to overcome the solubility issues related issues⁽¹⁴⁻¹⁷⁾.

III. FORMULATION

- 1. Stabilizer:** Stabilizer performs a vital function in the composition of nanosuspensions. Agglomeration can induce in the absence of appropriate stabilizer as high surface energy of nanosized particle which leads to aggregation of drug crystal. The main function of a stabilizer is to moist the drug particles very well. In a few instances, a combination of stabilizers is needed to obtain a stable nanosuspension.⁽¹⁴⁻¹⁵⁾
- 2. Organic Solvent:** Organic solvents may be required in the method of preparation of nanosuspensions if they're to be organized the use of an emulsion or microemulsion as a template. While formulating nanosuspension the acceptability of organic solvent inside a pharmaceutical area can have a toxicity ability so their elimination and less usage must be considered using emulsions or microemulsions as templates⁽¹³⁻¹⁶⁾
- 3. Surfactant:** Surfactants are integrated to improve the dispersion with the aid of reducing the interfacial stress. In addition, they act as wetting or deflocculating agents e.g. Tweens and Spans extensively used surfactants⁽¹⁴⁻¹⁷⁾.
- 4. Co-Surfactant:** The selection of co-surfactant is critical when the usage of microemulsions to formulate nanosuspensions. Because co-surfactants can substantially have an effect on phase behavior, the impact of co-surfactant on drug loading should be investigated e.g., Transcutol, glycofurol, ethanol and iso-propanol thoroughly used as co-surfactants. Additionally, bile salts and Dipotassium glycyrrhizinate can be used as co-surfactants⁽¹³⁻¹⁸⁾.
- 5. Other Additives:** Nanosuspensions can also incorporate additives together with buffers, salts, polyols, osmogent and cryoprotectant, depending on both the route of management or the type of the drug moiety (15-17).

6. Method of Preparation

- Homogenization in water
- Media milling.
- Homogenization in non-aqueous media
- Combined precipitation
- Nanojet technology
- Emulsification-solvent evaporation technique.
- Hydrosol method
- Supercritical fluid method.
- Dry co-grinding
- Emulsion as template
- Microemulsion as template
- Lyophilization and Probe sonication method

There are mainly two categories for the preparation:

- **Bottom-up Method:** It is the technique by which the nano range is acquired by increasing the size of particle from the molecular range to the nano range. The traditional methods of precipitation (hydrosol) are referred to as bottom-up technology. Using a precipitation method, the drug is dissolved in an organic solvent, and this solution is blended with a miscible anti-solvent. In the water-solvent combination, the solubility is low, and the drug precipitates. The primary task is that in the precipitation system, the development of the crystals needs to be controlled by the addition of surfactant to prevent the formation of microparticles⁽¹⁶⁻¹⁹⁾.
- **Top-down Method:** The method in which nano size particles is obtained by reduction in size of larger particles. In top- down method there are various method of preparation they are:
 - **High Pressure Homogenization (DissoCubes):** DissoCubes are engineered using piston-hole-type excessive-pressure homogenizers. High-pressure homogenization has been used to put together nanosuspensions of many poorly water-soluble drugs. Homogenization is consist of narrow aperture. The device can be operated at stress ranging from 100 to 1500 bars (2800–21300 psi) and as much as 2000 bars, with an extent capability of forty ml (for laboratory scale)⁽¹²⁻¹⁹⁾
 - **Media Milling (NanoCrystals):** This technology was developed in 1992. Formerly, the generation was owned by Nanosystems, but currently it has been acquired by Élan Drug Transport. In this method, the nanosuspensions are produced using excessive-shear media generators or pearl mills. The media mill includes a milling chamber, a milling shaft, and a recirculation chamber. The milling chamber charged with polymeric media is the energetic aspect of the mill. The mill may be operated in batch or recirculation modes. The milling process is performed at controlled temperatures. The standard residence time generated for a nanometre-sized dispersion with an average diameter of less than 200 nanometres is 30–60 minutes⁽¹⁶⁻²⁰⁾.

- **Homogenization in Non-Aqueous Media (Nanopure):** Nanopure is suspensions homogenized in unfastened media or water combinations, i.e., suspensions in the aqueous media will be homogenized at zero degrees centigrade, which is referred to as a deep freeze homogenizer. The drug with nanocrystals will disperse into the liquid polyethylene glycol or gelatin⁽¹⁶⁾.
- **Combined Precipitation and Homogenizing [Nanoedge]:** Mixed precipitation and homogenization (Nanoedge) in this drug are dissolved in a solvent and blended into an anti-solvent agent for precipitation. The Nanoedge is same of precipitation and homogenization. Within the water-solvent aggregate, the solubility is low, and the drug precipitates. Precipitation has additionally been coupled with high-shear processing. An aggregate of those strategies results in smaller particles and better balance in a shorter time. The most important drawback of the precipitation approach, together with the crystal increase and long time period balance, may be resolved by the use of the Nanoedge generation⁽¹⁵⁻¹⁹⁾.
- **Nano Jet Technology:** This method, known as ‘contrary flow or nano jet technology’, uses a chamber wherein a movement of suspension is split into or greater factors, which colloid with each other at excessive pressure up to 4000 bar at an immoderate pace of a thousand m/s. The organized nanosuspensions of atovaquone had been prepared using micro fluidization. The most problematic aspect of this technique is the wide variety of passes via the microfluidizer (up to 75 passes) and the fact that the product acquired includes a substitute mixture of rapid precipitation and moderate strain homogenization. The fast addition of a drug method to an antisolvent results in the unexpected generation of extraordinary crystalline or amorphous solids⁽¹⁶⁾.
- **Emulsification-Solvent Evaporation Technique:** This method entails getting a drug ready, followed by its emulsification in some other liquid that is not a solvent for the drug. Evaporation of the media leads to precipitation. Crystal and particle aggregation can be managed with the aid of growing shear forces and the use of an excessive-pace stirrer⁽¹⁶⁻²⁰⁾.
- **Supercritical Fluid Technology:** It can be used to provide nanoparticles from a drug solution. The various techniques attempted are rapid expansion of the supercritical system (RESS), supercritical anti-solvent technique, and precipitation with a compressed anti-solvent process (PCA). It cause the enlargement of the drug solution in supercritical fluid , which cause loss of solvent which further form precipitation .The drug solution is atomized into a chamber consist of compressed CO₂. Because the solvent is removed, the solution becomes supersaturated and, as a consequence, precipitates are obtained. The supercritical anti-solvent system makes use of a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is miscible with the supercritical fluid. The drug is then presented as pleasant crystals⁽¹⁶⁾.
- **Dry Co-grinding:** Nanosuspensions prepared by high-pressure homogenization and media milling using a pearl ball mill are moist-grinding strategies. These days, nanosuspensions can be obtained through dry milling techniques. The formation of

colloidal particles in many poorly water-soluble tablets, including Griseofulvin, Glipalamide, and Nifedipine, by way of grinding with polyvinyl pyrrolidone (PVP) and Sodium dodecyl sulphate (SDS), Many soluble polymers and co-polymers, including PVP, Polyethylene glycol (PEG), Hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives, have been used. The physicochemical properties and dissolution of poorly water-soluble capsules had been advanced via co-grinding because of the development of surface polarity and the transformation from a crystalline to an amorphous drug. Recently, nanosuspensions have been received through dry milling techniques. Dry co-grinding may be finished without problems and economically, and it may be performed without natural solvents⁽¹⁸⁾.

- **Emulsion as Template:** Emulsion as a template that is applicable for drugs that are soluble in both organic and partially water-miscible solvents. There are two approaches to fabricating drug nanosuspensions by way of the emulsification approach. In the first approach, a natural solvent or mixture of solvents loaded with the drug is dispersed within the aqueous section containing appropriate surfactants to shape an emulsion. Optimizing the surfactant composition increases the consumption of the natural phase and, ultimately, the drug loading inside the emulsion. At the beginning, natural solvents, together with methylene chloride and chloroform, were used. However, environmental dangers and human safety issues associated with approximately residual solvents have restricted their use in routine production methods. Its composition, consisting of ethyl acetate and ethyl formate, can nevertheless be taken into consideration for use. The emulsion is prepared through the traditional approach, and the drug nanosuspension is acquired by simply diluting the emulsion. As a consequence, the nanosuspension must be made free of the internal phase and surfactants by di-ultrafiltration with the intention of making it appropriate for administration. But if all of the elements that are used for the manufacturing of the nanosuspension are found in a state perfect for the preferred direction of administration, then simple centrifugation sufficient to separate the nanosuspension⁽¹⁷⁾.
- **Microemulsion as Template/Lipid Emulsion:** Microemulsions are thermodynamically stable, which includes oil and water, stabilized through an interfacial film of surfactant and co-surfactant. Their advantages, along with excessive drug solubilization, long shelf-life and simplicity of manufacture, lead them to better drug delivery. Microemulsion structure taking benefit, Due to use of microemulsion during the manufacturing of nanosuspension. Oil-in-water microemulsions are preferred for this purpose. The inner phase of these microemulsions may be both a partially miscible liquid or an organic solvent. The drug may be each loaded inside the internal segment. The influence of the quantity and ratio of surfactant to co-surfactant at the uptake of inner segment and on the globule length of the microemulsion have to be investigated and optimized so that it will obtain the favored drug loading. The simple centrifugation or ultracentrifugation is enough to split the nanosuspension. The advantages and boundaries are similar to for emulsion templates. Additionally, the trouble will include large amounts of surfactant or stabilizers are required. e.g. Griseofulvin nanosuspension which is ready via using water, butyl lactate, lecithin and the sodium salt of tauro-deoxycholate, in which a great improvement within the dissolution phase of the drug (3-fold growth) in comparison to the industrial product⁽¹⁵⁻¹⁶⁾.

- **Lyophilization:** Lyophilization is a technique for formulating nanosuspension and many other formulations. It is valuable to the safety of substances that require low moisture content (less than 1%) so as to ensure balance and require a sterile and gentle maintenance manner. Lyophilization produces brilliantly pleasant products, both nutrients and prescription drugs, due to the moderate temperatures at which the process takes place, contributing to the formation of distinctly porous solids that preserve aroma, color, and flavor. Lyophilization is a technique or method through which a product is frozen (converting all matter to solid matter), after which water is removed via sublimation (primary drying) of the frozen water molecule (solid debris), i.e., ice. The whole system of freeze drying requires steps: freezing of the molecule in which water is present by using nucleation and lots of other methods; after that, the 2nd step is an important step for drying via sublimation of ice; secondarily, on this step, desorption of water occurs for stable particles; and within the remaining packing, packing should be accomplished in the vials or packing containers to restrict reabsorption of water and/or oxygen from the environment. With the aid of freeze-drying, a product that is risky, much less solid, decomposable, or degradative in the presence of moisture is converted into a dried and stable product. ⁽¹⁻⁶⁾.
- **Probe Sonication:** Sonication is the act of making use of sound energy to agitate particles in a sample for various functions. In laboratory science applications, Sonication is usually used in nanotechnology for dispersing nanoparticles in liquids. Sonication is applicable for the nano emulsion and nanosuspension formulations. The favoured effects from the ultrasonication of liquids, which include homogenization, dispersing, deagglomeration, milling, emulsification, extraction, lysis, disintegration, and sonochemical effects, are due to cavitation, a transducer, and a probe. The generator transforms the input electric power into an electrical signal that drives the transducer. This vibration is amplified as a longitudinal vibration inside the probe tip, causing the pattern to cavitate. Cavitation creates the ultrasound electricity, which causes the sample to disrupt and break down into smaller particles in the sonicator ⁽¹⁴⁾.

IV. APPLICATION

1. **Oral Drug Delivery:** The oral course is the preferred course for drug delivery due to its various advantages. The efficacy or performance of the orally administered drug normally depends on its solubility and absorption via the GIT. Hence, a drug candidate that is well-known to show poor aqueous solubility and/or dissolution-price-constrained absorption is believed to have low and/or extraordinarily variable oral bioavailability. Nano-sizing such drugs can cause a dramatic increase in their oral absorption and, in the end, bioavailability. The increase in oral bioavailability may be attributed to the adhesiveness of the drug nanosuspension, multiplied surface area (due to a discount in particle length via 10–50 fold), multiplied saturation solubility, leading to a multiplied awareness gradient among the gastrointestinal tract lumen and blood, and improved dissolution speed. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the remedy cost-effective and obliterating any undue drug dumping inside the body. ⁽¹²⁻²⁰⁾.
2. **Parenteral Drug Delivery:** Parenteral administration is used when a fast onset of action is required and the drug has a great first-pass metabolism or is not absorbed by the

gastrointestinal tract. Parenteral management of the drug with a solubilized shape or the drug with a particle length less than five micrometers so that blockage of capillaries no longer occurs. As Nanosuspensions have smaller particles in the nano variety, they may be appropriate candidates for parenteral drug transport. Various routes of parenteral management like intra-articular, intraperitoneal, and intravenous injection permit the management of the drug via nanosuspensions, certainly. Nanosuspensions will overcome the problems of solubilization ability, parenteral acceptability, bodily instability, high production costs, and difficulties in scale-up as in other parenteral formulations. Because of the direct nano-sizing of the drug particles, almost all drugs can be effortlessly processed for parenteral management. They display the increased efficacy of the drug. ⁽¹⁸⁻²⁰⁾.

- 3. Pulmonary Drug Delivery:** Drugs that might be poorly soluble in pulmonary secretions may be administered by using the formula of the nanosuspensions. These drugs are taken as suspension aerosols or as dry powders with the aid of dry powder inhalers. The nebulized form of the aqueous nanosuspensions is used for the delivery of medicine to the lungs. Nebulization is commonly completed by means of mechanical or ultrasonic nebulizers. Nanosuspensions can be used in all kinds of nebulizer. ⁽¹⁴⁻²⁰⁾.
- 4. Ocular Drug Delivery:** Nanosuspensions may be explored for the drugs that show off negative solubility in lachrymal fluids. Nanosuspensions provide the subsequent blessings for ocular drug delivery.
 - Extended residence time of drug within the cul-de-sac (desired for maximum ocular sicknesses for effective treatment).
 - Avoidance of excessive tonicity created through water soluble drugs ⁽²⁰⁾.
- 5. Drug Targeting:** Nanoparticulate systems have shown great potential in the targeting of drugs, especially in the brain. As the surface properties and in-vivo behaviour of nanosuspensions can be altered easily by changing the stabilizer, they are good candidates for targeted delivery. Commercially viable nanosuspensions for targeted delivery are being developed due to the versatility of the nanosuspension, easy scale-up, and commercial production of the nanosuspensions. Targeting can be achieved by modifying the surface of nanoparticles using suitable polymers. e.g., Brain targeting of the peptide has been done successfully by the modification of the nanoparticle surface using poly-isobutyl cyanoacrylate. ⁽¹⁵⁻²⁰⁾.
- 6. Mucoadhesion of the Nanoparticles:** When nanoparticles are obtained orally in the form of nanosuspension, they will diffuse the liquid across the mucosal surface. After adhesion, the concentrated suspension acts as a reservoir for particles and allows rapid adsorption. Step one before particle absorption is the direct contact of the particles with the intestinal cells through a bioadhesive segment. The adhesiveness of the nanosuspensions improves bioavailability as well as the concentration of parasites persisting inside the GIT ⁽²⁰⁾.
- 7. Vesicular Drug Delivery Systems:** Vesicular drug delivery systems are a class of advanced drug delivery systems that utilize vesicles as carriers to transport drugs to specific target sites within the body. These vesicles, also known as liposomes, are small

spherical structures composed of lipid bilayers, which closely resemble the structure of cell membranes.

The main advantage of vesicular drug delivery systems is their ability to encapsulate a wide range of drugs, including hydrophilic and hydrophobic compounds, within their aqueous core or lipid bilayers. This versatility allows for the effective delivery of various therapeutic agents, such as small molecules, proteins, peptides, and nucleic acids.

Their ability to encapsulate diverse therapeutic agents, modify their surface for active targeting, and control drug release makes them promising candidates for improving drug efficacy, reducing side effects, and advancing personalized medicine. Ongoing research and advancements in this field hold great promise for the development of more efficient and specific drug delivery systems in the future⁽²¹⁾.

8. The Objective of Vesicular Drug Delivery Systems

- Enhanced Drug Stability
- Improved Drug Solubility and Bioavailability
- Targeted Drug Delivery
- Controlled and Sustained Drug Release
- Minimized Systemic Toxicity and Side Effects
- Personalized Medicine^(21,22).

9. Advantages of Vesicular Drug Delivery System

- Enhanced Drug Stability.
- Increased Drug Solubility and Bioavailability
- Targeted Drug Delivery
- Controlled and Sustained Drug Release
- Reduced Systemic Toxicity and Side Effects

10. Disadvantages of Vesicular Drug Delivery System

- Manufacturing Complexity
- Stability Challenges
- Limited Drug Loading Capacity
- Lack of Long-Term Stability
- Clearance by the Immune System
- Cost^(21,22)

11. Classification for Vesicular Drug Delivery System⁽⁴³⁾: Vesicular drug delivery system is classified according to their composition. They are two types that are lipoidal biocarriers and non-lipoidal biocarriers.

Table 1: Types of Vesicular drug delivery system

| Lipoidal Biocarriers | Non-lipoidal Biocarriers |
|-----------------------------|---------------------------------|
| Liposomes | Niosomes |
| Emulsomes | Bilosomes |
| Enzymosomes | Aquasomes |
| Ethosomes | |
| Sphingosomes | |
| Transferosomes | |
| Pharmacosomes | |
| Virosomes | |

V. TRANSFEROSOMES

Transferosomes are a type of lipid-based drug delivery system that are designed to enhance the delivery of drugs through the skin or other biological barriers. They are composed of phospholipids, surfactants, and sometimes cholesterol, which form a bilayer structure that encapsulates the drug.

One of the key advantages of transferosomes is their ability to improve the bioavailability of drugs that have poor water solubility, which can limit their effectiveness when administered by traditional methods.

Additionally, transferosomes can be tailored to target specific tissues or cells, which can increase the efficacy of drugs while reducing the risk of side effects. Overall, transferosomes are a promising drug delivery system with potential applications in a wide range of therapeutic areas. Ongoing research is focused on improving the stability, efficacy, and safety of transferosomes, as well as exploring new ways to use them in clinical practice⁽²³⁾

Advantages of Transferosomes

- Enhanced Penetration
- Increased Drug Bioavailability
- Improved Stability
- Targeted Drug Delivery
- Versatile Formulation⁽²⁴⁾

Disadvantages of Transferosomes

- Complex Manufacturing Process.
- Stability Challenges
- Variable Performance
- Regulatory Considerations
- Limited Drug Loading Capacity⁽²⁵⁾.

Methods to prepare Transferosomes

- Ethanol Injection Method
- Thin Film Hydration Method
- Reverse Phase Evaporation
- Ether Injection
- Solvent Injection Method⁽²⁶⁾.

There are several methods used to prepare transferosomes. Here are some commonly employed techniques:

1. Thin Film Hydration Method:

This Technique has 3 steps: The process begins by dissolving phospholipids and surfactants in an organic solvent (chloroform-methanol) to create a thin film of vesicles. This mixture is then heated above the lipid's transition temperature using a rotary evaporator to remove the organic solvents. Any remaining traces of the solvent are eliminated by placing the film in a vacuum overnight. Next, the formed film is hydrated by adding an appropriate buffer and agitating it at a speed of sixty revolutions per minute for 60 hours. The vesicles formed are left at room temperature to swell. To create smaller vesicles, the prepared vesicles are subjected to sonication using a bathtub sonicator for 60 minutes at either room temperature or 50°C. In the case of a probe sonicator, the vesicles are sonicated by manually extruding them 200 times through a sandwich layer of two 100 nm polycarbonate membranes⁽²⁷⁾.

2. Modified Hand Shaking Method: Lecithin together with the edge activator (surfactant) and drug are dissolved in a mixture of chloroform and ethyl alcohol in the magnitude relation 1:1. The mixture is subjected to evaporation to get rid of the organic solvent using temperature higher than the transition temperature of lipid by hand shaking. The thin lipid film is left long to make sure complete removal of organic solvent.

The film that is formed is then hydrated with buffer of choices in conjunction with gentle shaking for quarter- hour. The suspension formed is further hydrated at 43°C for 1-2 hr

Variables that influence the method of preparation are Lecithin: Surface -active agent, Solvent used, Surfactant used, Hydration medium.

3. Reverse Phase Evaporation Method: In this method, a water-in-oil (W/O) emulsion is formed by dissolving lipids and the drug in an organic solvent and then adding an aqueous phase. The resulting W/O emulsion is subjected to high-speed homogenization, leading to the formation of a water-rich vesicle system, which is subsequently converted into transferosomes.

4. Ether Injection Method: Lipids and the drug are dissolved in an organic solvent mixture containing ether. The organic phase is then rapidly injected into an aqueous medium

under high-speed homogenization or sonication, resulting in the formation of transferosomes.

5. **Ethanol Injection Method:** Similar to the ether injection method, lipids and the drug are dissolved in an organic solvent mixture containing ethanol. The organic phase is rapidly injected into an aqueous medium under high-speed homogenization or sonication, leading to transferosome formation.

6. **Dehydration-Rehydration Vesicle Method:** This method involves the dehydration of preformed liposomes or multilamellar vesicles (MLVs) followed by rehydration with an aqueous medium containing the drug. The dehydration process can be achieved using freeze-drying, spray-drying, or other techniques, and the resulting dehydrated vesicles are subsequently rehydrated to form transferosomes.
 - **Lipid Film and Remote Loading Method:** This method combines the lipid film hydration technique with remote loading of the drug. Lipids are dissolved in an organic solvent to form a lipid film, which is then hydrated with an aqueous medium containing a pH gradient or an ion gradient. The pH or ion gradient drives the active ingredient into the vesicles during hydration, resulting in remote loading of the drug^(26,27,28).

7. **Silent Features of Transferosomes:** Transferosomes possess several distinctive features that make them a promising option for drug delivery. These features include:
 - Transferosomes exhibit high deformability, enabling them to effectively penetrate narrow constrictions and maintain the integrity of the vesicles.
 - Wide Range of Drug Solubility
 - Transferosomes are a versatile drug carrier capable of delivering drugs with varying molecular weights. They have been successfully employed to transport a diverse range of substances such as analgesics, anesthetics, corticosteroids, sex hormones, anticancer agents, insulin, gap junction proteins, and albumin.
 - Biocompatibility and Biodegradability
 - High Entrapment Efficiency
 - Protection from Metabolic Degradation
 - Controlled Release
 - Easy Scalability

Table 2: Composition of transferosomes

| Class | Example | Uses |
|------------------------|--|----------------------------|
| Phospholipids | Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline etc. | Vesicles forming component |
| Surfactant | Sod. Cholate, tween-80, Span-80 etc. | For providing flexibility |
| Alcohol | Ethanol, methanol | As a solvent |
| Buffering agent | Saline phosphate buffer (pH 6.4) | As a hydrating medium |

| | | |
|-------------|-------------|-------|
| Drug | Fluconazole | A.P.I |
|-------------|-------------|-------|

- 8. Mechanism of Transport:** The mechanism of transport involves the generation of an "osmotic gradient" resulting from water evaporation when a lipid suspension, known as transfersomes, is applied to the skin surface. The transport of these elastic vesicles is not dependent on concentration. The process relies on trans-epidermal hydration as the driving force for vesicle transport. Due to their elasticity, the vesicles can pass through the pores in the corneum, although these pores are smaller in diameter compared to the vesicles. When transfersomes are applied to an open biological surface, such as non-occluded skin, they tend to penetrate the barrier and migrate into the water-rich deeper layers to maintain sufficient hydration.

During penetration through the corneum, reversible deformation of the bilayer occurs. However, it is crucial to ensure that vesicle integrity, gradient, and barrier properties for underlying hydration affinity are not compromised during this deformation.

Since transfersomes are too large to diffuse through the skin, they need to identify and establish their own pathway through the organ. The effectiveness of transfersomes in drug delivery relies on their ability to expand and overcome hydrophilic pores within the skin. Intracellular drug transportation may involve diffusion of the vesicle lipid bilayer with the skin, similar to normal endocytosis involving the diffusion of vesicles through cytomembrane. The mechanism is intricate and incorporates advanced principles of elasto-mechanics, combined with material transport and hydration/osmotic forces⁽²⁸⁾.

9. Application of Transfersomes^(29,30,31):

- The use of transfersomes for delivering insulin offers a successful method of administering large molecular weight medications through the skin. Traditional subcutaneous administration of insulin can be inconvenient for patients. By encapsulating insulin in transfersomes (referred to as transfersulin), all the challenges associated with conventional insulin delivery can be overcome. Therapeutic effects can be observed within 90-180 minutes after the application of transfersulin on intact skin, depending on the composition of the carrier.
- Transfersomes also provide a solution for the delivery of corticosteroids. By incorporating corticosteroids into transfersomes, the issues associated with their delivery can be addressed. Transfersome encapsulation enables site-specific and safe delivery of corticosteroids into the skin through epicutaneous administration. The use of transfersomes technology also reduces the required dosage for achieving the biological activity of corticosteroids.
- Transfersomes have been widely employed as carriers for the transportation of proteins and peptides, allowing for their safe administration through transfersome technology. Proteins and peptides face challenges in transferring into the body due to their large molecular size and susceptibility to degradation in the gastrointestinal tract when administered orally. Therefore, injectables have been the preferred method of

administration. Various approaches have been developed to overcome this limitation. Transfersomes demonstrate bioavailability comparable to subcutaneous injection when used for protein suspension. Additionally, repeated epicutaneous application of transfersome preparations of proteins can elicit a strong immune response, demonstrating their potential in immunotherapy.

- Transfersomes can be utilized as carriers for delivering antiviral drugs such as INF (interferon). For example, leukocyte-derived INF- α , a naturally occurring protein with antiviral, antiproliferative, and immunomodulatory effects, can be delivered using transfersomes as drug delivery systems. Transfersomes enable controlled release of the administered drug and enhance the stability of labile drugs. Studies have shown promising delivery of IL-2 (interleukin-2) and INF- α through transfersomes for potential transcutaneous applications.
- Transfersomes offer a new approach for the transcutaneous delivery of anti-cancer drugs, particularly for skin cancer treatment. Methotrexate, when delivered using transfersomes technology, has shown favorable results.
- Transfersome applications extend to the delivery of anesthetics. The use of transfersomes containing anesthetics can induce topical anesthesia within approximately 10 minutes under appropriate conditions. The impact of transfersomal anesthetics is comparable to a subcutaneous bolus injection, with nearly 80% effectiveness, but the transfersome preparation provides a longer-lasting effect.
- Transfersomes can also be employed for the transdermal delivery of non-steroidal anti-inflammatory drugs (NSAIDs) to overcome the gastrointestinal adverse effects associated with most NSAIDs. Studies have been conducted on diclofenac and ketoprofen. In 2007, the Swiss regulatory agency (Swissmedic) granted regulatory approval to a transfersome formulation containing ketoprofen. This formulation is anticipated to be marketed under the brand name "Diractin." Furthermore, IDEA AG has ongoing clinical development plans for additional therapeutic products utilizing transfersome technology.
- Transfersome technology can also be utilized for the delivery of herbal drugs. Xiao-Ying et al. demonstrated higher topical absorption of transfersomes containing capsaicin compared to pure capsaicin^(32,33,34).

VI. INVASOMES

Invasomes represent a new type of vesicular system that exhibits superior transdermal penetration compared to traditional liposomes. These vesicles consist of phospholipids, ethanol, and terpenes, which contribute to their enhanced transdermal properties. The key advantage of these nanovesicles lies in their ability to enhance drug permeability into the skin while minimizing systemic absorption, thus restricting drug activity within the skin layer.

Similar to liposomes, invasomes share the same structural components but incorporate terpenes. Terpenes are hydrocarbon molecules commonly found in plant essential oils. The

inclusion of terpenes facilitates the formation of flexible vesicles, thereby improving the fluidity of the skin's lipid bilayers. This increased capacity to penetrate the epidermal layers enhances the effectiveness of invasomes. They achieve this by disrupting lipid and intracellular protein connections, thereby fluidizing the bilayer structure of the stratum corneum lipids.

Invasomes possess various characteristics that contribute to their efficacy, including size, surface shape, zeta potential, and stability⁽³⁵⁾.

1. Advantages of Invasomes

- Enhanced Transdermal Penetration:
- Controlled Drug Release
- Increased Drug Bioavailability
- Deformable Vesicles
- Targeted Delivery
- Improved Stability
- Versatility.

2. Disadvantages of Invasomes:

- Complexity of Formulation
- Potential Skin Irritation
- Limited Long-Term Stability
- Need for Specialized Manufacturing Techniques
- Limited Scalability
- Regulatory Considerations
- Cost⁽³⁶⁾

3. Penetration Mechanism of Invasomes: The enhancing effects of invasomes can be attributed to a combination of processes. At normal body temperatures, the lipid layer of the stratum corneum, which is the outermost layer of the skin, is tightly packed and highly organized in terms of its conformation. Ethanol, when incorporated into the invasome membrane, disrupts the structure of the skin's lipid bilayer. This disruption allows the invasomes to penetrate the stratum corneum.

Additionally, the presence of ethanol in invasomes leads to a less densely packed lipid membrane compared to conventional vesicles. Despite this, invasomes maintain their stability. This characteristic makes the invasome membrane more malleable, enabling it to squeeze through small spaces, such as the gaps formed by the disruption of the stratum corneum lipids.

In summary, invasomes' ability to enhance penetration is facilitated by the incorporation of ethanol, which disrupts the lipid bilayer structure of the skin and allows invasomes to enter the stratum corneum. The presence of ethanol also contributes to the deformability of invasomes, enabling them to navigate through narrow spaces within the skin barrier⁽³⁷⁾.

4. Method of Preparation

- **Mechanical Dispersion Method:** In the mechanical dispersion method, the invasomal formulation is prepared as follows: The drug and terpene or terpene mixtures are dissolved in an ethanolic phospholipid solution. The mixture is then subjected to vortexing for 5 minutes, followed by sonication for 5 minutes to achieve a clear solution. Phosphate buffer saline (PBS) with a pH of 7.4 is added to the solution using a syringe while constant vortexing is maintained for an additional 5 minutes. This process results in the final invasomal preparation.
- **Thin Film Hydration Method:** Another approach to prepare invasomes is the thin film hydration method, which involves the following steps: Phospholipids dissolved in ethanol are mixed with methanol:chloroform (2:1) solution. The mixture is then dried to form a thin film by gradually reducing the pressure from 500 to 1 mbar at 50°C using a rotary flash evaporator. The film is placed under vacuum (1 mbar) for 2 hours at room temperature and subsequently flushed with nitrogen gas. In order to generate invasomes, the thin film is hydrated through one of two methods. The first method involves hydrating the thin film for a duration of 30 minutes at the temperature corresponding to the lipid phase transition. This hydration process is accomplished using a mixture consisting of phosphate buffer (pH 7.4, PBS), ethanol, and terpenes. Alternatively, invasomes can also be formed by hydrating the thin film using PBS (pH 7.4) alone. Both methods result in the formation of invasomes, allowing for flexibility in selecting the appropriate hydration approach based on specific formulation requirements. Once the mixture has cooled down to room temperature, ethanol and either a single terpene or a mixture of terpenes are introduced into the formulation. This addition further enhances the properties and characteristics of the invasomes⁽³⁸⁾.

5. Application of Invasomes

- **Improving Bioavailability:** Asenapine Maleate (ASPM) is a second-generation antipsychotic utilized for treating schizophrenia. However, its oral bioavailability is limited due to extensive first-pass metabolism. Fatma Saeed EI Tokhy et al. explored the use of nanocarriers, specifically invasomes, as an alternative method for administering ASPM. This approach exhibited enhanced bioavailability and sustained action. Invasomes containing limonene demonstrated superior transdermal permeation compared to other carriers. The bioavailability of Asenapine increased from 3.5% to 54.5%.
- **Hyperpigmentation Disorder:** Hyperpigmentation disorder arises from excessive melanin production, resulting in abnormal melanin distribution on specific skin areas. Controlling tyrosinase activity is crucial in regulating melanin production. Phenylethyl resorcinol, a novel skin whitening agent, effectively inhibits tyrosinase activity. However, phenylethyl resorcinol-loaded invasomes and transfersomes face

challenges related to stability and water solubility. A comparative study involving conventional liposomes showed that invasomes and transfersomes demonstrated better reduction in melanin content and tyrosinase inhibition activity.

- **Acne Treatment:** Acne is a common chronic inflammatory skin infection that adversely affects young adults, causing emotional stress, discomfort, and scarring. Dapsone, a sulfone compound, effectively treats acne when administered topically. El-Nabarawi et al. prepared dapsone-loaded invasomes using different terpenes to evaluate their skin delivery capability. The study revealed that invasomes significantly improved the deposition of dapsone in the skin.
- **Photodynamic Therapy:** Photodynamic therapy is an intriguing approach that involves the use of photosensitizing compounds. These compounds accumulate in target cells and, upon exposure to visible light, induce local irritation. This leads to apoptosis or necrosis of the target cells. Dragicevicuric et al. developed an invasomal formulation of temoporfin, a lipophilic compound, using a blend of terpenes and ethanol. The research findings indicated that invasomes containing a 1% blend of terpenes showed increased temoporfin deposition in the stratum corneum compared to liposomes.
- **Transdermal Delivery for Benign Prostatic Hyperplasia:** Benign prostatic hyperplasia is a common condition in elderly men that causes pathological changes in urine flow and kidney function. Prasanthi and Lakshmi et al. investigated the transdermal delivery of finasteride, a model drug for treating this condition, using invasomes and the iontophoretic technique. The invasomes formulation, optimized using Taguchi's robust design method, included terpenes such as nerolidiol, carvone, and limonene. The study revealed that a sample containing 0.5% limonene exhibited 21-fold better penetration than the controls. Additionally, the optimized formulation proved effective in transdermal delivery of finasteride when combined with iontophoretic techniques.
- **Efficiency of Invasomes in Hydrophilic Drug Delivery:** Invasomes have proven to be successful drug delivery systems for hydrophilic drugs. Badran et al. conducted an in vitro study and found that invasomes containing a 1% mixture of terpenes outperformed aqueous solutions in dermal delivery of hydrophilic compounds. Furthermore, when combined with a Dermaroller, a microneedle device, the vesicles demonstrated improved drug permeation and penetration⁽³⁹⁾.

VII. NIOSOMES

Whether this control is of a temporal, spatial, or combined form, the goal of novel drug delivery systems is to offer some control amount of drug release in the body. The goal of novel drug delivery is to either maintain drug activity at a predetermined rate or to keep the body's effective drug level roughly constant while minimizing any adverse effects. It is also possible to target drug action by utilizing carriers or chemical derivatization to deliver the drug to a specific target cell type, or it is possible to localize drug activity by the spatial placement of controlled release systems adjacent to or within the diseased tissue or organ⁽⁴⁴⁾. When Paul Ehrlich envisioned a drug delivery system that would target specifically damaged

cells, he launched the period of development for targeted delivery in 1909 (Magic bullet). Drug targeting is the ability of a therapeutic substance to be directed directly to intended site of action with little or no interaction with non-target tissue⁽⁴⁵⁾. In these various carriers are used to deliver the drug to target site.

Pharmaceutical carriers come in a variety of forms, including particulate, polymeric, macromolecular, and cellular. Lipid particles, microspheres, nanoparticles, polymeric micelles, and other small particles are examples of the particulate type carrier, often known as the colloidal carrier system, and vesicular structures like liposomes, sphingosomes, niosomes, transfersomes, pharmacosomes, and virosomes. Certain amphiphilic building blocks are exposed to water, resulting in the formation of vesicular systems, which are highly organised assemblies of one or more concentric lipid bilayers. Many different types of amphiphilic building blocks can be used to create vesicles. The Bingham bodies were initially described as having a biological origin by Bingham in 1965 (Bingham et al., 1965). Due to the limited drugs penetration into cells, conventional chemotherapy is ineffective for treating intracellular infections. Vesicular drug delivery devices can be used to bypass this⁽⁴⁶⁾.

Niosomes are non-ionic surfactant vesicles that were initially developed in 1985 by Ballie et al. Niosomes are concentric bilayered vesicles that completely encapsulate an aqueous volume with a membranous lipid bilayer composed primarily of cholesterol and non-ionic surfactants. These are similar to liposomes which can entrap both hydrophilic and hydrophobic drugs⁽⁴⁷⁾.

Niosomes were first addressed in the cosmetic industry by Vanlerbeghe et al. in 1972. According to Handjanivila et al., a combination of cholesterol and a single alkyl chain non-ionic and non-toxic surfactant formed vesicles when it was hydrated. Since then, a variety of non-ionic surfactants, including polyglycerol alkyl ethers, glucosyl dialkyl ethers, crown ethers, polyoxyethylene alkyl ethers, ester-linked surfactants, steroid-linked surfactants, brij, and a number of spans and tweens, have been utilised to produce vesicles. Niosomes are the vesicles that result⁽⁴³⁾ and size vary from 10nm to 100nm.

Numerous mechanisms have suggested numerous ways for how niosomes might improve the transport of medicines through membranes. These include (i) Niosomes as transdermal drug delivery system reversible alteration of lipid organisation, which affect the stratum corneum's barrier function, (ii) increasing stratum corneum hydration by preventing transepidermal water loss, which causes the cellular structure of the stratum corneum to loosen, and (iii) niosome adsorption and/or fusion on the skin's surface, which creates a high thermodynamic activity. The binding of ligands on the niosomal membrane to particular receptors on the cell surfaces, which results in the direct transfer of the drug from the vesicles to the skin, may cause niosomes to adsorb onto the skin cell surfaces through the action of physical forces. On the other hand, total mixing of the niosomal contents with the cytoplasm can occur when niosomes fuse with the cell membrane. The entrapped niosomal material may potentially be released into the cell cytoplasm as a result of endocytosis of niosomes by skin cells and lysosomal breakdown⁽⁴⁸⁾.

1. Advantages^(43, 49)

- Similar to liposomes, entrap the solute.

- Increases the stability of the drugs that is entrapped and is osmotically active and stable.
- There are no additional requirements for handling or storing surfactants.
- Take into consideration drug substances with a variety of solubilities.
- Increase the oral bioavailability of drugs that are not well absorbed and can also increase drug penetration via the skin.
- Can be administered orally, parenterally, or topically to deliver the drug to the site of action.
- Niosomal surfactants are non-immunogenic, non-toxic, biodegradable, and biocompatible.
- By delaying the clearance of drug molecules from the bloodstream, shielding them from the biological environment, and limiting their effects to target cells, niosomes enhance the therapeutic effectiveness of drug molecules.
- They might increase how long the drug is trapped in circulation.
- Can be utilised to transport drugs that are hydrophilic, lipophilic, and amphiphilic, as well as pharmaceuticals with a wide range of solubility.
- Niosomes decrease the systemic toxicity of drugs including anti-infectives and anti-cancer medicines.

2. Disadvantages

- Physically unstable and it may form aggregation.
- Entrapped drug leakage may occur.
- Rarely, non-ionic surfactants interact with other components of the system and cause the formulation to become homogeneous or to precipitate.

3. Types of Niosomes ^(50,51): The classification of niosomes depends on several factors, including the number of bilayers (MLV, SUV), size (LUV, SUV), and manufacturing process (REV, DRV). The following is a description of the many niosome types:

- Multi lamellar vesicles (MLV) 1-5 μm size.
- large uni-lamellar vesicles (LUV) 0.1- 1 μm size.
- small uni-lamellar vesicles (SUV) 25-500 nm size.
- **Multi lamellar Vesicles (MLV):** It comprises many bilayers that each individually enclose the aqueous lipid compartment. These vesicles have a diameter that ranges from 0.5 to 10 micrometres. The most common niosomes are multilamellar vesicles. It is simple to produce and mechanically stable when kept in storage for an extended period of time. These vesicles are suitable for use as lipophilic compound drug carriers.
- **Large Uni-lamellar Vesicles (LUV):** These niosomes feature a high aqueous/lipid compartment ratio, allowing for more bioactive molecules to be entrapped while using membrane lipids much more sparingly.
- **Small Uni-lamellar Vesicles (SUV):** The majority of these tiny unilamellar vesicles are made from multilamellar vesicles by sonication, French press extrusion, and electrostatic stabilisation, which is accomplished by adding dicetyl phosphate to CF-loaded, Span 60-based niosomes with 5(6)-carboxyfluorescein (CF) loads.

4. Composition of Niosomes ^(52,53,54): For preparing niosomes, the main components are non-ionic surfactant, cholesterol and other additives.

- **Non-ionic Surfactant:** Unlike liposomes, which are mostly made of phospholipids, niosomes are primarily made of non-ionic surfactants. Non-ionic surface-active molecules are amphiphilic molecules having a polar head and a non-polar tail. Since surfactants don't carry any charge, they are more stable, compatible, and safe than anionic, cationic, and amphoteric surfactants. Non-ionic surfactants have the important property of inhibiting p- glycoprotein, in which the immersion can enhance and targeting of anticancer medicines, such as Doxorubicin, Daunorubicin, Curcumin, and Morusin, steroids such as hydrocortisone, HIV protease inhibitors such as Ritonavir, and cardiovascular medicines such as aspirin. The HLB of the surfactant affects the efficiency of niosome entrapment. The length of the alkyl chain and the size of the vesicle both grow when the HLB score increases. For the production of niosomes, surfactants with HLB in the range of 14–17 are unacceptable. Span (span 20, 60, 40,80,85) and tween (tween 20,40,60,80) and brij (Brij 30,35,52,58,72,76) are generally used for the preparation of niosomes.

Table 1.2: Different types of Non-ionic surfactants ⁽⁵⁴⁾

| Type of Non-ionic surfactant | Examples |
|------------------------------|---------------------------------------|
| Fatty alcohol | Cetyl alcohol, Steryl alcohol etc. |
| Ethers | Brij, Triton X-100, Nonoxynol-9 etc. |
| Esters | Glyceryl laurate, polysorbates, spans |
| Block copolymers | Polaxamers |

- **Cholesterol:** In the bilayer structure of niosomes, the hydrophilic head of a surfactant forms hydrogen bonds with cholesterol. The concentration of cholesterol in the niosome and how effectively it can enclose and sustain its loaded state have an impact on these physical and structural characteristics. Cholesterol influences the system's gel/liquid phase transition temperature and has an impact on membrane fluidity through interactions with nonionic surfactants ⁽⁵⁵⁾. Due to its effect on niosome stability and rigidity, cholesterol is effective in preventing leakage and may change the efficiency of drug entrapment in niosomal formulations by altering the cholesterol content. The amount of cholesterol that must be added depends on the HLB value of the surfactants. The cholesterol concentration must be raised when the HLB value rises in order to offset the effect of the larger head groups on the critical packing parameter (CPP) ⁽⁵³⁾.
- **Other Additives:** Niosomes' capacity to change their structure and physicochemical characteristics by adding various additives is one of their advantages. As a result, since vesicle features rather than the physicochemical qualities of the drug play a more significant part in determining pharmacokinetics and the drug delivery process, both processes may be further enhanced. To impart desired properties, several additives may be added to the niosomal composition ⁽⁵⁵⁾.

5. Factors Affecting the formation of Niosomes

- **Selection of Surfactants and Additives:** To make niosomes, a surfactant has to have a hydrophilic head and a hydrophobic tail. One, two, or perhaps one or more alkyl, perfluoroalkyl, or in certain situations, steroidal groups may make up the hydrophobic tail. The single-chain alkyl tail of ether-type surfactants makes them more hazardous than their dialkyl corresponding bodies. Since ester-linked surfactants are in vivo degraded by Esterases to triglycerides and fatty acids, they are chemically less stable than ether-type surfactants and less hazardous than the latter. For the creation of niosome, surfactants with alkyl chains ranging from C12 to C18 are appropriate. Surfactants from the Span series with an HLB number of 4 to 8 can generate vesicles⁽⁵⁵⁾.
- **Drug:** The interaction of the solute with surfactant head groups, which raises the charge and mutual repulsion of the surfactant bilayers, increases the vesicle size when the drug is trapped in niosomes. Some drugs get trapped in the lengthy PEG chains in polyoxyethylene glycol (PEG) coated vesicles, which lessens the tendency for them to expand in size. The degree of entrapment is influenced by the drug's hydrophilic-lipophilic balance⁽⁵⁶⁾.
- **Charge and Cholesterol Content:** Cholesterol increases niosome hydrodynamic diameter and trapping efficiency. In general, cholesterol acts in two ways: on the one hand, it boosts the chain order of bilayers in the liquid state, and on the other, it lowers the chain order of bilayers in the gel state. The gel state changes into a liquid-ordered phase at high cholesterol concentrations. A decrease in the release rate of the material that was encapsulated and an increase in the stiffness of the resulting bilayers were caused by an increase in the cholesterol content of the bilayers. In a multilamellar vesicle structure, the presence of charge tends to increase the interlamellar distance between succeeding bilayers and results in a greater total entrapped volume.
- **Resistance to Osmotic Stress:** When a hypertonic solution is introduced to a Niosomal suspension, the size of the Niosome reduces. In a hypotonic salt solution, where niosomes are kept, the drug is initially slowly released, resulting in swelling. The slower release might be due to vesicle fluid eluting being inhibited. A quicker releasing phase was later seen. The breakdown of the niosome's mechanical structure as a result of mechanical stress may be what leads to this quicker release phase^(53,56).
- **Critical Packing Parameter:** The critical packing parameter affects the shape of the vesicle during niosomal formation. The shape of nanostructures produced by the self-assembly of amphiphilic molecules may be anticipated based on the CPP of a surfactant. The following Equation may be used to define the critical packing parameter, which relies on the symmetry of the surfactant:

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

Where, v = area of the hydrophilic head group,

l_c = crucial hydrophobic group length, and
 a_o = hydrophobic group volume.

Small hydrophobic tail spherical micelles may develop if $CPP \leq 1/3$, for instance, correlating to a bulky head group. Bilayer vesicles can form if $1/2 \leq CPP \leq 1$ and non-spherical micelles can form if $1/3 \leq CPP \leq 1/2$. When the surfactant is made up of a large hydrophilic tail and a short hydrophobic tail, inverted micelles develop if $CPP \geq 1$. The self-assembled structure and its morphological transition in amphiphilic liquids may be realised, explained, and predicted using CPP.

6. Methods of Preparations ^(57,58,59): By hydrating nonionic surfactants with hydration medium, niosomes are usually prepared. But there are so many methods to formulate the niosomes they are:

- Transmembrane pH gradient method,
 - Thin Film Hydration technique,
 - Reversed-phase evaporation,
 - Ether injection Method,
 - Bubbling of nitrogen,
 - Sonication,
 - Enzymatic method,
 - Single-pass technique and
 - Microfluidization
 - Formation of Niosomes from proniosomes
-
- **Transmembrane PH Gradient Method:** This theory states that the inside of the niosome has an acidic pH, which is lower than the outside. The niosome membrane is crossed by the additional unionised basic drug, but once inside, it becomes ionised in an acidic medium and is unable to exit the niosome, increasing the effectiveness of entrapment for such medications. Surfactant and cholesterol were dissolved in chloroform, and under low pressure, these will evaporate and form a thin film. By vortex mixing, this film is hydrated with an acidic chemical solution (often citric acid), and the result is kept freeze-thawed to produce niosomes. The aqueous solution containing the drug is added to the niosomal suspension. Phosphate buffer is added to increase the PH, and the interior of the niosomes becomes more acidic than the exterior medium. This will make the unionised form of the drug pass the bilayers of niosomes, and after the drug enters the niosomes, it ionises in an acidic medium and makes successful entrapment.
 - **Thin Film Hydration Technique:** Thin-film hydration is a common technique used for preparing niosomes. Cholesterol and surfactant are dissolved in organic solvents (Chloroform: Ethanol) in a round bottom flask (fig 1) and kept for rotary evaporator along with speed, temperature and pressure. The thin film will be formed on the walls of the flask, and this was hydrated with preheated buffer and again kept for rotary evaporator for stirring. After sometimes the vesicles will be formed.



Figure 4: Rotary Evaporator

- **Reversed Phase Evaporation:** Surfactant and cholesterol are dissolved in organic solvent (ethanol, chloroform), and an aqueous solution containing the drug was added and sonicated with a temperature of $4^{\circ}\text{C} - 5^{\circ}\text{C}$. Further, after adding phosphate buffer saline (PBS), keep for sonication resulting in the formation of gel and temperature is increased, and pressure is reduced to 40°C to evaporate the solvent. The PBS is added again and kept for the bath sonicator at 60°C for 10min, and niosomes were formed.
- **Ether Injection Method:** Ether injection method is prepared by dissolving non-ionic surfactant and cholesterol in diethyl ether and taking the entire solution into a syringe. This solution is slowly introduced 1ml/min into a preheated buffer and kept for stirring until vesicles form. The gradual vaporisation of the solvent causes an ether gradient to extend towards the aqueous non-aqueous interface, which is likely what causes the development of bigger unilamellar vesicles. The creation of the bilayer structure may be due to the former. The vesicle's diameter ranges from 50 to 1000 nm, depending on the parameters used. This method's drawback is that it's challenging to get rid of the trace amounts of ether that are commonly present in the vesicles suspension.
- **Bubbling of Nitrogen:** Organic solvents are not used in this procedure. Phosphate buffer saline (PBS), additives, and surfactants were put into a glass reactor with three necks. The reactor is set in a water bath to regulate the temperature. The thermometer is placed in the second neck, nitrogen gas enters the first neck, and water refluxes into the third neck. After 15 seconds of high-shear homogenizer mixing, these components are combined. Niosomes were produced when nitrogen gas was bubbled at 70°C .
- **Sonication:** The surfactant-cholesterol combination is initially distributed in the aqueous phase using this approach. Multilamellar vesicles (MLV) are created when this dispersion is probe sonicated for 10 min at 60°C . Unilamellar vesicles are created after additional ultrasonication of these MLVs, either by a probe sonicator or a bath sonicator.
- **Enzymatic Method:** In this method, niosomes are generated from a mixed micellar solution via an enzymatic approach. Esterases degrade molecules such as polyoxyethylene and cholesterol, which when coupled with diacetyl phosphate and

other lipids form multilamellar niosomes. The surfactants used in this process include polyoxyethylene cholesteryl sebacetate diacetate and polyoxyethylene stearyl derivatives.

- **Single-pass Technique:** It is a patented approach that involves the continuous extrusion of a lipid solution or suspension through a nozzle after passing through a porous device. It combines homogenization and high-pressure extrusion to provide niosomes a limited supply of sizes between 50 and 500 nm.
- **Microfluidization:** To create unilamellar vesicles with a certain size distribution, a new approach has been developed. This approach is based on the submerged jet concept, in which two fluidized streams contact precisely designed microchannels inside an interaction chamber at extremely high speeds. It is designed such that the energy provided to the system stays in the region of niosomes production when thin liquid sheets impact along a common front. The niosomes that are produced as a result are smaller, more consistent, and more repeatable ⁽⁶⁰⁾.
- **Formation of Niosomes from Proniosomes:** A water-soluble carrier, such as sorbitol or mannitol, is coated with surfactant when using the proniosome approach. A dry formulation is used because of the coating process. This substance is known as "Proniosomes" and has to be hydrated before usage. The inclusion of the aqueous phase results in the formation of the niosomes. This approach provides ease in dosing and storage while decreasing physical stability issues including the aggregation, leakage, and fusion problem. It also produces better outcomes than conventional niosomes.

7. Applications of Niosomes ^(61,62,63,64)

- **To Increase Oral Bioavailability:** As compared to the drug alone, it has been shown that the formulation of niosomes increased the oral bioavailability of acyclovir and griseofulvin. Similar to this, when provided as micellar solution together with the POE-24- cholesteryl ester in the bile duct of rats, poorly absorbed peptide and ergot alkaloid absorption can be boosted.
- **Anticancer Drug Delivery:** In order to increase the therapeutic index of the anticancer drugs by localising the cytotoxic effects to target cells, methotrexate-loaded niosomes were initially used as a more reliable and cost-effective alternative drug delivery technology to liposomes. When vincristine was enclosed in niosomes, its anti-tumour action was also enhanced in mice having Ehrlich ascites and S-180 sarcoma. Additionally, in the two tumour types indicated above, Span 60 bleomycin niosomes enhanced bleomycin's anti-tumour effects. Doxorubicin's cytotoxic side effects were lessened when it was enclosed in C16G2 niosomes. The dosages chosen for usage in vivo did not cause hemolysis in vitro when doxorubicin copolymer-loaded niosomes were used. On the liver and spleen, C16G2 niosomes likewise had localised, long-lasting effects. In addition, niosomal delivery systems for 5-fluorouracil based on Span 40 and Span 60 demonstrated a sustained and increased local concentration of the drugs in the liver and kidney of the rats when compared to the

injectable drug solution. Recently, drug release has been effectively regulated using niosomes for the magnetic targeting of doxorubicin to a particular organ with no further toxicity.

- **NSAIDS:** The preparation of NSAID-loaded niosomes has been done by a number of different companies. Adverse reactions including mucosal irritation are possible with these drugs. Topically applied NSAID-loaded niosomes can considerably improve drugs penetration. Marianecchi et al. developed ammonium glycyrrhizinate (AG) loaded niosomes with various surfactants and cholesterol concentrations to investigate the potential use of niosomes for anti-inflammatory drug delivery. The characterization of drug entrapment effectiveness, anisotropy, cytotoxicity, skin tolerability, and other criteria was investigated. The AG- loaded niosomes demonstrated great skin tolerability, non toxin, and the capability to ameliorate anti-inflammatory exertion in mice. Additionally, when applied to chemically produced human skin erythema, the anti-inflammatory effect of the medication supplied through niosomes was shown to be enhanced.
- **Antiviral Drugs:** The capacity of niosomes to distribute different antiviral drugs has also been established. Zidovudine, the first anti-HIV drug licensed for clinical use, was developed by Ruckman and Sankar. They then entrapped niosomes and evaluated the effectiveness of their entrapment as well as the sustainability of release. The ratios of Tween, Span, and cholesterol were combined to create niosomes. Tween 80 niosomes caught a large amount of zidovudine, and the addition of diacetyl phosphate extended the duration of drug release. Compared to niosomes maintained at 4°C for 90 days, the drug leakage from Tween 80 formulations held at room temperature was substantial. Further evidence that Tween 80 formulations containing diacetyl phosphate were eliminated from circulation after five hours came from the results of a pharmacokinetic research conducted on rabbits.
- **Cosmetics:** The cosmetic products developed by L'Oreal were the source of the first report of non-ionic surfactant vesicles. In the 1970s and 1980s, L'Oréal invented and patent niosomes. Lancôme debuted "Niosome," the first product, in 1987. The benefits of employing niosomes in cosmetic and skin care products include their capacity to improve the bioavailability of chemicals that are difficult to absorb as well as skin penetration.
- **Peptide Drug Delivery:** It has long been difficult to avoid the enzymes that would break down peptides used in drug administration. Investigations are being done on the potential use of niosomes to successfully shield peptides from peptide breakdown in the gut. An in vitro study utilising a vasopressin derivative trapped in niosomes indicated that drug entrapment significantly increased peptide stability⁽⁶⁵⁾.
- **Antibiotics:** Antibiotic and anti-inflammatory drug delivery can be accomplished using niosomal carriers. These carriers have been employed often to increase drugs retention in the skin and to improve ineffective skin penetration. Rifampicin, a niosomal delivery system-encapsulated wide range antibiotic, was developed by Begum and her colleagues. This work demonstrated that the niosomal formulation of

rifampicin is capable of providing constant and sustained release of the medication. They studied the activity of this system in in vitro environments.

- **Antifungal Agents:** When compared to other carriers, the use of niosome as a drug carrier, particularly for antifungal drugs, produces better results. The capacity to encapsulate both hydrophilic and hydrophobic drugs, as well as their prolonged stability in circulation, are all major characteristics of niosomes. They also considerably improve drug penetration through the skin. They may make suitable candidates for the treatment of fungi-related disorders since the cost of the raw ingredients (mainly surfactants) is lower than that of liposomes⁽⁶⁶⁾.

VIII. CHARACTERIZATION

In Vitro Evaluation

1. **Particle Charge (Zeta Potential):** Zeta potential determines the stability of the particle. A zeta potential of minimum $\pm 30\text{mV}$ is required for electrostatically stabilized formulation⁽¹⁸⁾.
2. **Crystalline State and Particle Morphology:** It's vital to recognize the crystal morphology of the drug. Polymorphic or morphological modifications in drugs that occur throughout nanosizing may be determined by the crystalline phase and particle morphology. It gives data about the changes in the physical type of the drug particles as well as the volume of the amorphous fraction. Differential scanning calorimetry can also be used. Scanning electron microscopy is also used to get specific statistics about particle morphology. The impact of excessive strain homogenization on the crystalline structure of the drug is envisioned by using X-ray diffraction analysis in aggregate with differential scanning calorimetry. Strategies like scanning electron microscopy (SEM), atomic pressure microscopy (AFM), or transmission electron microscopy (TEM) are preferred for figuring out the exact length and morphology of formulation.⁽¹¹⁻¹⁶⁾
3. **Drug Content:** Drug content can be completed by extracting the formulation in suitable solvent mixture, like Methanol : THF (1:1) combination, shaken properly, after which centrifuged. The supernatants can be separated and diluted with same solvent mixture and the absorbance may be measured at appropriate λ_{max} . The drug content material then can be calculated using the calibration curve⁽¹²⁻¹⁸⁾.
4. **Diffusion Study:** The diffusion study is done by using two compartment one is donor and another one is receptor.

The sample was placed on the donor compartment while in receptor consist of 7.4 PH buffer.

For every half an hour interval the sample was collected and check under UV spectroscopy⁽¹⁶⁾.



Figure 3: Franz diffusion Cell

5. Evaluation of the Surface Modified of Particles

- **Entrapment Efficiency:** The entrapment efficiency is done using ultracentrifugation technique in which it kept for 40 minutes at 14,000 rpm speed. In this specified amount of nanosuspension kept under the ultracentrifugation after specified time the supernatant liquid is collected and check under UV spectrometer⁽¹²⁾.

IX. CONCLUSION

Solubility is seen as a major concern in the formulation of dosage forms. The conventional drug delivery system has limitations, which lead to poor solubility and bioavailability. A novel technique showed a major contribution to improving the solubility effects of various poorly soluble drugs. By developing nanosuspension and vesicular drug delivery systems (Transferosomes, invasomes, and Niosomes), Solubility issues will improve, and the drug will show its effect on the target site.

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