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Transdermal Drug Delivery Using Lipid-Based Nanocarriers: A Systematic Comparative Overview

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Abstract: Lipid-based nanocarriers have emerged as highly promising systems in the development of advanced pharmaceutical formulations aimed at improving therapeutic efficacy, drug penetration, and safety profiles. Their intrinsic biocompatibility, biodegradability, and structural resemblance to biological membranes allow these carriers to encapsulate both hydrophilic and lipophilic drugs efficiently while minimizing systemic toxicity. Transdermal drug delivery, an important route for managing local and systemic conditions affecting the skin, eyes, rectum, and vagina, benefits greatly from these nanoscale systems due to their ability to overcome the barrier properties of the stratum corneum. The inherent flexibility, small size, and lipid composition of nanocarriers such as liposomes, transferosomes, invasomes, and ethosomes facilitate deeper skin penetration and controlled or sustained release of therapeutic agents. As a result, lipid-based nanocarriers enhance drug stability, prolong residence time, and improve patient compliance when compared to conventional dosage forms. Their application extends across various therapeutic areas, including dermatological disorders, inflammatory conditions, localized infections, and targeted chemotherapy. This review provides a comprehensive overview of the types of lipid-based nanocarriers employed in transdermal drug delivery, highlighting their structural characteristics, mechanisms of skin permeation, advantages, and inherent limitations. Furthermore, it discusses commonly used preparation techniques, including thin-film hydration, ethanol injection, ultrasonication, high-pressure homogenization, and microemulsion methods, along with key characterization parameters such as vesicle size, zeta potential, entrapment efficiency, deformability, and stability. Overall, the paper emphasizes the growing significance of lipid-based nanocarriers as versatile, effective, and innovative tools for enhancing transdermal drug delivery and expanding the future possibilities of topical and systemic therapeutic interventions.

Keywords: Lipid-based nanocarriers 1; Transdermal drug delivery 2; Liposomes 3; Biocompatibility 4; Drug encapsulation 5; Characterization 6; Novel drug delivery systems 7.

I. INTRODUCTION

Lipid-based Transport methods are receiving a lot of attention. from researchers developing novel formulations to improve medication safety and therapeutic efficacy¹. Lipid-based nanocarriers are perfect methods for delivering drugs for transdermal administration because of biocompatibility and biodegradability. Their lipophilicity and/or similarity to the natural lipids of the epidermis enable intermolecular interactions with the lipid membrane, resulting in effective passage through the skin². The transdermal route is favorable for drug administration, especially due to its noninvasive character. Other benefits include its controlled release capability, the avoidance of presystemic metabolism (first-pass effect), and the reduction in side effects. However, it is not often selected due to the limitations that still exist. Among other functionalities, the skin serves as a physiological barrier, being impervious to certain compounds and thus limiting drug permeation. Additionally, it appears that there is also skin-mediated metabolism. Bearing in mind that skin is a dynamic system, the degree of a drug's penetration is dependent on skin condition and hydration as well³. Additionally, Active Pharmaceutical Ingredients (APIs) that are ionizable molecules and/or have a molecular weight over 500 Dalton face difficulties permeating the skin⁴.

Even when it comes to APIs that could penetrate the stratum corneum successfully, passing through the skin multilayer can be a slow process, leading to ineffective therapeutic drug levels⁵. Strategies to exceed such barriers involve physical and chemical methods. Ionto-, sono-, thermo, and magnetophoresis; electroporation; microneedles; and microdermabrasion are the existing physical methodologies, whereas chemical techniques include the usage of prodrugs or excipients that enhance skin permeation, such as terpenes, alcohols, glycols, etc⁶. Both approaches show several disadvantages, including irritation and other side effects. Alternatively, the use of novel formulations utilizing nanoparticulate systems as drug delivery platforms is a good strategy for transcutaneous administration. Nano-drug systems are innovative carriers comprising a broad spectrum of natural and/or chemical materials, such as inorganic, organic, or both. Their common feature—and main advantage—is their size, as being on the nanoscale results in them having an increased surface area⁷.

II. ADVANTAGES

Lipid-based Topical medication delivery methods providesignificant advantages over traditional creams and ointments by improving how a drug interacts with the skin. Here are the primary advantages:

A. Enhanced Drug Permeation

The skin's outer layer (stratum corneum) is a highly effective barrier that blocks most substances. Lipid-based carriers are designed to overcome this.

- Improved Penetration: The lipids in the carrier are similar to the skin's own lipids. This compatibility allows them to "fluidize" or temporarily loosen the skin barrier, permitting the encapsulated drug to pass through more easily.
- Close Contact: Systems like nanoparticles are so small that they ensure a large surface area of contact with the skin, increasing the potential for the drug to be absorbed.
- Follicular Delivery: Certain nanocarriers have the ability to target hair follicles and use them as a means of delivering medications to the deeper layers of the epidermis.⁸

B. Biocompatibility and Reduced Side Effects Tolerated by the body.

- High Biocompatibility Usually, they are composed of physiological lipids (similar to those already in your body) that are biodegradable and non-toxic.
- Lower Irritation: This biocompatibility indicates that they are less prone to cause the skin irritation, redness, or sensitization often seen with conventional formulations that use harsh chemical penetration enhancers.

C. Drug Protection and Stability

The lipid carrier acts as a protective shell for the active drug.

- Prevents Degradation: It shields sensitive drug molecules from environmental factors like light and air (oxidation) in add to from enzymes on the skin that would otherwise break them down.
- Improves Chemical Stability: This protection extends the shelf life of the product and ensures the drug is still active when applied¹⁰.

D. Controlled and Sustained Release

Instead of delivering a single, high dose of a drug at once, lipid carriers provide a more controlled effect.

- "Reservoir" Effect: The carriers can accumulate in the upper layers of the skin, forming a "depot" or reservoir. From here, the drug is released slowly and steadily over a prolonged period.
- Longer-Lasting Action: This sustained release means the therapeutic effect lasts longer, and the product may require less frequent application.¹¹

III. DISADVANTAGES

- 1) Storage Stability: These can be prone to instability during storage, leading to aggregation, leakage of encapsulated substances, or changes in size and structure.
- 2) Scalability: Their broad usage in large-scale pharmaceutical manufacture may be limited by the difficulty and expense of scaling up production.
- 3) Uniformity: Achieving uniformity in size and composition can be difficult, affecting their performance and reproducibility.¹²

- 4) **Short Circulation Half-Life:** They can be rapidly cleared from the bloodstream by the body's immune system, limiting their time window for drug delivery.
- 5) **Immunogenicity:** Some formulations may trigger an immune response, potentially causing adverse reactions in the body.
- 6) **Limited Drug Loading:** They have a finite capacity for drug loading, which can be a limitation when trying to deliver high doses of certain drugs.
- 7) **Complexity:** Researchers and producers may not be able to obtain formulas due to their complexity and need for specialized knowledge.¹³

IV. TYPES OF LIPID-BASED NANO CARRIERS

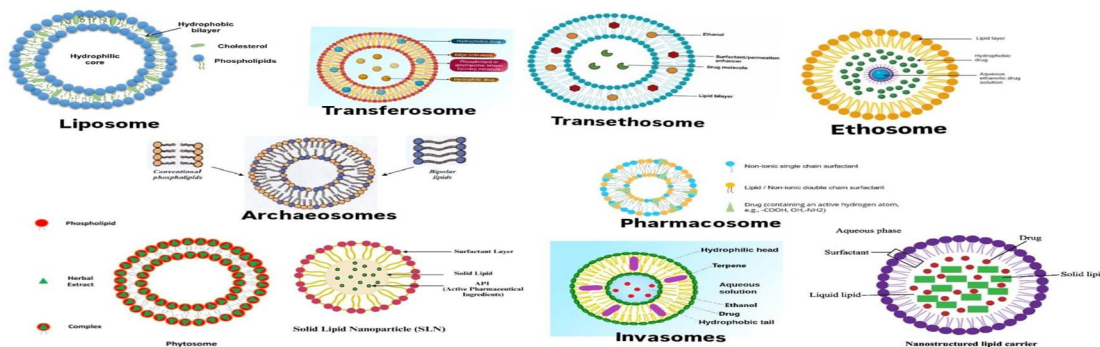


Figure 1: Types Of Lipid Based Nano Carriers

V. COMPOSITION OF LIPID BASED NANO CARRIERS

Table 1: Types And Composition Of Lipid Based Nano Carriers

S. No.	TYPE	COMPOSITION
1.	Liposome	Phospholipids (Phosphatidylcholine (PC), Phosphatidylethanolamine (PE)), Cholesterol, Targeting Ligands, PEGylated Lipids, Other Lipids (glycolipids or sphingolipids)
2.	Transfersomes	Amphipathic Lipids (soya phosphatidylcholine or egg phosphatidylcholine), Edge Activators, Solvent and Hydrating Medium (3–10% alcohol)
3.	Ethosomes	hydro alcoholic or hydro/alcoholic/glycolic phospholipid like phosphatidic acid (PA), hydrogenated phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylglycerol (PPG), phosphatidylinositol
4.	Transethosomes	Phospholipids, Surfactant, Alcohol, Stabilizer,
5.	Archaeosomes	archaeal lipids (ether-linked lipids), using caldarchaeol (tetraether) lipids
6.	Phytosomes	Phytoconstituents, Phospholipids, Phosphatidylcholine (PC),
7.	Solid Nano Particles	solid lipids (glyceryl monostearate, stearic acid), surfactants (poloxamers)
8.	Nano structured Lipid Nano Particles	Solid and liquid lipids (oleic acid with stearic acid), and surfactants
9.	Invasomes	Phospholipids, ethanol, terpenes (or a combination of terpenes)
10.	Pharmacosomes	Phospholipids (phosphatidylcholine), Solvent (methanol, dichloromethane or chloroform), Spacer

VI. METHOD OF PREPARATIONS

Lipid-based nanocarriers are highly effective for topical and dermal medication delivery because of their capacity to interact with skin lipids, be biocompatible, and ability to encapsulate both hydrophilic and lipophilic drugs. They enhance drug penetration through the stratum corneum and improve skin deposition while reducing systemic exposure. Common types include liposomes, SLNs, NLCs, transferosomes, and nanoemulsions. Preparation methods such as thin-film hydration, high-pressure homogenization, ultrasonication, microemulsion techniques, and solvent-based approaches influence particle size, stability, drug loading, and release behavior, resulting in stable nanoscale systems with prolonged therapeutic effects.

Table 2: methods of preparation of lipid based nanocarrier

S. No.	Lipid based nanocarrier	Method of preparation
1	Liposomes	Thin Film Hydration, Ethanol/Ether Injection, Reverse phase evaporation, Detergent depletion, Micro fluidic channel, Heating method, Sonication
2	Transferosomes	Thin Film Hydration, Ethanol/Ether Injection, Reverse phase evaporation, Suspension Homogenisation process, Centrifugation process, modified hand shaking method
3	Ethosomes	Thin Film Hydration, Cold method, hot method
4	Transethosome	Thin Film Hydration, Cold method, hot method, Ethanol/Ether Injection, Reverse phase evaporation,
5	Archaeosome	Thin Film Hydration, Micro fluidic channel, Reverse phase evaporation, Sonication, Extrusion method
6	Phytosome	Solvent evaporation, Anti-solvent precipitation, Rotary evaporation, Freeze drying method
7	Pharmacosome	Solvent evaporation, Ether Injection, Super critical fluid process, Anhydrous cosolvent lyophilisation method
8	Solid Lipid nanoparticles	Hot high-pressure homogenization, Cold high-pressure homogenization, Microemulsion technique, Emulsification solvent evaporation, Solvent diffusion method
9	Invasomes	Mechanical dispersion technique, Film hydration technique, Thin film hydration technique, Reverse phase evaporation
10	Nanostructured lipid carrier	High-pressure homogenization, Microemulsion technique, Melt-emulsification and ultrasonication method, Emulsification-solvent diffusion, Evaporation solvent injection, Multiple emulsion techniques, Phase inversion

A. Thin Film Hydration Method (Bangham Method)

In this widely used technique, phospholipids (PL) and surfactants—serving as vesicle formers and edge activators—are dissolved in a suitable organic solvent mixture, typically methanol and chloroform in an appropriate volume ratio. If the formulation includes a lipophilic drug, it is incorporated into this mixture at this stage. After that, the solvent combination is put in a flask with a circular bottom and rotated under low pressure at a temperature higher than the lipid phase changeover point. As a result, a thin, homogeneous lipid coating forms along the flask's inner wall. To load a hydrophilic drug, the dry lipid film is hydrated using a buffered aqueous solution with an appropriate pH. The hydration process involves continuous rotation at a controlled temperature for a defined time, resulting in the development of multilamellar, enlarged vesicles. Then, using a bath or probe sonicator, these vesicles are decreased in size and homogenized using sonication. The sonicated dispersion is extruded through polycarbonate membrane filters with pore diameters ranging from 200 nm to 100 nm for additional length homogeneity and enhanced vesicle quality.¹⁴

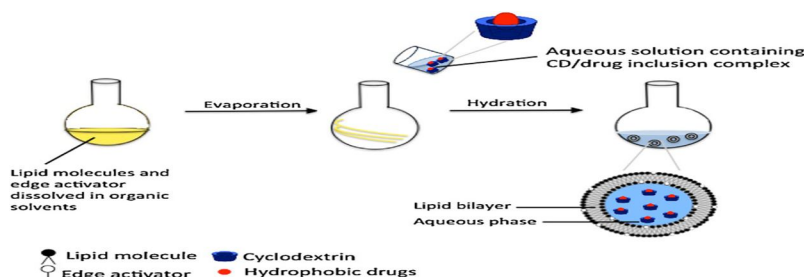


Figure 2: Thin Film Hydration Method

B. Suspension Homogenization Process

In this method, transferosomes are prepared by dissolving phospholipids—commonly soybean phosphatidylcholine—and an edge activator such as sodium cholate in an ethanol solution. This lipid mixture is then combined with a pre-prepared buffer solution, typically triethanolamine-hydrochloride (TEA-HCl), to achieve the desired total lipid concentration.

Following this, the resulting suspension undergoes a series of processing steps including freezing, sonication, and thawing—usually repeated two to three times. These actions are necessary for vesicle size reduction, uniform distribution, and improved stability of the final transferosomal formulation.¹⁴

C. Centrifugation Process

In this method, all formulation components—including phospholipids (PLs), a surfactant (edge activator), and any lipophilic drug—are first dissolved in an appropriate organic solvent. The mixture is then subjected to rotary evaporation under reduced pressure, typically using a rotary evaporator, to remove the solvent and form a thin lipid film along the flask walls. Any residual solvent is further eliminated under vacuum conditions to ensure purity and safety.

Following solvent removal, a buffer solution of appropriate pH is added to hydrate the lipid film. This hydration step is carried out at room temperature, and hydrophilic drugs can be incorporated at this stage. The lipid film swells upon hydration, resulting in the formation of multilamellar vesicles.

These vesicles are then subjected to sonication at ambient temperature to reduce their size and improve uniformity. This process yields stable, deformable transferosomal vesicles suitable for further characterization and drug delivery applications.¹⁵

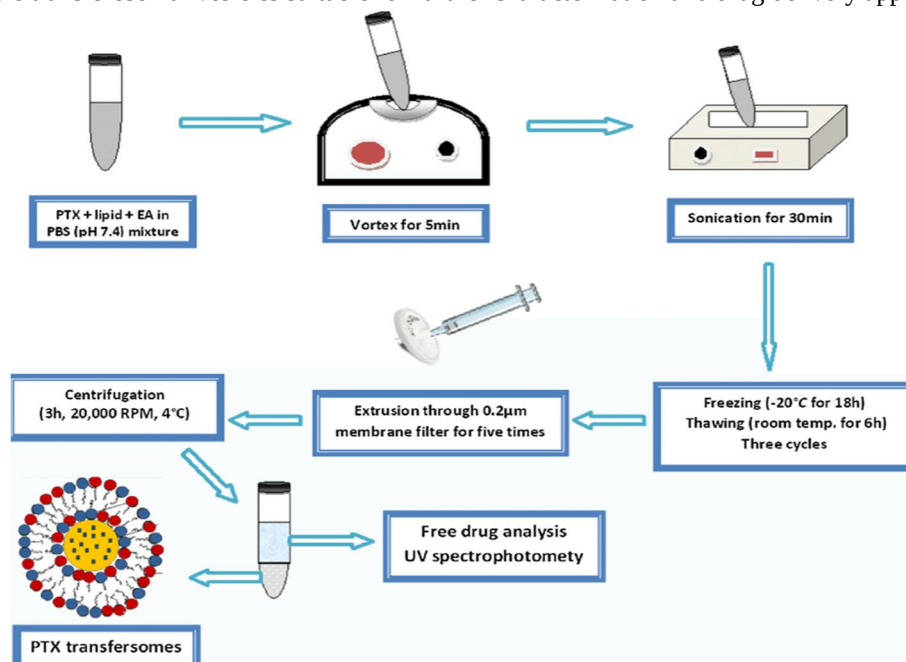


Figure 3: Centrifugation Process

D. Modified Hand Shaking Method

In this method, the drug, lecithin (phosphatidylcholine, PC), and edge activator are dissolved in a mixture of ethanol and chloroform in a 1:1 volume ratio. The resulting solution is placed in a round-bottomed flask and subjected to gentle manual rotation or shaking at a temperature above the lipid phase transition point (typically above 43°C), facilitating the evaporation of the organic solvents. This rotation aids in the formation of a uniform thin lipid film along the inner wall of the flask. To ensure complete removal of residual solvents, the thin film is left to dry overnight under ambient conditions. Subsequently, the dried film is hydrated using phosphate buffer (pH 7.4), with moderate shaking at room temperature for approximately 15 minutes. Following this initial hydration, the transferosomal suspension is further hydrated by storing it at 2–8°C for an additional hour, allowing the vesicles to fully swell and stabilize.¹⁶

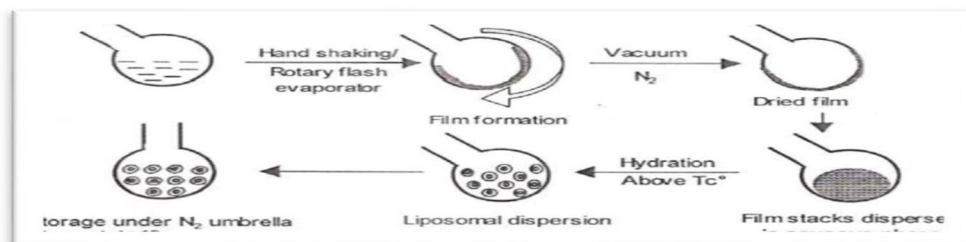


Figure 4: Modified Hand Shaking Method

E. Reverse Phase Evaporation Method

In this technique, phospholipids are first dissolved in an organic solvent such as **chloroform, methanol, or ethanol**. The resulting solution is transferred into a flask containing a hydrophilic aqueous phase, which includes a surfactant or edge activator (EA), depending on the formulation requirements. To prevent oxidation and maintain a controlled environment, the system is purged with **nitrogen gas**. The drug is incorporated into either the lipophilic or hydrophilic phase, depending on its solubility profile. Sonication is then used to emulsify the two phases, creating a homogenous, transparent dispersion. The emulsion is typically observed for at least half an hour to guarantee phase stability, and sonication is continued until homogeneity is attained. Ultimately, durable, ultra-deformable transferosomal vesicles are formed by progressively removing the organic solvent under low pressure. This technique works especially well for encapsulating both lipophilic and hydrophilic medications.¹⁷

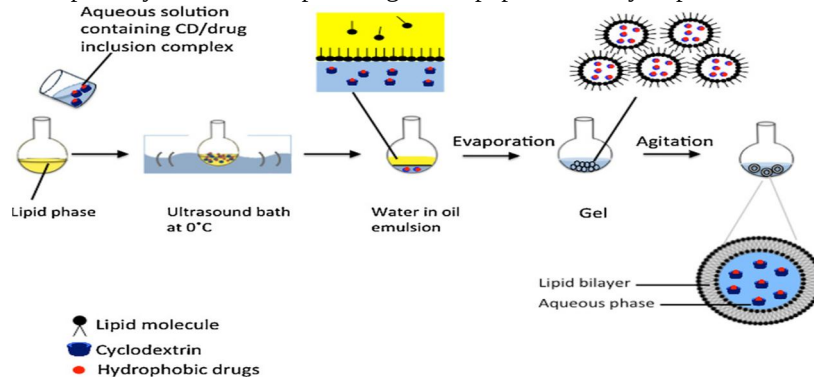


Figure 5: Reverse Phase Evaporation Method

F. Ethanol Injection Method

In this technique, the drug is first dissolved in an aqueous solution, which is maintained at a controlled temperature under **constant stirring**. Separately, phospholipids and edge activators are dissolved in ethanol to form a lipidic organic phase.

This ethanolic lipid solution is then slowly injected into the aqueous phase under continuous stirring. Upon contact, the **lipid molecules spontaneously precipitate**, forming bilayered vesicular structures **due to the sudden change in solvent polarity and miscibility**. The method is noted for its simplicity, reproducibility, and scalability, making it suitable for both laboratory-scale and industrial-scale production of transferosomes. It is particularly advantageous when a clean, solvent-free aqueous environment is desired for sensitive drug molecules.^{18,19}

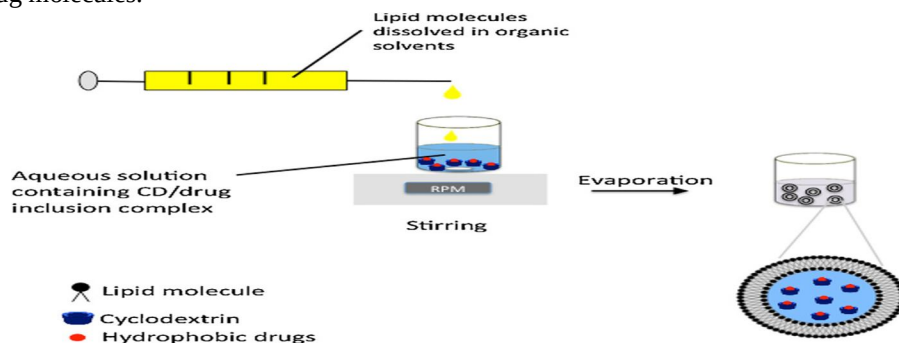


Figure No. 6: Ethanol Injection Method

G. Cold Method

The cold method is widely used, particularly for heat-sensitive drugs, due to its low operating temperatures. Procedure is as follows

- 1) Add the phospholipid (e.g., soy phosphatidylcholine) and the active drug to a container with ethanol (typically 20–45%) and optional polyols like propylene glycol.
- 2) Cover the vessel to prevent ethanol evaporation and mix the contents vigorously using a magnetic stirrer at room temperature.
- 3) Heat the mixture in a 30°C water bath.
- 4) In a separate vessel, heat deionized water to 30°C.
- 5) Add the heated water slowly and in a fine stream to the ethanolic solution over about five minutes while stirring at a consistent speed (e.g., 700 rpm).
- 6) Cool the mixture to room temperature, and then homogenize it using a sonicator or extruder for a specific duration to achieve the desired vesicle size and uniformity.
- 7) Store the final ethosomal suspension under refrigeration to maintain its stability.²⁰

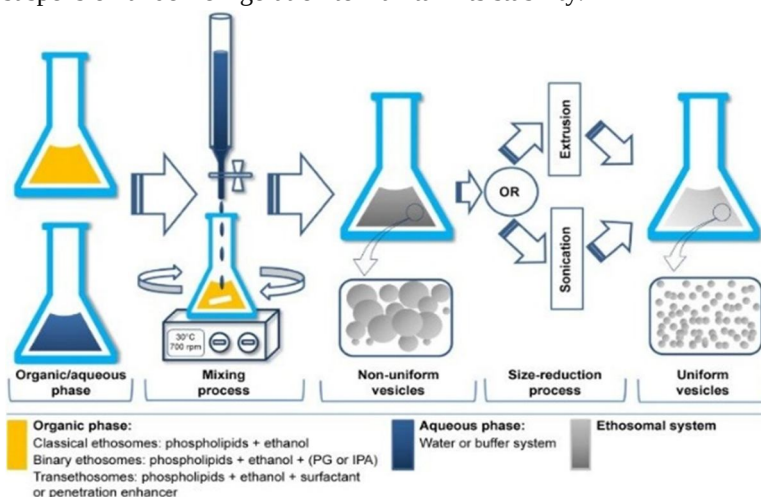


Figure 7: Cold Method

H. Hot method

The hot method is suitable for thermally stable drugs and is known for producing ethosomes with high encapsulation efficiency. Procedure is as follows

- 1) Disperse the phospholipid in water by heating it in a water bath at 40°C until a colloidal solution is formed.
- 2) In a separate vessel, combine the drug, ethanol, and any other lipid components and heat the mixture to 40°C.
- 3) Add the organic, ethanolic phase to the aqueous, phospholipid-in-water dispersion while stirring continuously for several minutes.
- 4) After the emulsion forms, sonicate or extrude the mixture to reduce the size of the vesicles.
- 5) Allow the formulation to cool and store it in the refrigerator.²¹

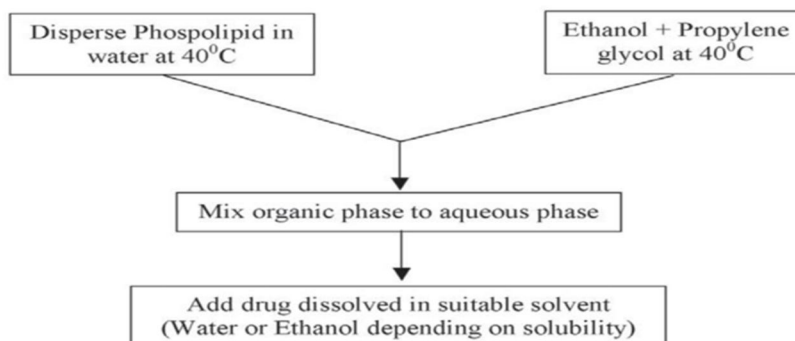


Figure 8: Hot Method

I. Detergent Depletion Method

This process creates homogenous liposomes for a range of drug delivery applications. This method evaluates the solubility of lipids by forming detergent lipid micelles by adding the proper cleanser to an organic solvent at the critical micelle concentration. After the detergent is removed, the micelles become more phospholipid-rich and finally combine to create liposomes. Detergents should be removed using dialysis. A commercial device known as LipoPrep is used to remove detergent. Dialysis bags immersed in sizable buffers free of detergents were used for equilibrium dialysis. The shape & homogeneity of liposomes made with the detergent approach depend on the rate and degree of detergent clearance in addition to the phospholipid to detergent ratio.²²

J. Microfluidic Channel Method

Jahn et al. developed the microfluidic approach for regulated liposome production. This technique involves dissolving lipids in isopropyl alcohol, that subsequently travels through the middle of the two tubes that hold aqueous medium. The lipids in the isopropyl alcohol stream then mixed to form liposomes. Lipid contents in microfluidic channels and laminar flow regulate liposome size and size distribution. This is a useful technique for directly encapsulating the medication to create self-assembling liposomes.²³

K. Heating method

The heating technique for obtaining liposomes was created by Mortazavi and Mozafari. This approach involves continuously stirring the phospholipids at 60° or 120°C for one hour while using glycerol and PEG/ethylene glycol to hydrate them. To extract the liposomes, the liquid must be centrifuged for 15 minutes at 4000 rpm after chilling. Because this procedure requires a high temperature of 120 °C, sanitation is not required, and liposomes made using this method do not experience phospholipid degradation. Furthermore, the Mozafari approach is an improved heating technique that involves hydrating the lipid components in aqueous medium and then heating the components without the use of organic solvents. This increases stability and is utilized to administer flavorzyme [a de-bittering agent].²⁴

L. Sonication method

SUVs are frequently prepared using the sonication process. MLVs can be sonicated using one of two methods: a bath type ultrasound device or a probe-type sonicator in a significant atmosphere.

- 1) Sonication of probes: The sonicator tip is quickly filled with the liposome dispersion. Heating is caused by the interaction power at the tip, and a significant quantity of energy is absorbed into the distributed lipid. For up to an hour throughout the sonication process, the vessel should be submerged in a water/ice bath. Titanium may contaminate the mixture and de-esterify over five percent of the lipids.
- 2) Bath sonication: Liposome dispersion is taken in a cylinder and is placed into a bath sonicator. In this the temperature should be controlled in contrast to probe sonication. The material being sonicated can be protected in a sterile vessel under inert atmosphere.²⁵

M. Solvent evaporation method:

The solvent evaporation methods involve integration of the phytoconstituents and PC during a flask containing organic solvent. This reaction mixture is kept at an optimum temperature usually 40°C for specific interval of 1 hr to achieve maximum drug entrapment within the phytosomes formed. Thin film phytosomes are separated by 100 mesh sieves and stored in desiccators for overnight²⁶

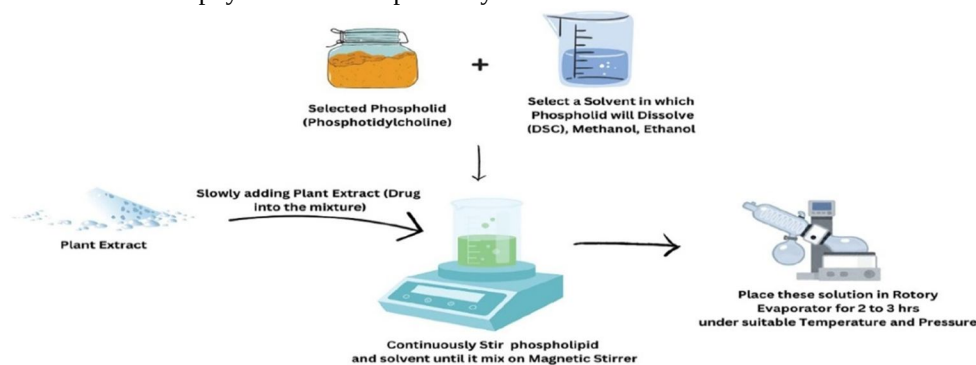


Figure 9: Solvent Evaporation Methods

N. Anti-solvent Precipitation

Dissolve the plant extract and phospholipids in a suitable solvent, such as acetone, and reflux the mixture. Concentrate the solution to a smaller volume. Add a low-polarity antisolvent like n-hexane to precipitate the phytosomes. Filter the precipitate and dry it in a desiccator, then store it^{27,28}.

O. Freeze-Drying (Lyophilization)

This method can be used as a final step after the solvent evaporation method to ensure long-term preservation. A solution of the phytosome complex is frozen and then subjected to a vacuum to remove the solvent as a vapor. The resulting dry powder is stable and can be easily formulated into capsules or other dosage forms.²⁹

P. Supercritical fluid process (Solution enhanced dispersion by complex supercritical fluid)

Supercritical CO₂ is used in the SEDS process to quickly create lipid nanocarriers. In this procedure, supercritical CO₂ is heated to the necessary temperature and pressure after the medicine and lipid have been scattered throughout an organic solvent. Through a coaxial nozzle, the mixture and SC-CO₂ are co-injected. CO₂ immediately absorbs the solvent, resulting in fast supersaturating and precipitate of lipid nanoparticles. After the freshly created nanocarriers are gathered in a chamber and depressurized to eliminate CO₂, dry, solvent-free lipids nanocarriers with regulated size and homogeneity are produced.²⁸

Q. Anhydrous co-solvent lyophilization method:

Solvent System: Lipids and active pharmaceutical ingredients (APIs) are dissolved using a mixture of organic solvents, such as ethanol and tert-butanol. The solvents used are chosen according to how well they work with the lipid matrix and how volatile they are.

Lipid Dispersion: Lipids are dissolved in the co-solvent system along with surfactants and stabilizers. The mixture is homogenized to form a uniform dispersion.

Freeze-Drying: The dispersion is frozen rapidly and subjected to lyophilization under reduced pressure. The absence of water minimizes hydrolytic degradation and enhances shelf stability.

Reconstitution: Upon rehydration, the lyophilized powder forms nanocarriers with preserved particle size and encapsulation efficiency.³⁰

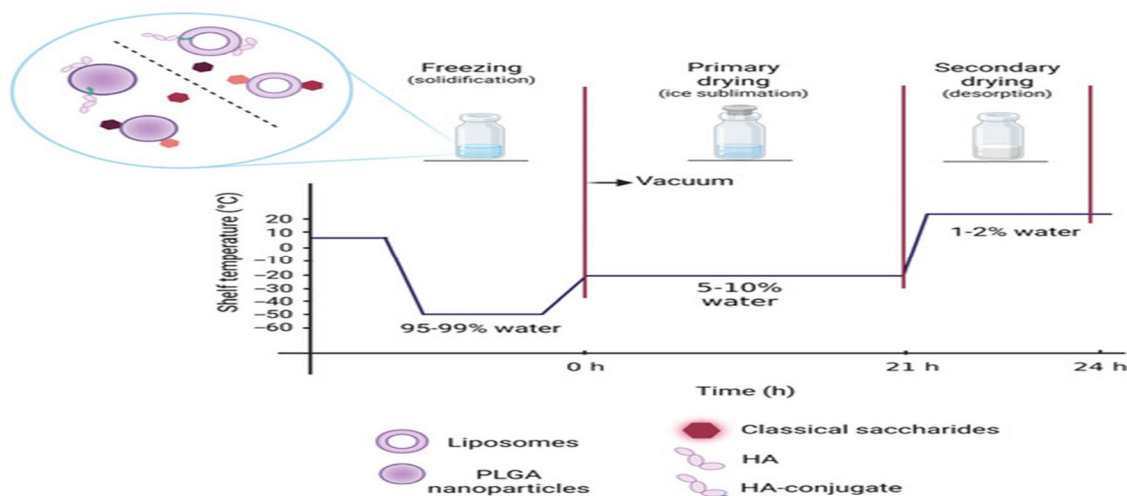


Figure 10: Anhydrous Co-Solvent Lyophilization Method

R. Hot High-Pressure Homogenization (Hot HPH)

In this widely used method, the lipid and drug are melted (typically 5–10 °C above the lipid melting point) and emulsified into a hot aqueous surfactant solution using a high-pressure homogenizer at 500–1500 bar. The hot emulsion is then cooled to solidify the lipid into nanoparticles. Advantages include scalability and suitability for Excellent load effectiveness lipophilic medications. Limitations include the possible degradation of heat-sensitive drugs and drug partitioning into the aqueous phase if homogenization is too vigorous.³¹

S. Cold High-Pressure Homogenization (Cold HPH)

Here, the drug-lipid melt is rapidly cooled (e.g., with liquid nitrogen) and milled into microparticles, which are then dispersed in a cold surfactant solution and homogenized at a low temperature (0–4 °C). This prevents drug migration and avoids thermal degradation, making it suitable for thermolabile and hydrophilic drugs. Limitations include broader particle size distributions and slightly lower process efficiency compared to hot HPH.³¹

T. Microemulsion Technique

A hot, clear oil-in-water microemulsion is formed by mixing molten lipid (with dissolved drug) into an aqueous surfactant/co-surfactant solution at elevated temperature. Quick dilution using cold water (2–10 °C) then causes the lipid to crystallize into nanoparticles. This method is solvent-free and reproducible but requires high surfactant concentrations and large water volumes, necessitating post-process concentration.³²

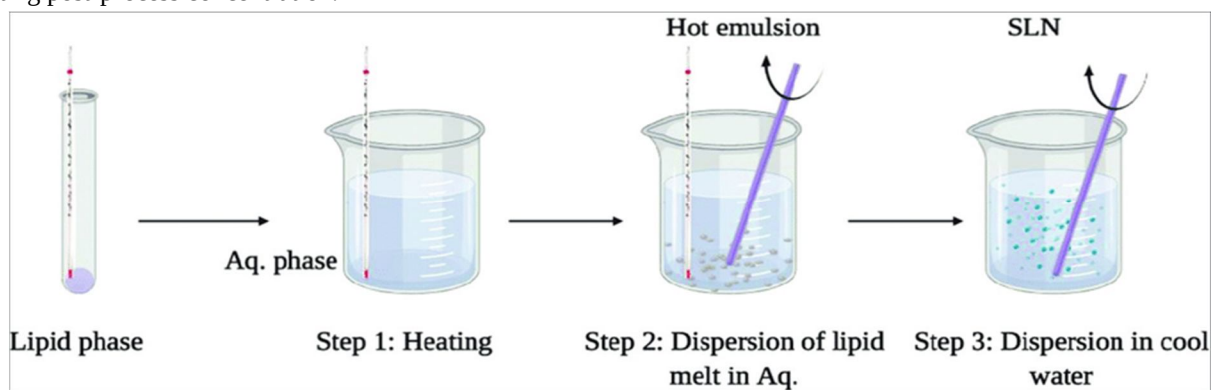


Figure 11: Microemulsion Technique

U. Emulsification–Solvent Evaporation

This method involves dissolving the medication and lipid in an organic solvent that is insoluble in water, such as dichloromethane, and then emulsifying the mixture into a water-based surfactant phase. Solid lipid nanoparticles are precipitated by solvent evaporation. One benefit is that it can be used with medications that are sensitive to heat. Limitations include reduced hydrophilic drug loading efficiency and the total elimination of organic solvents.³³

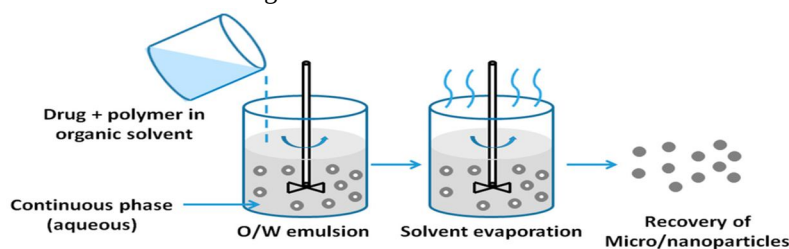


Figure 12: Emulsification–Solvent Evaporation

V. Solvent Diffusion Method

In order to produce lipid nanoparticles using the solvent diffusion approach, a solvent water-based emulsion containing the lipid must first be prepared. Water-miscible, low-toxicity solvents like butyl lactate or benzyl alcohol were employed. Dispersion of the organic solution causes droplets of the dispersed state to solidify as lipid nanoparticles when a temporary oil-in-water emulsion is transferred into water and continuously stirred.³⁴ Additionally, nearly 99.8% of the benzyl alcohol is removed from the suspension using ultrafiltration purification. This method was used by Trotta et al. to create SLNs utilizing glycerylmonostearate and various surfactant combination pairs. Lecithin, taurodeoxycholic acid sodium salt, and glycerylmonostearate (2%–5%) were employed to produce SLNs with average diameters of 320 nm for butyl lactate and 205 nm for benzyl alcohol (20). Clobetasol propionate was merged with monostearin SLNs using a new solvent diffusion technique. The medication and lipid were dissolved in ethanol and acetone at 50°C, and the resulting organic solution was then mixed with an acidic water-based solution (pH 1.1) with 1% polyvinyl alcohol while being vigorously stirred at room temperature. Centrifugation produced the drug-loaded SLNs fast and with ease.³⁵

W. Melt-emulsification and ultrasonication method

- 1) Lipid Phase Preparation: Melt the solid lipid (e.g., glyceryl monostearate) at 5–10 °C above its melting point. Dissolve the lipophilic drug in the molten lipid if drug loading is required.
- 2) Aqueous Phase Preparation: Heat an aqueous surfactant solution (e.g., Tween 80, Poloxamer) to at the exact temperatures as the phase of lipids.
- 3) Emulsification: Add the hot aqueous phase to the molten lipid phase under high-speed stirring (e.g., magnetic stirrer or homogenizer) to form a coarse pre-emulsion.
- 4) Ultrasonication: Subject the pre-emulsion to probe or bath ultrasonication for a specific time (e.g., 5–10 minutes) to reduce particle size and form a nanoemulsion.
- 5) Cooling and Solidification : Rapidly cool the nanoemulsion to room temperature or below, allowing the lipid to recrystallize and form solid lipid nanoparticles.^{36,37}

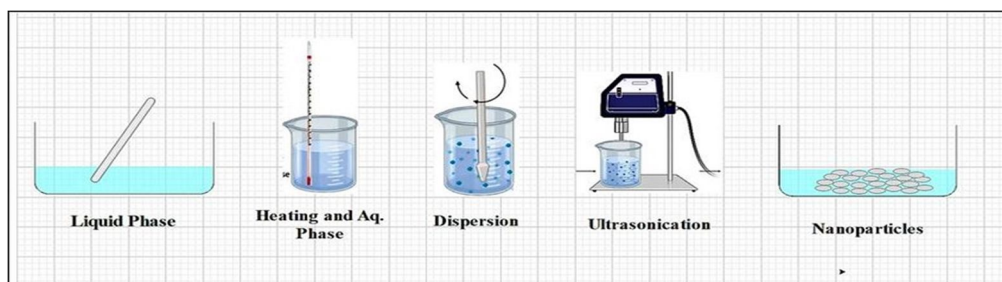


Figure 13: Melt-Emulsification And Ultrasonication Method

VII. CHARACTERIZATION OF LIPID BASED NANOCARRIERS

The evaluation involves various parameters, including vesicle size and shape distribution, zeta potential, vesicle morphology, vesicle concentration (number per cubic millimeter), entrapment efficiency, polydispersity index (PDI), skin permeability, and degree of deformability. These qualities are necessary for optimizing formulation stability, drug delivery efficacy, and batch-to-batch consistency.

A. Vesicle Size, Zeta Potential and Morphology

Vesicle size is a critical parameter during the preparation, scale-up, and storage, as it directly influences the physical stability and encapsulation efficiency of the formulation. Vesicles smaller than 40 nm tend to fuse easily due to high membrane curvature, whereas larger vesicles with neutral charge may come together via van der Waals forces because of increased membrane contact areas. The vesicle size also affects drug encapsulation: lipophilic and amphiphilic drugs generally require a higher lipid-to-core ratio, while hydrophilic drugs benefit from larger aqueous core volumes. Measurement of vesicle size is frequently carried out utilizing photon correlation spectroscopy (PCS) or dynamic light scattering (DLS), with samples typically diluted in distilled water or saline after filtration through a 0.2 µm membrane filter to ensure uniformity. The Malvern Zetasizer system is widely used to determine both vesicle size and zeta potential via electrophoretic mobility analysis. Transmission electron microscopy (TEM) or phase contrast microscopy are typically used for morphological analysis, which offers information on the shape and structural integrity of vesicles. These combined characterization techniques are vital for ensuring the reproducibility and performance of transferosomal formulations.³⁸

B. Number of Vesicles Per Cubic Millimeter

The quantification of vesicles per cubic millimeter is a key parameter for optimizing the formulation composition and processing conditions. To measure this, typically diluted fivefold using 0.9% sodium chloride solution. The diluted sample is then analyzed using a hemocytometer under an optical microscope. Transferosomes with vesicle sizes larger than 100 nm can be effectively visualized and counted using this method, enabling accurate assessment of vesicle concentration in the preparation.³⁹

The number of transfersomes in small squares are counted and calculated using the following formula:

Total number of transfersomes per cubic mm

= (Total number of transfersomes counted × dilution factor × 4000)/Total number of squares counted

C. Entrapment Efficiency (%EE)

Entrapment efficiency (%EE) refers to the proportion of the drug successfully encapsulated within the vesicles. To determine %EE, the free (unentrapped) drug is separated from the vesicle-bound drug using techniques such as mini-column centrifugation or ultracentrifugation. In the direct method, after ultracentrifugation, the drug's free-floating supernatant is extracted, and the sedimented vesicles are lysed using an appropriate solvent capable of disrupting the lipid bilayer. The lysate is then diluted and filtered through a syringe filter (0.22–0.45 μm) to eliminate impurities. The drug concentration in the filtered solution is quantified using analytical techniques tailored to the active pharmaceutical ingredient (API), such as modified high-performance liquid chromatography (HPLC) or UV-visible spectrophotometry.

% Entrapment efficiency = (Theoretical-Practical) / Theoretical drug content $\times$ 100

D. Degree of Deformability

The degree of deformability is a critical parameter influencing the permeation efficiency of formulations through the skin. The transferosome suspension is usually passed through micro pores with predetermined pore diameters ranging from 50 to 400 nm in order to assess this property. Dynamic light scattering (DLS) is used to determine the vesicle size and size distribution after each filtration stage in order to evaluate deformation-related changes. In this assay, pure water serves as the reference standard.

The degree of deformability (D) is calculated using the equation:

$$D = J(rv/rp)$$

where

- DD= degree of deformability,
- J= amount of suspension extruded within 5 minutes,
- rv = vesicle size, and
- rp = pore size of the membrane.

This parameter reflects the ability to squeeze through pores smaller than their own size, a key factor in their enhanced skin penetration.

E. Stability of Vesicles

The main way to assess vesicles' stability is to track how their size and structure change over time. Methods like Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS) are frequently employed to assess the average vesicle size and identify any structural changes, respectively. Optimized formulations are typically stored in tightly sealed amber vials under various temperature and humidity conditions to assess their stability. According to the International Conference on Harmonization (ICH) guidelines for stability testing of new drug substances and products, the recommended storage conditions are:

- Long-term storage: $25 \pm 2^\circ\text{C}$ with 60% relative humidity (RH) $\pm$ 5%, or $30 \pm 2^\circ\text{C}$ with 65% RH $\pm$ 5%, for a duration of 12 months.
- Accelerated stability testing: $40 \pm 2^\circ\text{C}$ with 75% RH $\pm$ 5% for six months.
- Refrigerated storage: $5 \pm 3^\circ\text{C}$ for 12 months, with an accelerated study at $25 \pm 2^\circ\text{C}$ and 60% RH $\pm$ 5% for six months.
- A notable alteration in the drug product is defined as a failure to meet its predetermined specifications during these stability studies.⁴⁰

F. Surface charge

The zeta potential, which was determined using Helmholtz-Smoluchowski from their electrophoretic mobility, served as the foundation for measuring surface charge. Zeta potential was measured using a zetasizer on a big bore measuring cell with an electromagnetic strength of 20 V/cm. Samples were diluted to attain a conductance of 50l S/cm using 0.9% NaCl.^{41,42}

G. pH measurement

A digital pH scale (Jyoti Laboratories) was used to measure the pH of a few improved formulations. The pH tester should be calibrated using buffer solutions with pH values of 4, 7, and 9 prior to each pH measurement. Following calibration, the electrode that was used was submerged in the vesicles for as long as they covered it. The chosen formulation's pH was then measured, and the results displayed on the screen were documented.⁴³

VIII. APPLICATIONS FOR LIPID BASED NANOCARRIERS

- 1) Enhanced skin penetration: Lipid carriers such as liposomes and ethosomes improve drug permeation through the stratum corneum, This makes them useful in the treatment of skin diseases including eczema and psoriasis.
- 2) Localized drug delivery for infections: Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are used to deliver antibiotics and antifungals directly to infected skin areas, reducing systemic exposure.⁴⁴
- 3) Wound healing and tissue regeneration: Lipid-based formulations promote healing by delivering anti-inflammatory agents and growth factors to wounds, accelerating repair and reducing scarring.
- 4) Transdermal delivery for systemic effects: Lipid vesicles like transferosomes enable drugs such as hormones and analgesics to reach systemic circulation through the skin, offering a non-invasive alternative to injections.⁴⁵
- 5) Cosmetic and anti-aging treatments: Lipid carriers deliver antioxidants, vitamins, and peptides to deeper skin layers, improving hydration, elasticity, and reducing signs of aging.
- 6) Topical chemotherapy: Lipid-based systems are being explored for delivering anticancer agents to skin tumors, allowing localized treatment with minimal systemic toxicity.
- 7) Vaccine delivery via skin: Emerging research supports Utilizing lipid vesicles for transcutaneous immunization, offering a needle-free route for vaccines.⁴⁶
- 8) Management of acne and follicular disorders: Lipid nanoparticles enhance drug deposition inside hair follicles, improving the action of retinoids and antimicrobials while minimizing surface irritation.⁴⁷
- 9) Topical antifungal therapy: SLNs/NLCs promote deeper and more sustained accumulation in the stratum corneum, improving treatment of superficial fungal infections.⁴⁸
- 10) Topical antioxidant and anti-ageing treatments: Lipid carriers protect unstable cosmetic actives and improve their passage through the skin barrier, enhancing anti-ageing and skin-repair outcomes.⁴⁹
- 11) Hyperpigmentation therapies: Lipid nanoparticles facilitate deeper targeting of melanocytes and improve the stability of depigmenting agents like kojic acid or arbutin.⁵⁰
- 12) Photoprotection and sunscreen enhancement: Nano emulsion and liposomal systems increase the uniform distribution of UV filters, improve photostability, and reduce the whitening effect.⁵¹
- 13) Localized immune modulation: Lipid vesicles can deliver immunomodulatory molecules to specific skin layers for conditions such as vitiligo or chronic inflammatory diseases. ⁵²
- 14) Topical enzyme-based treatments: Nanocarriers protect sensitive enzymes and assist in their controlled delivery for applications such as debridement or exfoliation. ⁵³
- 15) Pruritus management: Encapsulation of antipruritic agents improves their skin residence time and reduces systemic absorption, enhancing itch relief.⁵⁴

IX. CONCLUSION

Lipid nanoparticles represent a promising and versatile platform for transdermal drug delivery, offering distinct advantages over conventional topical formulations. Their small size, biocompatibility, and ability to encapsulate both hydrophilic and lipophilic compounds enable enhanced drug stability, controlled release, and improved penetration through the stratum corneum. Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and related lipid-based systems have demonstrated the capacity to overcome major barriers of the skin by modifying surface properties, optimizing lipid composition, and leveraging occlusive effects that enhance hydration and permeation. Despite these advances, several challenges remain, including long-term stability, large-scale production, variability in skin permeation, and the need for standardized evaluation methods. Continued research integrating advanced characterization techniques, innovative lipid materials, and in-vivo validation will be critical to translate these systems from laboratory research to clinical applications. Overall, lipid nanoparticles hold significant potential to transform transdermal therapy by enabling non-invasive, patient-friendly, and efficient drug administration.

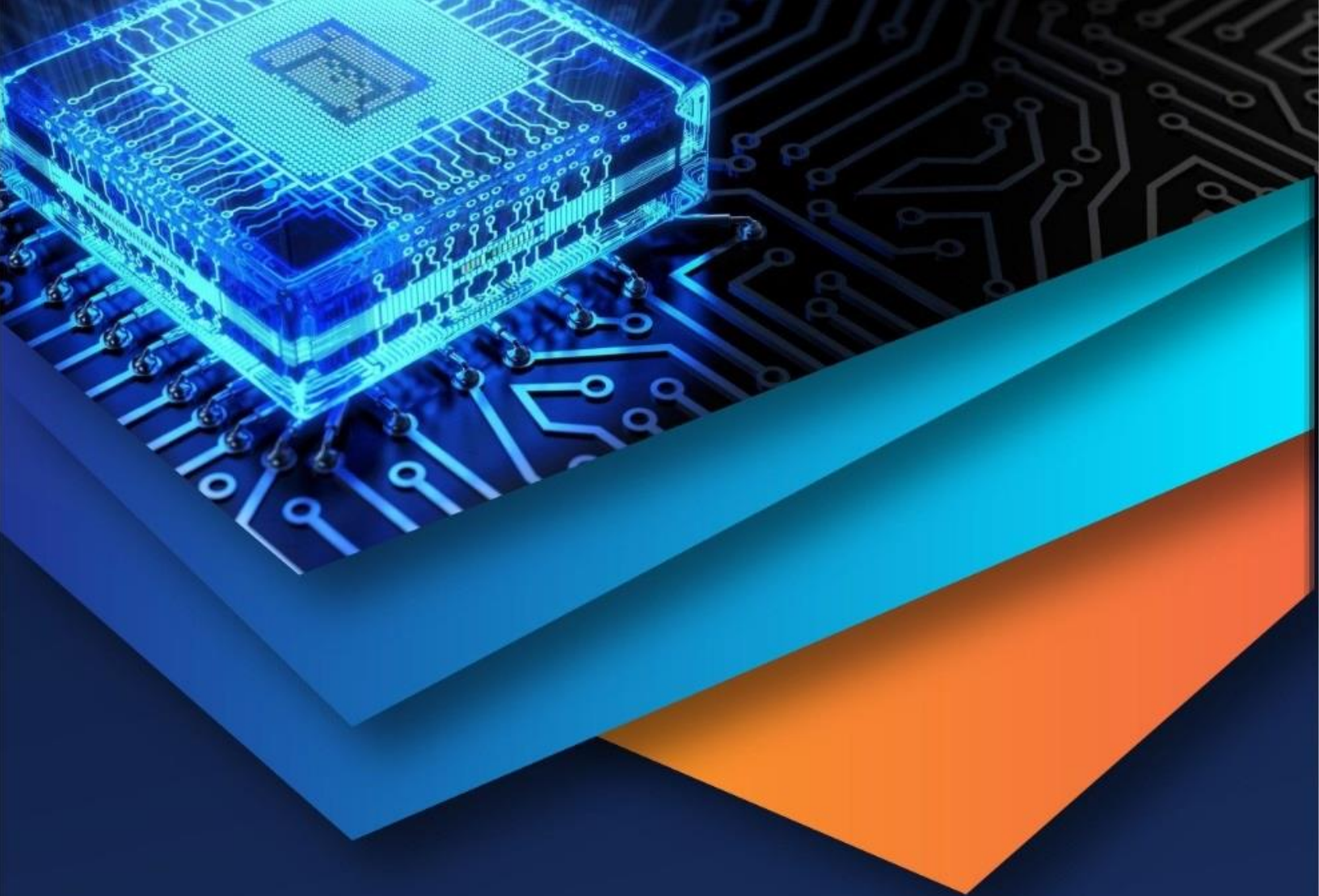
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