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Advances in Lipid Nanocarriers for Enhancing Oral Absorption of Poorly Soluble Drugs

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Abstract: Because of its affordability, patient compliance, and ease of administration, the oral route is the most popular way to administer medication. However, many medications' poor water solubility restricts their absorption and therapeutic efficacy. This problem is addressed by lipid-based systems such self-emulsifying drug delivery systems (SEDDS), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). These nano systems improve solubility and shield medications from gastrointestinal deterioration. By bypassing first-pass metabolism, they also enhance absorption via the lymphatic route. According to studies, SLNs offer gastrointestinal protection and sustained release. NLCs enhance controlled release, stability, and drug loading. SEDDS improve lymphatic absorption, systemic availability, and dissolution. Additionally, lipid nanocarriers enhance drug performance, circulation time, and tissue distribution. Despite these advantages, issues such excipient safety, large-scale production, and stability. Even with these benefits, there are still problems like stability, large-scale production, and the safety of excipients. Lipid nanocarriers are a promising way to deliver drugs that don't dissolve well in water. BCS Class II drugs don't dissolve well, so they don't get into the body very well. The prodrug method can make a drug more bioavailable, but it needs a lot of safety testing first. Marinization, nanosizing, crystal engineering, solid dispersions, and cyclodextrins are just a few of the other methods that are used. Lipid-based carriers like SLNs, NLCs, and lipid-polymer hybrid nanoparticles make things more soluble and easier to pass through. These systems let you control the release and delivery of drugs.

Keywords: *Solid Lipid Nanoparticles, Self- Emulsifying Drug Delivery System, Oral Drug Delivery, Nanostructured Lipid Carriers, Lipid.*

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I. INTRODUCTION

The oral drug delivery method is the best because it's easy for the patient to take and doesn't cost much. However, a significant challenge in modern pharmaceutics is that the aqueous solubility of the majority of therapeutic agents restricts their oral bioavailability and therapeutic efficacy.[1]

Drugs that don't dissolve well usually don't get absorbed well in the stomach, have a lot of first-pass metabolism, and have pharmacokinetics that are hard to predict. This makes it hard to get plasma levels that are stable. Conventional methodologies, such as particle size reduction, salt formation, and excipient dissolution, have proven inadequate in addressing these challenges.

Lipid-based nanocarriers, including SLNs, NLCs, and SEDDS, have emerged as the most promising approach to enhance the solubility, stability, and oral bioavailability of poorly soluble drugs. There are a lot of good things about lipid nanocarriers when it comes to delivering oral drugs. They can trap hydrophobic drugs in a biocompatible lipid, protect them from breaking down in the gut, and move them through the intestinal lymphatic system, which prevents first-pass metabolism.

LNCs can also provide sustained or controlled release, better pharmacokinetics, and targeted tissue distribution. Animal studies and preclinical research showed that the systems worked well to make drugs more bioavailable, speed up circulation, and improve their therapeutic effects. The feasibility, limitations, and mechanistic characteristics of lipid-based nanocarriers are crucial for successful translation into clinical settings.[2]

Oral route contributes to about 60% of drug administration is commercially available drugs. About 70% of the chemicals under investigation have poor solubility. Some drugs have low solubility, and they come under the second category of BCS, while others have a large first-pass effect. It is therefore important to increase the solubility and

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rate of dissolution of the drug, as it ultimately influences the oral bioavailability of the drug. [3]

Because of its ease of use and patient acceptability, oral delivery is one of the most conventional routes. However, because of the strong barriers posed by the GI tract, poorly soluble, poorly permeated, and poorly stable biological agents in the GI tract also have poor oral bioavailability and are not often used for oral drug delivery. [4]

The lipid nanocarriers have several advantages in the context of delivering oral drugs. They are able to entrap hydrophobic drugs into a biocompatible lipid, protect them from degradation by the gastrointestinal environment, and transport them across the intestinal lymphatic system thereby avoiding first-pass metabolism. In addition, LNCs are able to deliver sustained or controlled release, improved pharmacokinetics, and targeted tissue distribution.

The efficacy of the system in improving the bioavailability of drugs, the circulation time, and the therapeutics effects was adequately validated by animal studies and preclinical research. The feasibility, limitations, and mechanistic aspects of lipid based nanocarriers are thus significant in being successfully translated into clinical settings. [5]

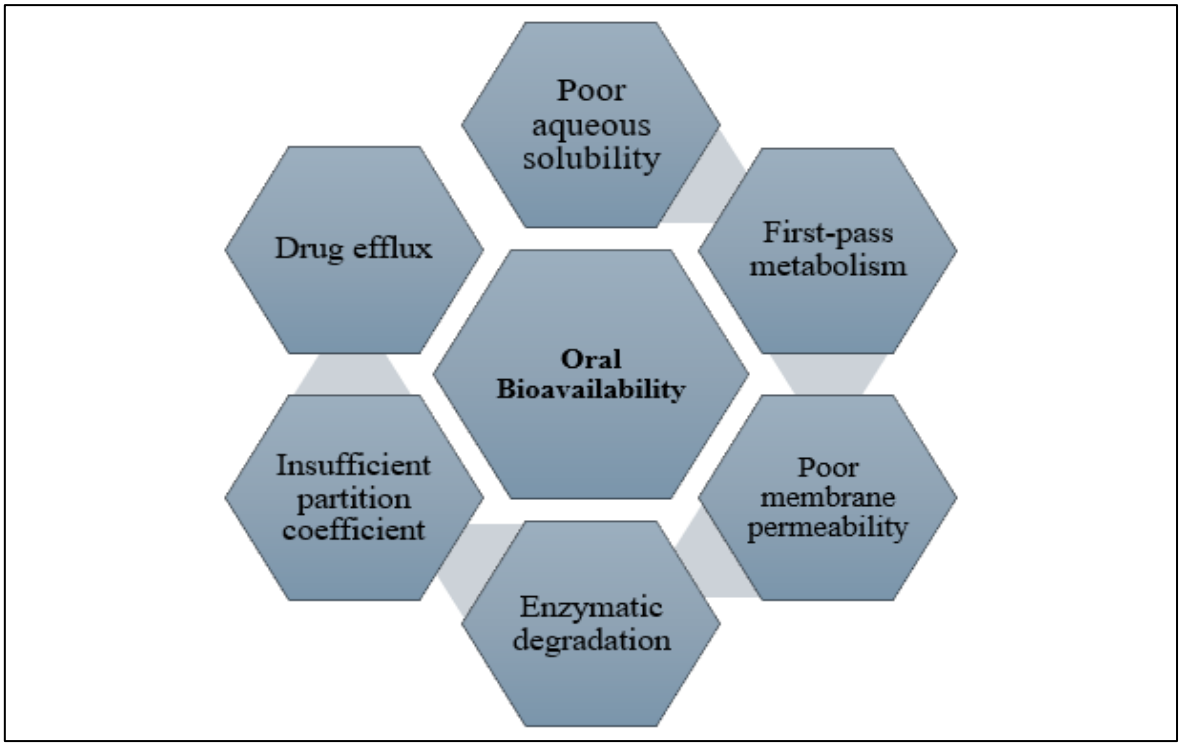

Fig 1 Factor Affecting Oral Bioavailability of the Poor Water-Soluble Drugs

II. POORLY SOLUBLE DRUGS

The development of formulations for poorly water-soluble drugs has been an issue of concern for pharmaceutical scientists all along and it is anticipated to grow more difficult in the future considering the fact that up to 40% or higher number of novel chemical entities discovered via drug discovery programs are poorly soluble in aqueous medium. The difficulty is further magnified when dealing with drugs like itraconazole and carbamazepine which are poorly soluble not only in aqueous media but also in organic solvents and those drugs whose log p (Logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is known as log P) value is 2. These drugs typically display highly unpredictable absorption patterns and inconsistent bioavailability due to being dissolution rate-limited in addition to being impacted by whether the patient has had food or is fasting. [6,7]

When the drug is delivered orally in a solid dosage form such as tablets or suspensions, it needs to be liberated from the dosage form and dissolve in the gastrointestinal fluids before absorption takes place. For most insoluble drugs, their bioavailability is restricted by the dissolution rate, which, in turn, is regulated by the surface area available for dissolution.

Two successive processes may be used to characterize the process of oral absorption of drugs from solid formulations:

- The dissolution of the drug within the body to generate a solution
- The movement of the dissolved drug through the gastrointestinal membrane.

The processes can each be described using the rate constant. If the rate of dissolution of the drug is much lower than that of the rate of absorption, then the dissolution of the drug becomes the rate limiting process in the absorption process. Consequently, numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption4.

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And the particle size of the drug in of great importance in the transport from the gastrointestinal (GI) tract to the site of action by increasing the dissolution rate in the GI tract [8]

III. LIPID NANOCARRIER

Lipid-based nanocarriers are a versatile and promising platform for gene therapy, drug delivery, and diagnostics. By encasing therapeutic compounds in naturally occurring lipids, these nanocarriers enhance stability, bioavailability, and targeting capabilities.

These modifications can enhance the nanocarriers' stability, targeting capacity, and overall efficacy.[9] Liposomes are made from phospholipids. Vesicle-based micelles are made of a single layer of phospholipids, with the head group facing the outside and the hydrophobic tails forming the micelle core in a hydrophilic environment, like blood, as opposed to liposomes, which are composed of phospholipid bilayers like cell membranes.[10]

The oral route is currently the most popular method of administering lipid colloidal particles due to its low cost and non-invasiveness, which boosts patient compliance and raises the possibility that it will be considered a potential therapeutic option. As was already indicated, the oral route of administration has presented a number of difficulties, the most of which can be resolved by employing lipid colloidal particles. Lipid colloidal particles are less poisonous, exhibit outstanding membrane permeability, and are more stable in the gastrointestinal environment. [11,12]

➢ *Advantages*

- Making bioactive chemicals more soluble.
- Transporting chemicals in large quantities.
- The biodegradability of the lipids used.
- Including hydrophilic and lipophilic biomolecules.
- Less expensive when compared to alternative delivery choices.
- An organic solvent-free method based on water.
- Extended and regulated release of bioactive compounds.
- Large production due to the ease of preparation.
- Precise particle size.
- Increased physical stability.[13]

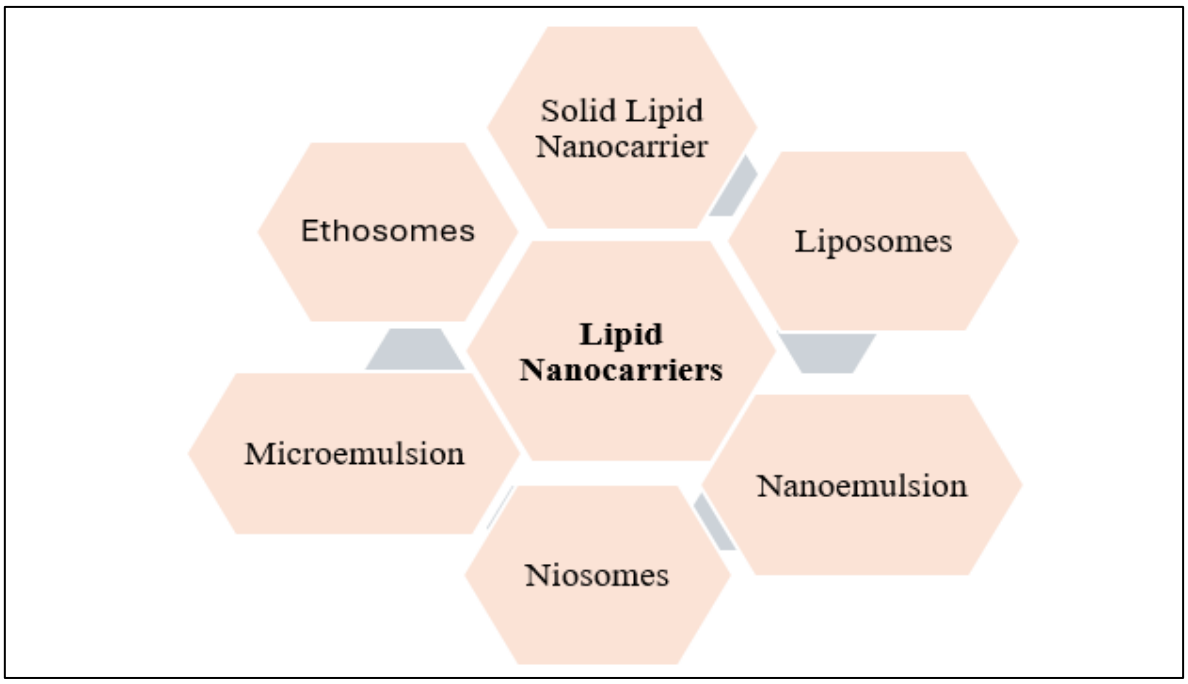

Fig 2 Lipid Nanocarriers

IV. SOLID LIPID NANOCARRIER

Lipid nanocarriers have surfaced in recent decades as possible carriers for getting over the current restrictions. The SLNs are nanoscale colloidal carriers mostly made of biocompatible lipids that are physiologically acceptable and distributed in a water-based surfactant solution.[14]

SLNs have dominated the drug and other payload delivery module market since their invention in 1991. SLNs are spherical in shape and have an average size range fluctuation of 10 to 1,000 nm.[15]

Solid lipid nanoparticles (SLNs), formerly known as lipospheres, are a possible kind of pharmacological nanocarrier designed for the controlled release of medications.[16] The benefits of polymer and lipid nanocarriers are integrated in SLNs. Their biocompatibility, biodegradability, medication stability in the gastrointestinal tract (GIT), and membrane penetration are all improved by the lipid component. While the loaded medication is shielded by the solid matrix and released gradually [17]

SLNs are a perfect option for oral medication delivery to improve therapeutic results because of these two characteristics. SLNs have been studied for oral, parenteral,

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transdermal, and ocular uses thus far. SLNs have been observed to improve drug solubility, membrane penetration, and oral bioavailability after oral delivery.[18]

A. Composition of SLNs

Lipid and stabilizers or surfactants make up the structural framework of SLNs. Additionally, SLNs were made using charge modifiers, co-surfactants/co-stabilizers, and preservatives. By lowering the interfacial tension between the hydrophobic lipid surface and the aqueous surface, the surfactants aid in stabilizing the SLN formulations.[19]

Beeswax, stearic acid, cholesterol, caprylic/capric triglyceride, acetyl palmitate, glyceryl stearate (mono and tri), glyceryl Tri laurate, glyceryl Tri myristate, glyceryl behenate (Comprisal), glyceryl tripalmitate, monostearate mononitrate, solid paraffin, and behenic acid are among the lipids utilized for SLNs. Phosphatidylcholine, soy and egg lecithin, poloxamer, polo amine, and polysorbate 80 are the surfactants utilized in the SLN formulations.

Tyloxapol, sodium oleate, sodium dodecyl sulphate, taurocholate sodium salt, sodium glycocholate, and butanol are the co-surfactants utilized. Gelatine, glucose, mannose, maltose, lactose, sorbitol, mannitol, glycine, polyvinyl alcohol, and polyvinyl pyrrolidone are employed as cryoprotectants. Additionally, stearyl amine, demystify phosphatidylglycerol, diacetyl phosphate, and dipalmitoyl phosphatidylcholine are charge modifiers used to create SLNs with desirable characteristics.[20]

B. Absorption Mechanism of SLNs

The drug's absorption from the GIT after oral administration involves multiple transport mechanisms.[21]

Research has indicated that there are two possible pathways for the uptake of NPs: intracellular uptake via the gut's M-cells and intercellular or paracellular uptake [22]

Additionally, the absorption of SLNs is further increased by lipase-mediated chylomicron production. When the medication is substantially transferred to the systemic circulation via the intestinal lymphatic system, the M-cell uptake is size-dependent. As SLN size decreases, the uptake rises.[23]

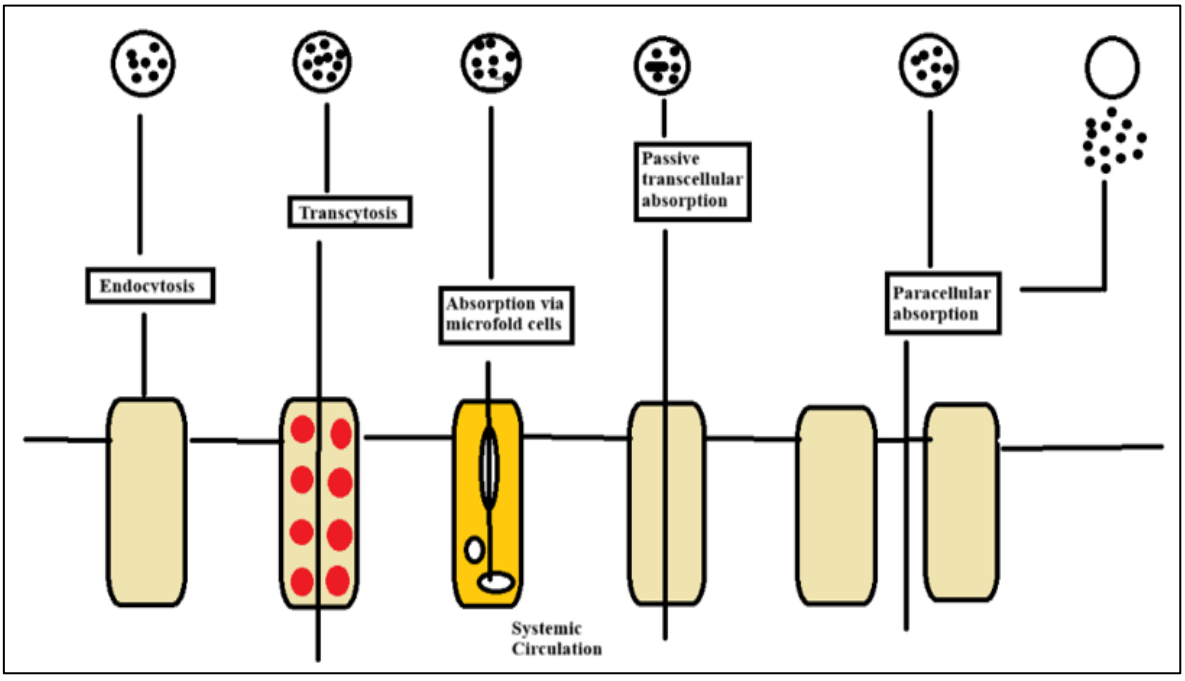

Fig 3 Absorption Mechanism of SLNs

C. Formulation Methods of SLNs

➢ *Homogenization at High Pressure*

For the preparation of SLN, high-pressure homogenization (HPH) has been a dependable method. Homogenizers of various sizes are produced at affordable prices by a number of firms. At high shear stress and cavitation compulsion, submicron-sized particles are produced. HPH produces nano emulsions for parenteral feeding. HPH forces the liquid through a small area (range of a few microns) at high pressures (100–2,000 bar). The fluid travels at a high velocity over a short distance. Even high lipid concentrations could be converted into nano dispersions using homogenization [24]

➢ *Types of Homogenizations at High Pressure*

- *Hot Homogenization*

For this technique, temperatures above the lipid's melting point are chosen; this can therefore be regarded as the homogenization of an emulsion. Lipid and medication are combined at the same temperature using an aqueous surfactant. An oil-in-water emulsion is produced by heating a pre-emulsion using a high shear mixing apparatus. The

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product is then allowed to cool, which causes the production of SLNs and the beginning of lipid crystals. Three to five homogenization cycles at 500–1,500 bar are required to produce flawless SLNs. [25]

- *Mechanism*

✓ *Lipid Melting and Drug Incorporation*

- The solid lipid is melted about 5-10 degree Celsius above its melting point, and the drug is dissolved or dispersed in this molten lipid.

✓ *Formation of Hot Pre-emulsion*

- Aqueous surfactant solution is heated to the same temperature as the lipid phase.
- The molten drug-lipid phase is dispersed into this hot surfactant solution by high-speed or high-shear mixing to form a coarse O/W emulsion.

✓ *High Pressure/ High-Shear Homogenization*

- The pre-emulsion is further processed either by high-pressure homogenization or intense shear/ ultrasonication to reduce droplet size into the nanometre range.
- High temperature lowers viscosity and promotes droplet breakup, giving smaller particles.

✓ *Cooling and Solidification*

- The hot O/W nano emulsion is cooled to room or lower temperature; the lipid phase recrystallizes, turning lipid droplets into solid lipid nanoparticles.
- Cooling rate affects polymorphism, stability, and final particle size; overly rapid cooling can deteriorate product quality. [26]

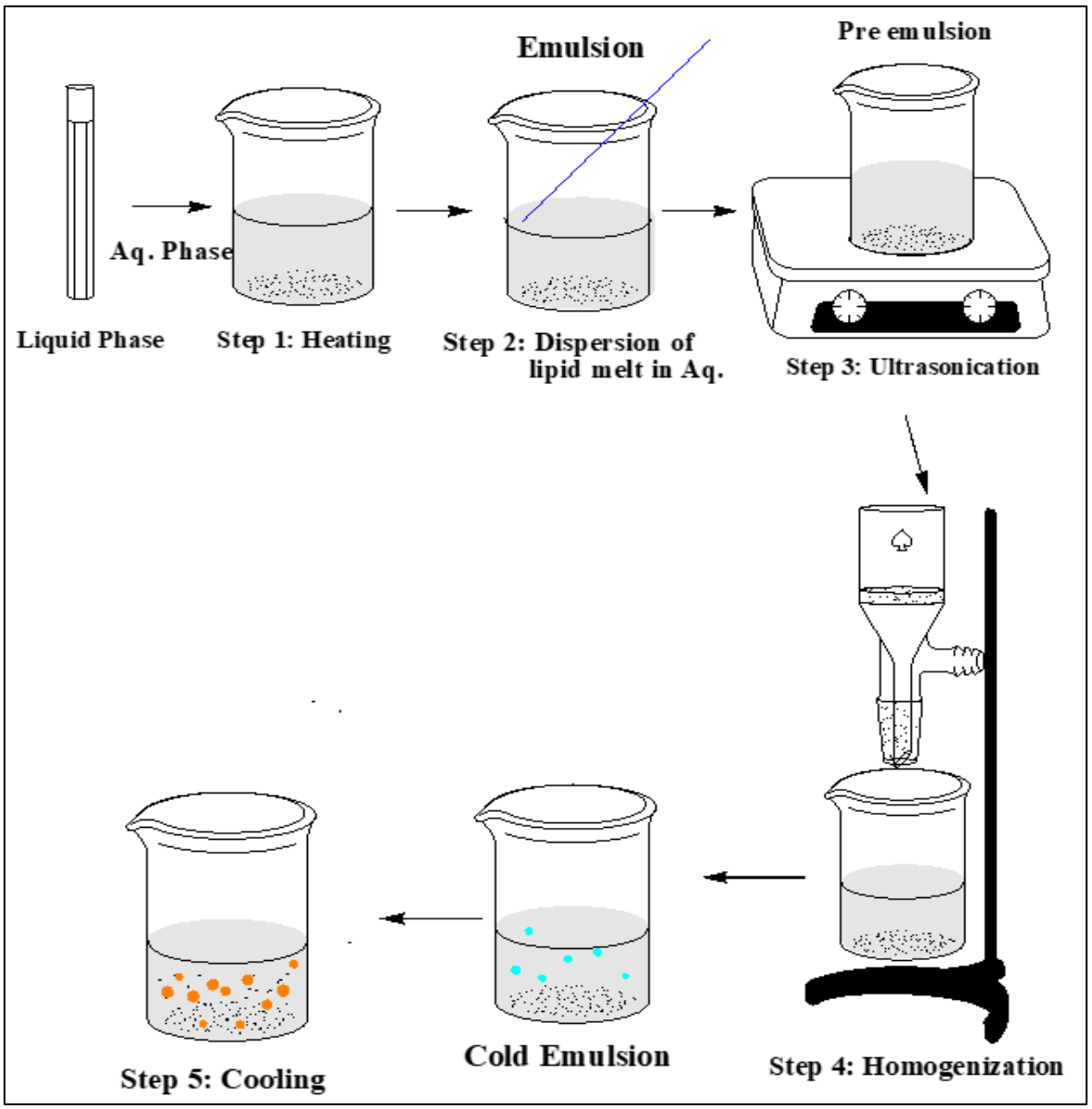

Fig 4 Hot Homogenization Technique

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- *Cold Homogenization*

This method was created to address the issues with hot homogenization, including drug loss during homogenization into the aqueous phase, faster deterioration owing to high temperatures, and unknown polymorphic changes of the lipid because of the intricacy of crystallization. The first basic stage, which involves the drug's solubilization in the lipid melt, is identical to the hot homogenization procedure. The subsequent procedures are changed; in order to achieve a uniform drug distribution lipid matrix, the drug-containing melt is quickly chilled with the help of liquid nitrogen or solid carbon dioxide. A ball mill is then used to levigate the solid into a fine dust. The typical dust size that is reached is between 50 and 100 μm.[27]

- *Mechanism*

✓ *Drug Incorporation into Molten Lipid*

- The drug is dissolved, dispersed, or solubilized in a melted lipid

✓ *Rapid Solidification*

- The drug-lipid melt is rapidly cooled with liquid nitrogen or dry ice, forming a solid mass with the drug homogeneously distributed in the lipid matrix.
- Fast cooling helps “freeze in” a uniform drug distribution.

✓ *Micronization of Solid Lipid*

- The solidified drug-lipid mass is ground or milled to obtain lipid microparticles or about 50-100 micrometre.

✓ *Formation of cold pre-suspension*

- These microparticles are dispersed in a cold aqueous surfactant solution, producing a coarse pre-suspension of micronized lipid in water.

✓ *High-Pressure Cold Homogenization*

- The pre-suspension is passed through a high-pressure homogenizer at low temperature
- Mechanical forces break the micronized lipid particles down to the nanometre range, yielding SLNs with the lipid still in a solid state [28]

➢ *Micro-Emulsion Technology*

Gasco and associates created SLN preparations by lowering the concentration of microemulsions. [27] These microemulsions are biphasic units composed of exterior and interior media. Combination consists of a low melting fatty acid (e.g., stearic acid), an emulsifier (e.g., polysorbate 20, polysorbate 60, and soy phosphatidylcholine), coemulsifiers (e.g., butanol and sodium mono cetyl phosphate), and water. In the chilly water (2°C–3°C), the heated microemulsion is spread. The dilution process can be fixed based on the microemulsion combination. This technique uses no additional energy to achieve the submicron size. [29]

- *Mechanism*

✓ *Formation of Hot Microemulsion*

- A solid lipid is melted above its melting point and mixed with water, surfactant and co-surfactant at the same temperature to form a transparent O/W microemulsion.
- Pseudo ternary phase diagrams are often used to find the composition range where clear microemulsion form.

✓ *Nanodroplet Template*

- In the microemulsion, the lipid exists as nanoscopic liquid oil domains dispersed in water; this droplet size and stability are governed by surfactant/ co-surfactant ratio and lipid type.

✓ *Quenching/Dilution and Solidification*

- *Hot Microemulsion Dilution*

✓ The hot microemulsion is rapidly dispersed into excess cold water under mild stirring.
✓ Sudden temperature drop causes the lipid droplets to precipitate and recrystallize, turning each nanodroplet into an SLNs of similar size.

- *Cold Dilution of Microemulsion*

✓ A microemulsion is made using a solid lipid dissolved in a partially water-miscible solvent as the oil phase.
✓ On dilution with water, the solvent diffuses out; the lipid loses solubility and precipitates as solid nanoparticles.

✓ *Resulting SLN properties*

- Final particle size and polydispersity depend on:
- Microemulsion structure and droplet size
- Lipid chemistry
- Surfactant/ co-surfactant system
- Dilution ratio and cooling rate [30]

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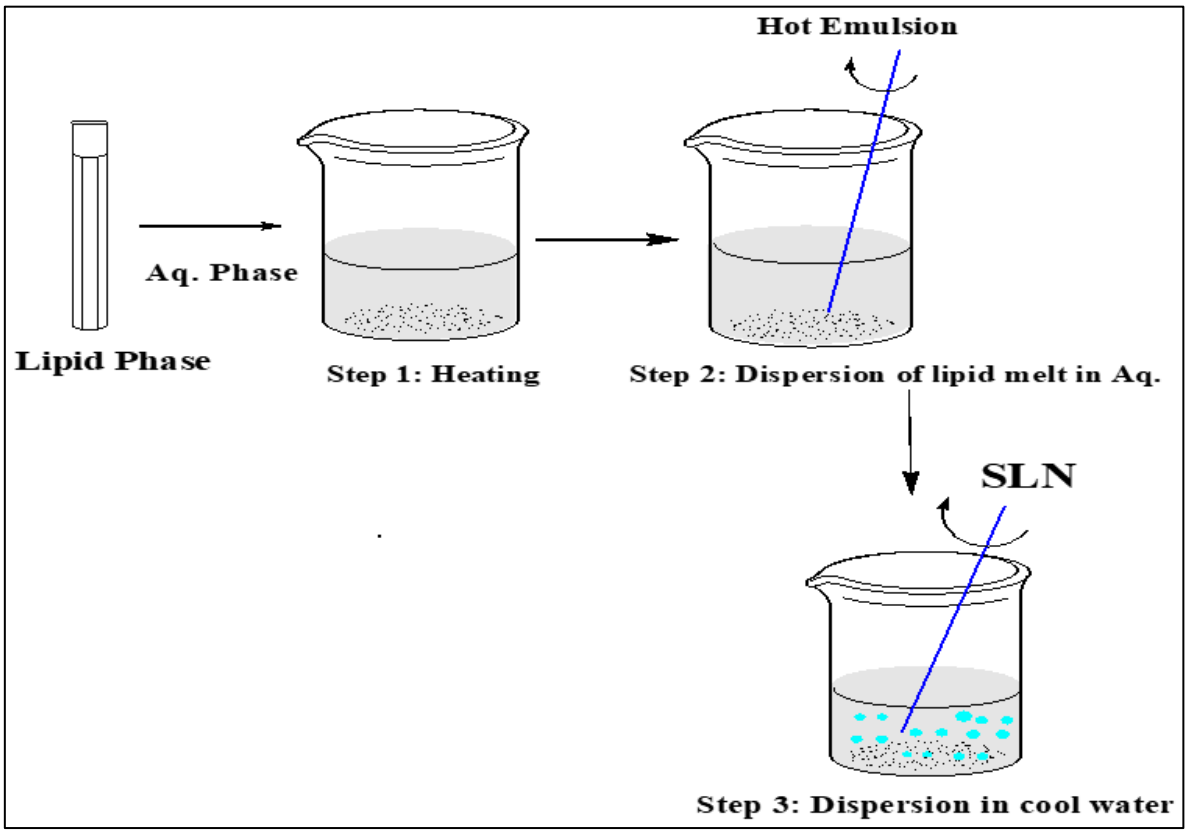

Fig 5 Micro-Emulsion Technology

➢ *Membrane Contactor Method*

In this technique, a particular membrane contactor is employed for the preparation of SLNs and NLCs. In this process, a lipid phase is forced through the membrane pores at a temperature above the melting point of the solid lipid. This process leads to the formation of small droplets. Simultaneously, an aqueous phase with surfactants is circulated on the other side of the membrane in a module. The aqueous phase flows tangentially along the membrane surface and removes the droplets formed at the pore outlets. SLNs and NLCs are prepared by allowing the hot emulsion to cool to room temperature. [31]

- *Mechanism*

✓ *Preparation of Phases*

- Lipid phase: Solid lipid is melted above its melting point.
- Aqueous phase: Surfactant solution is prepared and circulated through the membrane module, usually at or near the lipid melting temperature.

✓ *Droplet Generation at the Membrane*

- The molten lipid phase is pressed through porous membranes under controlled pressure.
- At each pore outlet, uniform lipid droplets are formed on the membrane surface.
- The flowing aqueous phase sweeps away these droplets, creating an oil-in-water nano emulsion whose droplet size is mainly governed by pore size, transmembrane pressure, and cross-flow velocity.

✓ *Solidification into SLNs*

- The nano emulsion is then cooled below the lipid melting point, so droplets crystallize into solid lipid nanoparticles. [32]

➢ *Ultrasonication*

Additionally, SLN was generated by sonication or high-speed stirring. This method's obstacles are common in all laboratories. The primary cause of physical instability with this technique is its wider particle size distribution, which extends into the micro meter range. Potential metal decay and particle gain during storage are serious issues with this approach. It was demonstrated after extensive investigation that high-speed stirring and ultrasonication, when used in tandem at high temperatures, produce a stable formulation. [33]

- *Mechanism*

✓ *Melt and Emulsify*

- Solid lipid is heated above its melting point.
- Aqueous surfactant solution is heated to the same temperature and mixed with the molten lipid to form a coarse emulsion.

✓ *Ultrasonication Nano Emulsification*

- The coarse emulsion is exposed to probe or bath ultrasonication at controlled power, pulse and time.

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- Ultrasound generates acoustic cavitation: formation, growth, and collapse of microbubbles, producing intense local shear, microjets and turbulence that:

- Break coarse droplets into nanodroplets
- Disrupt aggregates and narrow the size distribution.

✓ *Cooling and Solidification*

- The hot nano emulsion is rapidly dispersed into cold water or cooled in an ice bath to solidify the lipid droplets, yielding SLNs. [34]

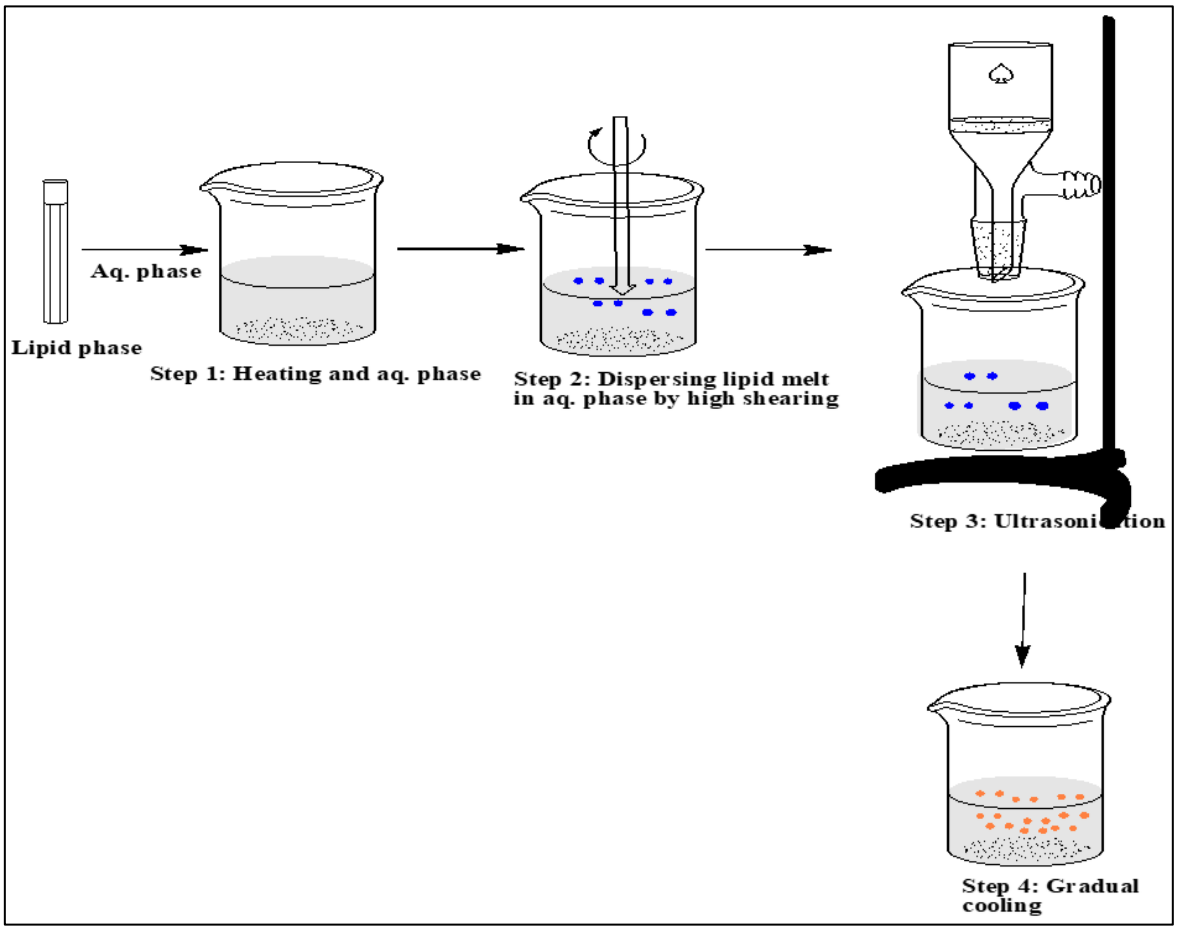

Fig 6 Ultrasonication Method

➢ *Spray Drying Technique*

It is an alternative process to lyophilization for turning an aqueous dispersion into a medication. Compared to lyophilization, this process is more cost-effective. Because of the high temperature, shear forces, and partial particle melting, there is a possibility of particle accumulation. [35]

It is advised that lipids having a boiling point greater than 70°C be chosen for spray drying. Spray drying with an SLN concentration of 1% in a trehalose solution in water or 20% in ethanol–water mixtures (10/90 v/v) produced the greatest results. [36]

➢ *Double emulsion method*

This technique, which is based on solvent emulsification–evaporation, is used to create hydrophilic loaded SLNs. The medication is dissolved in a liquid melt after first being dissolved in aqueous-based solutions. The primary emulsion is stabilized using a stabilizer. [37]

The water/oil/water (w/o/w) emulsion is created by dispersing these primary emulsions in an aqueous phase that contains a hydrophilic emulsifier. Lipid precipitation results in SLNs and NLCs dispersions following solvent evaporation. [38]

- *Mechanism*

✓ *Primary W/O Emulsion*

- Drug solution is emulsified into a melted lipid or lipid + organic solvent phase containing lipophilic surfactant, forming water-in-oil droplets.

✓ *Secondary W/O/W Emulsion*

- This W/O emulsion is then dispersed into an external aqueous phase with hydrophilic surfactant, forming water-in-oil-in-water double emulsion droplets.
- Hydrophilic drugs or proteins remain mainly in the internal water droplets protected by the surrounding lipid layer.

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✓ *Solidification of the Lipid Phase*

- Solvent evaporation or cooling of molten lipid removes the organic solvent and lowers temperature, causing lipid crystallization around the inner droplets and forming solid lipid nanoparticles.
- The result is SLNs where hydrophilic or lipid-insoluble drug is entrapped in inner aqueous pockets within a solid lipid matrix. [39]

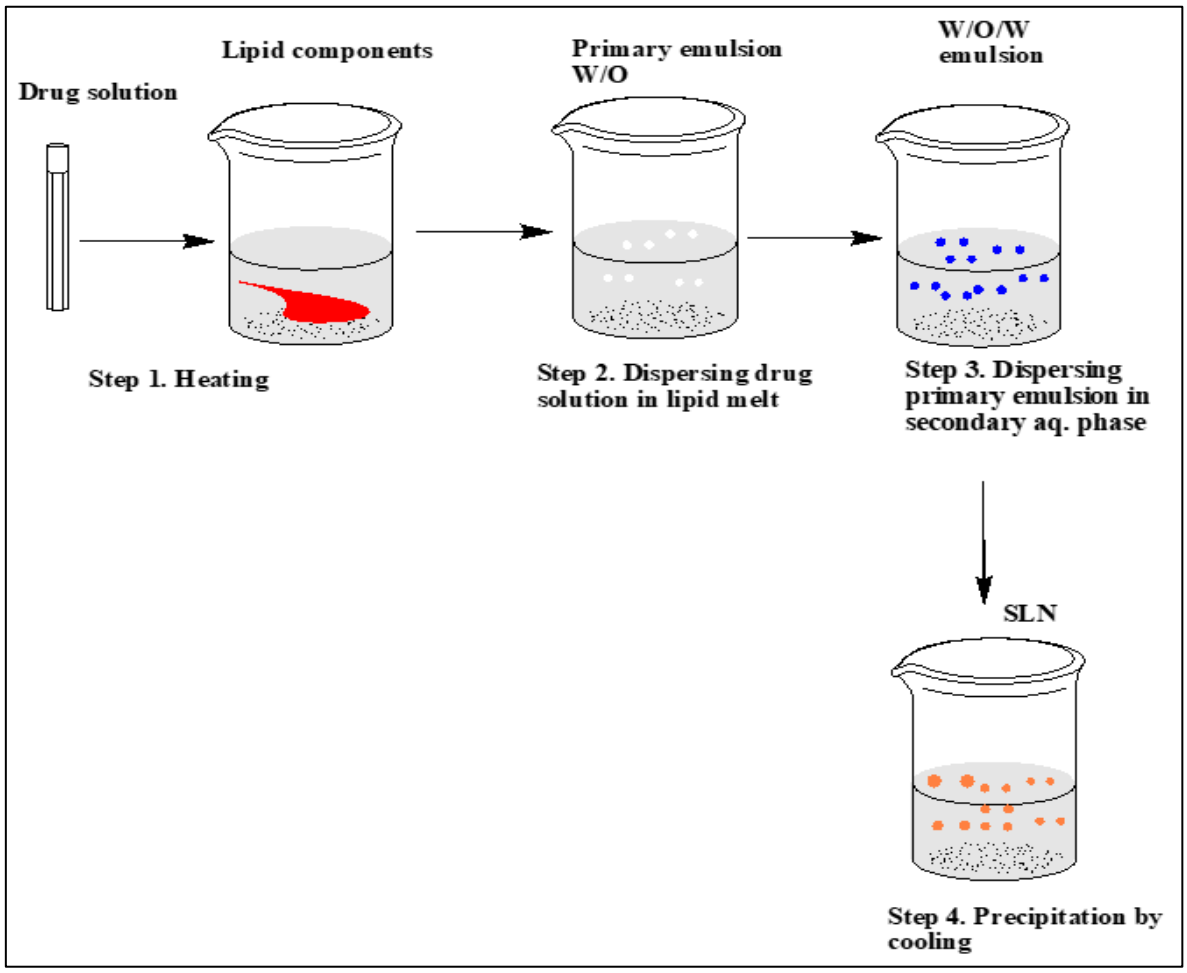

Fig 7 Double Emulsion Method

➢ *Super Crystal Fluid Method*

Supercritical fluids, such as supercritical CO2, were used in a number of SLN and NLC production processes. An o/w emulsion is made first, and then the organic solvent is super critically fluid extracted using the supercritical fluid extraction of emulsions (SFEE) method. In an extraction column, the emulsion is usually poured from the top, while supercritical CO2 is fed from the bottom in a counter-current fashion. Compared to other techniques that include evaporation, diffusion, and dilution, SFEE offers a substantially higher solvent extraction efficiency. Lipid precipitation results from the rapid and total removal of the solvent. Additionally, the resulting SLNs and NLCs have a consistent particle size distribution. [37]

- *Mechanism*

✓ *Supercritical Assisted Injection in a Lipid Antisolvent*

- Step 1- Expanded liquid formation: Lipid is dissolved in an organic solvent. CO_2 is dissolved into this solution under pressure, forming an expanded liquid with lower viscosity and surface tension.
- Step 2- Atomization into antisolvent: The expanded liquid is atomized through a nozzle into an aqueous surfactant solution, which acts as liquid antisolvent.
- Step 3- Supersaturation and Precipitation: On contact, solvent diffuses into water, lipids lose solubility, and rapid supersaturation causes nucleation and growth of solid lipid nanoparticles.
- Step 4- Stabilization: Surfactant adsorbs on nuclei, stopping growth and aggregation; stable SLN suspensions are obtained.

✓ *Supercritical Fluid Extraction of Emulsions*

- Step 1- Make o/w emulsion: Lipid + drug in organic solvent are emulsified into water to form an oil-in-water emulsion.
- Step 2- Contact with SC CO_2: The emulsion flows through an extraction column where SC CO_2 selectively extracts the organic solvent.

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- Step 3- Rapid solvent removal: Fast solvent extraction around droplets produces local supersaturation of lipid and drug, leading to solidification into SLNs, often<30 nm.
- Step 4- Output: Aqueous nanosuspension with very low residual solvent.

✓ *Rapid Expansion of Supercritical Solutions and Related*

- Step 1- Dissolution in SCF: Lipid are dissolved directly in SC CO_2 under high pressure.
- Step 2- Rapid expansion: The SC solution is expanded through a nozzle into low pressure; CO_2 loses density and solvating power, giving instantaneous supersaturation and precipitation of solid lipid. [40]

➢ *Solvent Emulsification Diffusion Method*

Polymeric nano-carriers are mostly made via the solvent emulsification-diffusion process. Trotta et al. initially produced SLNs and NLCs using this method in 2003. Organic solvents like methyl acetate, ethyl acetate, isopropyl acetate, benzyl alcohol, and butyl lactate that are slightly miscible with water are typically used in this procedure. To achieve the initial thermodynamic equilibrium of both phases, the organic solvent and water are first mutually saturated. To create an o/w emulsion, lipids and medications are dissolved in the water-saturated solvent, which is subsequently emulsified in the aqueous phase (solvent-saturated water with stabilizer) while being stirred. [41]

- *Mechanism*

✓ *Phase Preparation and Mutual Saturation*

- A partially water-miscible organic solvent is first saturated with water, and the aqueous phase is saturated with the solvent to reach thermodynamic equilibrium.
- The lipid and drug are dissolved in the water-saturated solvent
- The external phase is an aqueous solution of surfactant/ stabilizer also saturated with solvent.

✓ *Emulsification*

- The organic phase is emulsified into the aqueous surfactant phase using stirring or homogenization, forming an oil-in-water emulsion of solvent-lipid droplets.

✓ *Solvent Diffusion and Droplet Shrinkage*

- The emulsion is diluted with additional water.
- This creates a concentration gradient, so the organic solvent diffuses from internal droplets into the continuous aqueous phase.
- As solvent leaves the droplets, they shrink and become enriched in lipid, and their interfacial area changes; surfactant stabilizes these shrinking nanodroplets.

✓ *Lipid Precipitation and Nanoparticle Solidification*

- Continued solvent diffusion leads to supersaturation of lipid inside droplets, causing lipid crystallization/ precipitation in nanoparticulate form.
- The result is solid lipid nanoparticles dispersed in water, stabilized by surfactant.

✓ *Solvent Removal and Post-Processing*

- Residual solvent is removed to obtain a purified SLN dispersed or dry product [39]

Table 1 Formulation Composition of SLNs

Drug	Method	Lipid/ polymer	Excipients	Reference
Curcumin	Hot Homogenization	Glyceryl monostearate	Chitosan	[42]
Ibuprofen	Hot Homogenization	Stearic acid	PEG	[43]
Camptothecin	Hot Homogenization	Stearic acid	Soya lecithin, Poloxamer 188	[44]
Docetaxel	Cold Homogenization	Compritol 888 ATO	Poloxamper 407	[45]
Simvastatin	Cold Homogenization	Glyceryl monostearate	Tween 80	[46]
Cyclosporine A	Microemulsion	Medium-chain triglycerides	Tween 80	[47]
Paclitaxel	Microemulsion	Caprylic triglycerides	Cremophor EL	[48]
Fenofibrate	Membrane contactor	Cetyl palmitate	Poloxamer 188	[49]
Ketoprofen	Membrane contactor	GMS	Tween 80	[50]
Quercetin	Ultrasonication	Compritol 888 ATO	Poloxamer 407	[51]
Diclofenac	Ultrasonication	Chitosan	Tween 80	[52]
Atorvastatin	Spray drying	HPMC	PEG 400	[53]
Celecoxib	Spray drying	PVP K30	Tween 80	[54]
Ketoconazole	Double emulsion	PLGA	Tween 80	[55]
Rifampicin	Double emulsion	PLGA	PVA	[56]

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Tamoxifen	Super crystal fluid	HPMC	PEG 400	[57]
Nimodipine	Super crystal fluid	HPMC	PEG 400	[58]
Clozapine	Solvent emulsification diffusion	Eudragit RS 100	PVA	[59]
Glibenclamide	Solvent emulsification diffusion	Ethyl cellulose	Tween 80	[60]

Table 2 Evaluation Parameter of Formulation Composition of SLNs

Drug	Method	Particle size	Entrapment efficiency	Drug release	Disintegration	Ref.
Curcumin	Hot Homogenization	100-220nm	85-95	Sustained	Fast	[42]
Ibuprofen	Hot Homogenization	150-300nm	60-80	Controlled	Fast	[43]
Camptothecin	Hot Homogenization	150-250nm	70-85	Sustained	Fast	[44]
Docetaxel	Cold Homogenization	150-250nm	90-98	Controlled	Stable due to high lipid crystallinity	[45]
Simvastatin	Cold Homogenization	80-200nm	70-90	Sustained	Fast disintegration in GI improves absorption	[46]
Cyclosporine A	Microemulsion	20-80nm	75-90	Sustained	Fast	[47]
Paclitaxel	Microemulsion	10-80nm	85-95	Sustained	Slow	[48]
Fenofibrate	Membrane contactor	120-220nm	~85	Sustained	Fast	[49]
Ketoprofen	Membrane contactor	180-320nm	~70	Sustained	Moderate	[50]
Quercetin	Ultrasonication	90-200nm	80-95	Controlled	Good stability	[51]
Diclofenac	Ultrasonication	100-250nm	65-85	Controlled	Fast	[52]
Atorvastatin	Spray drying	1-5 micro meter	~85	Sustained	Fast	[53]
Celecoxib	Spray drying	2-8 micro meter	~80	Fast dissolution	Fast	[54]
Ketoconazole	Double emulsion	200-350nm	~85	Sustained	Moderate	[55]
Rifampicin	Double emulsion	200-400nm	~75	Sustained	Moderate	[56]
Tamoxifen	Super crystal fluid	1-5 micro meter	~80	Controlled	Moderate	[57]
Nimodipine	Super crystal fluid	500nm-2 micro meter	~80	Sustained	Fast	[58]
Clozapine	Solvent emulsification diffusion	200-350nm	~75	Sustained	Moderate	[59]
Glibenclamide	Solvent emulsification diffusion	150-300nm	~85	Sustained	Fast	[60]

V. LIPOSOMES

Since Alec Bangham discovered liposomes in 1964, they have proven to be revolutionary medication delivery technologies. These spherical vesicles, which are made up of one or more phospholipid bilayers, are attractive candidates for drug delivery applications because of their striking structural resemblance to real cell membranes. [61]

Because phospholipids are amphipathic, they can form closed bilayer structures in aqueous settings, forming separate hydrophilic and hydrophobic compartments inside a single vesicular system. [62]

Liposomes' structure makes it possible to encapsulate medicinal substances with different physicochemical characteristics. Lipophilic substances incorporate into the phospholipid bilayer, whereas hydrophilic medicines are confined inside the aqueous core. Liposomes are better drug carriers than traditional delivery methods because of their dual encapsulation capability, biocompatibility, and biodegradability. [63]

A. Formulation Methods of Liposomes

- *Thin Film Hydration Method*

The fundamental method for preparing liposomes is the Bangham method. Phospholipids and cholesterol are dissolved in organic solvents (usually a 2:1 ratio of chloroform to methanol) and then evaporated under low pressure. At a temperature higher than the lipid phase transition temperature, the resulting thin lipid layer is hydrated using an aqueous buffer. Multilamellar vesicles (MLVs) with diameters between 400 and 3500 nm are produced by this technique. [64]

Depending on the drug's physicochemical characteristics, the encapsulation efficiency varies greatly;

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for hydrophilic molecules, it usually reaches 5–15%, whereas for lipophilic pharmaceuticals, it can reach 80%. [65]

- *Mechanism*

✓ *Thin Lipid Film Creation*

- Lipids are dissolved in an organic solvent, spread in a round-bottom flask or vial, then solvent is removed under vacuum, leaving a dry, thin lipid layer on the surface.
- Film properties depend on solvent, rotation speed, and vacuum, which strongly affect later vesicle size and homogeneity.

✓ *Hydration and Self-Assembly*

- An aqueous medium is added and the film is agitated above the lipid transition temperature.
- Water penetrates and swells stacked bilayers; entropically favored self-assembly drives rearrangement of amphiphiles into closed bilayer structures to minimize edge energy, forming multilamellar vesicles.
- Hydrophilic cargos are passively entrapped in the aqueous core/ lamellae; hydrophobic cargos reside in the lipid region. [66]

➢ *Reverse Phase Evaporation Method*

Large unilamellar vesicles (LUVs) with up to 65% encapsulation efficiency for hydrophilic substances are produced using this method. The drug-containing aqueous phase and the phospholipid-containing organic phase combine to generate a water-in-oil emulsion. Lipid-stabilized water droplets burst into vesicles when the organic solvent is subsequently removed under lower pressure. The generated LUVs usually have a diameter of 200–500 nm. [67]

- *Mechanism*

✓ *Dissolve Lipids in Organic Solvent*

- Phospholipids are dissolved in diethyl/ isopropyl ether, chloroform-ether, or similar solvents in a round-bottom flask.

✓ *Remove Solvent Dry Lipid Film*

- Rotary evaporation under reduced pressure forms a thin lipid film; nitrogen purging removes residual solvent.

✓ *Redissolve Lipids in Organic Phase*

- Lipid film is redissolved in ether or ether-chloroform mixtures to form a homogeneous organic phase.

✓ *Add Aqueous Phase Water-in-Oil Emulsion*

- Asmall volume of aqueous phase is added; the two-phase system is sonicated or stirred to form inverted micelles or a stable water-in-oil emulsion.

✓ *Slow Solvent Evaporation Under Reduced Pressure*

- As organic solvent is removed, the dispersion first becomes a viscous gel, then collapses into an aqueous suspension of liposomes
- In this transition, invested micelles reorganize: water droplets coalesce, lipid redistributes to form bilayers around aqueous cores, yielding large unilamellar/ oligolamellar vesicles with large internal volume.

✓ *Post-Processing*

- Size reduction and homogenization by extrusion through polycarbonate membranes; number of passes and pore size determine final size distribution.
- Unencapsulated solute is removed by techniques like size-exclusion chromatography. [68]

➢ *Microfluidic Method*

By manipulating fluid dynamics at the microscale, microfluidic devices allow for precise control over liposome production. The method uses specialized microchannels to mix lipids in an organic phase with an aqueous phase under regulated conditions. Important factors influencing vesicle properties include:

- Total flow rate (TFR)
- Channel geometry
- Lipid concentration

These technologies reliably generate tiny unilamellar vesicles (SUVs) with good batch-to-batch repeatability and narrow size distributions (50–150 nm). [69]

- *Mechanism*

✓ *Initial Setup: Streams in the Chip*
✓ *Hydrodynamic Flow Focusing*

- Lipids are dissolved in a water-miscible solvent and injected as a central stream.
- Aqueous buffer flows in side channels and sheathes/focuses the lipid stream, or mixes via patterned structures that create chaotic advection.

✓ *Mixing and Lipid Desolation*

- At the solvent-water interface, ethanol diffuses into water and water into the alcohol stream under laminar flow.
- When local alcohol concentration drops below the lipid solubility limit, lipids precipitate and self-assemble.
- Intermediate structures form: oblate/disc micelles or bilayer discs at the interface.

✓ *Vesiculation into Liposomes*

- Bilayer discs micelles close into vesicles to minimize edge energy, producing unilamellar nanoliposomes
- Membrane fluidity controls how easily these discs bend and thus the final vesicle size.

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✓ *Outcome Control and Variants*

- Higher FRR and more rapid mixing, more monodisperse liposomes.
- Chaotic micromixers and vortex focusing accelerate mixing but still rely on the same diffusions-driven desolvation and disc-to-vesicle transition. [70]

➢ *Supercritical Fluid Technology*

Supercritical carbon dioxide (scCO2) is used in place of organic solvents in this eco-friendly method. The process creates vesicles instantly by rapidly depressurizing a supercritical mixture of lipids and aqueous phase through a nozzle. The method has benefits like:

- Removal of organic solvent residues
- Processing in a single step
- Potential for scalability
- Improved thermolabile compound stability [71]

- *Mechanism*

✓ *CO_2-Lipid-Ethanol Homogeneous Phase*

- Phospholipids are dissolved in ethanol and contacted with SC-CO_2 to form a single expanded liquid phase.

✓ *Emulsion or Water Contact*

- A defined amount of water is introduced under stirring, creating water droplets dispersed in the CO_2/ethanol/lipid phase.

✓ *Pressure Reduction/Expansion*

- Controlled depressurization reduces CO_2 and ethanol content; lipids lose solubility and migrate around water droplets, forming bilayer shells.
- Droplets fall into an aqueous pool or remain suspended, transforming into liposomes.

✓ *Final Suspension*

- Submicron liposomes with high encapsulation efficiency and very low solvent residue. [72]

Table 3 Formulation Composition of Liposomes

Drug	Method	Lipid/ Polymer	Excipients	References
Diclofenac Sodium	Thin film hydration	Phosphatidylcholine	Cholesterol	[73]
Ibuprofen	Thin film hydration	PC	Cholesterol	[74]
Amphotericin B	Reverse phase evaporation	PC	Cholesterol	[75]
Paclitaxel	Reverse phase evaporation	PEG	Cholesterol	[76]
Curcumin	Microfluidic	Cholesterol	DSPC	[77]
Quercetin	Microfluidic	DSPC	PEG	[78]
Resveratrol	Super critical fluid	DSPC	Cholesterol	[79]
Tamoxifen	Super critical fluid	Cholesterol	DSPC	[80]

Table 4 Evaluation Parameter of Formulation Composition of Liposomes

Drug	Method	Particle size	Entrapment efficiency	Drug release	Disintegration	Ref.
Diclofenac Sodium	Thin film hydration	150-300nm	65-80	Sustained	Diffusion	[73]
Ibuprofen	Thin film hydration	200-400nm	70-85	Controlled	Bilayer disruption	[74]
Amphotericin B	Reverse phase evaporation	1300-1450nm	~95	Sustained	Membrane Fusion	[75]
Paclitaxel	Reverse phase evaporation	150-300nm	80-90	Controlled	Lipid erosion	[76]
Curcumin	Microfluidic	70-150nm	80-92	Sustained	Lipid diffusion	[77]
Quercetin	Microfluidic	80-140nm	80-90	Sustained	Lipid erosion	[78]
Resveratrol	Super critical fluid	100-160nm	75-88	Sustained	Diffusion	[79]
Tamoxifen	Super critical fluid	120-200nm	85-92	Controlled	Diffusion	[80]

VI. CONCLUSION

Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), self-emulsifying drug delivery systems (SEDDS), and liposomes, offer a promising way to improve the oral delivery of poorly water-soluble drugs. These systems effectively tackle key issues like low solubility, slow dissolution rate, instability in the gastrointestinal tract, and significant first-pass metabolism. By integrating drugs into biocompatible lipid matrices, these nanocarriers improve solubility, protect drugs from breaking down, and promote lymphatic uptake. This leads to a notable increase in oral bioavailability. SLNs provide sustained release and protect the gastrointestinal

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tract, while NLCs improve upon SLN limitations by allowing for higher drug loading and better stability. SEDDS enhance drug dissolution and enable rapid absorption, and liposomes offer flexible encapsulation for both hydrophilic and lipophilic drugs. These delivery systems also allow for controlled and targeted drug release, better pharmacokinetics, longer circulation time, and improved tissue distribution. Their use in various therapeutic areas—including cancer, heart diseases, infections, and neurological disorders—shows their wide clinical potential. However, despite these benefits, challenges remain. Issues like formulation stability, production scalability, reproducibility, regulatory matters, and the safety of excipients need careful attention for successful clinical application.

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