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Solid lipid nanoparticles: Methods of preparation and applications

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ABSTRACT :

Solid lipid nanoparticles were developed in the early 1990s as an alternative to other common colloidal carriers such liposomes, polymeric nanoparticles, and emulsions because they offer advantages like targeted drug delivery, controlled drug release, and enhanced durability. The utilization of solid lipid nanoparticles (SLNs) technology is a promising new approach for lipophilic drug delivery. Nanoparticles are solid colloidal particles that range in size from 10 to 1000 nm. SLNs can also be used to boost a medication's bioavailability. Two of the most significant kinds of lipid-based nanoparticles are strong lipid nanoparticles, also known as nanostructured lipid transporters (SLNs). The focus of this review paper is on employing advanced production techniques, such as homogenization and solvent evaporation, to reduce negative impacts. Electron microscopy, nuclear magnetic resonance, differential scanning calorimetry (DSC), dynamic light scattering (DLS), and other contemporary analytical methods are employed in the preparation of the solid lipid nanoparticle. Benefits, drawbacks, and preparatory strategy for this new technique are evaluated. An important use for SLNs is targeted medication delivery.

Keywords: Solid Lipid Nanoparticles, Nanoparticles, Nanomedicine, Nanocarrier system, Biocompatibility, Drug Incorporation, Drug Delivery

INTRODUCTION :

Particularly small particles like microparticles and colloidal systems in the nanometer range have been shown to have a great deal of potential for medication delivery. Colloidal particles that have a size between 10 and 1000 nm are known as nanoparticles. In order to deliver drugs in an effective manner and maximize therapeutic efficacy while minimizing toxicity and side effects, nanoparticles must be able to penetrate several anatomically distinct sites in the body over a predetermined period of time. A sustained release of nanoparticles might occur at the target site for a few days or even weeks when biodegradable materials are utilized to create them.

The benefits of using nanoparticles for drug delivery include enhanced therapeutic effect and decreased toxicity and side effects due to the small size of the particles, which allows them to pass through tiny capillaries, be absorbed by cells, and release the drug at the proper rate and dose at specific body sites for a predetermined amount of time. The fact that nanoparticles are biodegradable, non-toxic, and have a longer shelf life makes them an excellent choice for a medication delivery method. Because of these characteristics, nanoparticles are better suited for improving bioavailability and achieving sustained release.[1]

These lipid nanoparticles are referred to as solid lipid nanoparticles (SLNs), and formulators from all over the world are becoming increasingly interested in them. The benefits of employing nanoparticles for drug delivery include their ability to enter tiny capillaries, be absorbed by cells, and release medications at the appropriate rate and dosage when used. Solid lipid nanoparticles, or SLNs, were first introduced in December 1991 as an alternative to traditional colloidal carriers for the delivery of medications. SLNs are composed of nanoscale stable lipid cell ranges that are frequently dispersed in water or in fluid surfactant arrangements.[2]

The targeted delivery system is one of the hardest concepts to understand in pharmacy school. Improving drug delivery has encountered a new obstacle with the development of colloidal delivery methods like liposomes, micelles, and nanoparticles. Because of their remarkably diverse spectrum of properties, SLNs and NLCs are useful for many tasks, such as topical drug administration, parenteral, cutaneous, and pulmonary. The items are designed to decrease the side effects of strong medications and to greatly improve the effectiveness of treatment. Notable among other things is that they developed a strong program for industrializing food and cosmetic ingredients and for gene transfer.[3]

Applications of SLN to safeguard acid-labile active molecules and improve the absorption and bioavailability of poorly soluble medications being explored. This research also highlights the significance of creating SLN-based systems to address three major and escalating public health concerns of the present day: antibiotic resistance, neurological illnesses, and cancer. How SLN can increase bioavailability, target therapeutic agents, and lessen side effects is made clear in the review section.[4]

Lipids have lately found application as the precursor for nanoscale drug carriers and as excipients in a range of pharmaceutical formulations, such as emulsions, suppositories, and ointments. Emulsions are flexible delivery systems capable of dispersing materials soluble in oil in a variety of ways. Oxidation, instability processes, and rapid drug release are characteristics of these. For O/W emulsions, they are made up of a liquid lipid material that has been dispersed into an aqueous phase. A novel class of drug carrier known as solid lipid nanoparticles (SLN) was developed in the 1990s to solve issues with conventional emulsions. These are solid lipid dispersions with submicron size particles that are stabilized by a surfactant and stay solid at both room temperature and biological temperature.[5-6]

At a mean photon correlation spectroscopy (PCS) diameter of approximately 50–1000 nm, solid lipid particles (SLNs) are dispersed in water or an aqueous surfactant solution. A solid hydrophobic core is encased in a monolayer of phospholipid coating. In a lipid matrix inside the solid core, the drug is distributed or dissolved. Hydrophilic or lipophilic drugs may be transported by them.[7]

1.1 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) have been considered the most successful lipid-based colloidal carrier since their inception in the early 1990s. This is one of the most popular ways to improve the oral bioavailability of low water soluble medicines. SLNs consist of room-temperature, solid, physiologically appropriate lipid components that range in size from 50 to 1000 nm, or sub microns. Because of their system's physical stability, solid lipid nanoparticles have many advantages, such as superior biocompatibility, less toxicity, and enhanced administration of lipophilic medications. Solid lipid nanoparticles may provide a workable sustained-release and drug-tracking method for lipophilic CNS anticancer medicines.[1]

Solid lipid nanoparticles are a fantastic choice for medicinal applications. Active pharmaceutical ingredients (APIs) have limited water solubility and are mostly still under development, which results in a low bioavailability.[2] A graphic comparison is made between the advantages of several particulate drug carriers, such as liposomes and emulsions, and solid-lipid nanoparticles (SLNs), which combine the benefits of polymeric nanoparticles, fat emulsions, and liposomes.[8] recommendations for the SLNs.

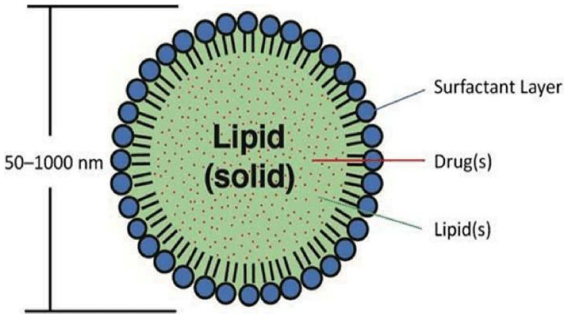

Figure1: Solid Lipid Nanoparticle Structure [36]

This method divides chemical compounds into four classes: class II compounds are low permeability and highly soluble, whereas class IV compounds are low permeability and poorly soluble. Therefore, your best choice for creating solid lipid nanoparticles is probably to use materials from classes II and IV. Part II: Biopharmaceuticals Hoffman explained the theoretical foundations for the increase in bioavailability attained by the use of solid lipid nanoparticles. [9–10] The physical and chemical properties of SLNs impact both in vivo and in vitro behaviours. Solid lipid networks (SLNs) are typically composed of solid lipid (often at a temperature of 25°C to 28°C), emulsifiers injected periodically, and the right solvent to dissolve the lipid and non-lipid components. When SLNs are formulated, the conventional SLNs are composed of lipid components combined. [11]

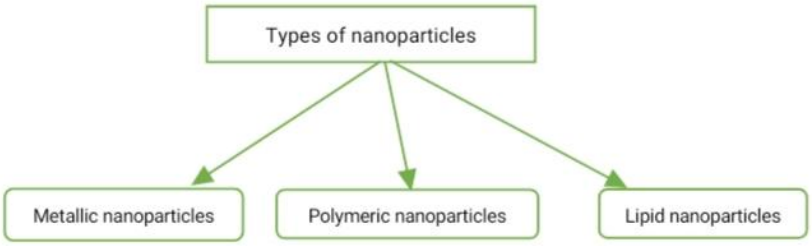

Figure 2: Classification of nanoparticles [3]

Particulate drug carriers, particularly small particles like microparticles and colloidal systems in the nanometre range, have been linked to a high potential for drug delivery. Particulate drug carriers have been shown to have a great potential for drug delivery, particularly small particles like microparticles and colloidal systems in the nanometre range. With metallic and polymeric nanoparticles, the main concern is thought to be their potential for toxicity, given the lipids used in their synthesis are normally classified as GRAS (normally Known as Secure) components. Lipid nanoparticles can be broadly classified into two types: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).[2]

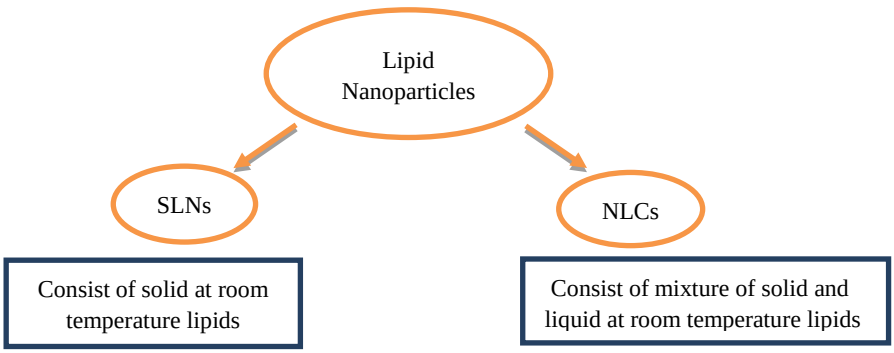

Figure 3: The main difference between both basic kinds of lipid nanoparticles [3]

1.2 THE MAIN ADVANTAGES AND DISADVANTAGES OF SLN:

The Advantages of SLN It reduces the risk of both acute and chronic toxicity by employing physiological lipids that degrade naturally and avoids the need for organic solvents throughout the production process.

1. It makes poorly soluble chemicals in water more bioavailable.
2. By employing dermal via a procedure called site-specific medicine administration, it enhances the delivery of medication into the skin.
3. It controls the potential for drug release as well as drug targeting.
4. It protects delicate molecules in the intestine from chemically labile reducing agents and the external environment.
5. SLNs perform better than liposomes in terms of stability.
6. It encourages trapped bioactive B bioavailability and integrated labile chemical synthesis component.
7. A strong emphasis on fully functioning molecules.
8. Lyophilization is a possibility.[3]

1.2.1 SLNs combine the advantages of liposomes, fat emulsions, and polymeric nanoparticles:

1. The integrated medication may be made available for release for a few weeks under strict supervision. Moreover, coating or ligand-attaching SLNs broadens the scope of medication targeting.
2. There has outstanding biocompatibility.
3. No toxic metabolites are produced.
4. Exceptionally high or improved pharmacological stability throughout the long term.
5. Good reproducibility when the preparation step is a low-cost pressure homogenization process.
6. The practicality of incorporating both hydrophilic and hydrophobic drugs.
7. Much easier to make than biopolymer-based nanoparticles.
8. It is easily scaled up and can be sterilized using commercial methods.
9. Avoid using organic solvents.
10. Reduces the required number of dosages. [12]

1.2.2 The Disadvantages of the SLNs

1. Limited capacity for pharmaceutical packaging.
2. Drug extraction following a polymeric shift that happens in storage.
3. A rather high percentage of dispersed water (70–99.9%).
4. The low loading capacity of water-soluble drugs during the production cycle was caused by the partitioning effects.
5. Incredible mobility of polymeric transitions.[3]

1.2.3 Potential disadvantages of solid lipid nanoparticles are such as;

1. Poor drug loading capacity is one of the possible drawbacks of solid lipid nanoparticles.
2. Drug ejection following the polymeric transition while being stored.
3. The dispersions' comparatively high water content.
4. Particle growth.
5. A tendency for unpredictable gelation
6. Surprising dynamics in polymeric transition.[12]

1.3 PREPARATION OF SOLID LIPID NANOPARTICLES SLNs[8]:

1. High pressure homogenization
    a. Hot homogenization
    b. Cold homogenization
2. Ultrasonication/high speed homogenization
3. Solvent Emulsification Evaporation Technique
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method

9. Precipitation technique
10. Solvent injection technique
11. Membrane contractor technique
12. Film-ultrasound dispersion

1.3.1 High pressure homogenization

This process is dependable and efficient for creating SLNs. High pressure homogenizers are devices that drive a liquid at high pressure (100–2000 bar) through a small hole (a few microns or less). The fluid accelerates to a very high velocity (about 1000 km/h) over a very short distance. Extremely strong shear stress and cavitation forces break down particles to submicron sizes. Usually, 5–10% lipid content is used, while studies have also been done with up to 40% lipid content. Both of the primary HPH techniques, hot homogenization and cold homogenization, are predicated on the notion of mixing a substantial quantity of lipid melt with the drug.[8,13] Both hot and cold homogenization are procedures utilized in the production of SLN. In both cases, there is an early phase. To reduce the danger of both immediate and long-term harm, this method makes use of lipid matrix that has been separated from physiological lipids.[11]

A] Hot homogenization technique

A high shear device disperses the medication loaded in melted lipid in an aqueous surfactant solution at room temperature during the hot homogenization process. A hot pre-emulsion was created, and then the medication and fat were heated to 70 °C and homogenized under high pressure. It was then time to prepare the aqueous phase. The oil phase was produced by dissolving poloxamer 188, poloxamer 407, and the emulsifying agents Cremophore in distilled water and heating it to the same temperature (70°C). Lipid phase that was melting and heated aqueous phase were combined. After cooling a heated nanoemulsion to room temperature, a probe sonicator was used to sonicate the pre-emulation for ten minutes. spread across a prescription watch glass are deposited solid lipid nanoparticles. [14,15]

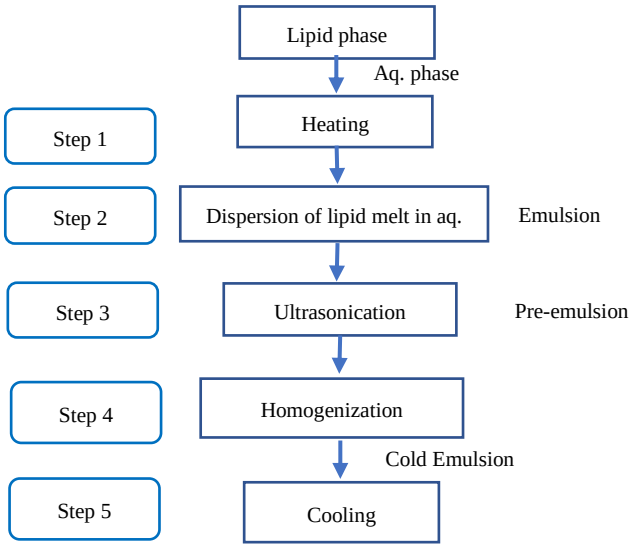

Figure 4: Hot Homogenization Technique [11]

B] Cold homogenization technique

To obtain drug-loaded lipid, the drug containing lipid melt is chilled using dry ice or liquid nitrogen. Fast cooling causes the medication to form in a solid solution (uniform distribution) in the lipid matrix. The solid lipid is then crushed into lipid microparticles, which are between 50 and 100 mm in size. These lipid microparticles are then disseminated in a cold surfactant solution, producing a pre-suspension. To achieve the desired particle size, this pre-suspension is then homogenized at room temperature or below.[16,7]This approach protects heat-sensitive pharmacological entities because it assumes that the high shear homogenization process won't increase the dispersion's temperature. This procedure could lessen the quantity of hydrophobic medication that separates from lipid into the aqueous phase during homogenization and the development of solid lipid nanoparticles.[17]

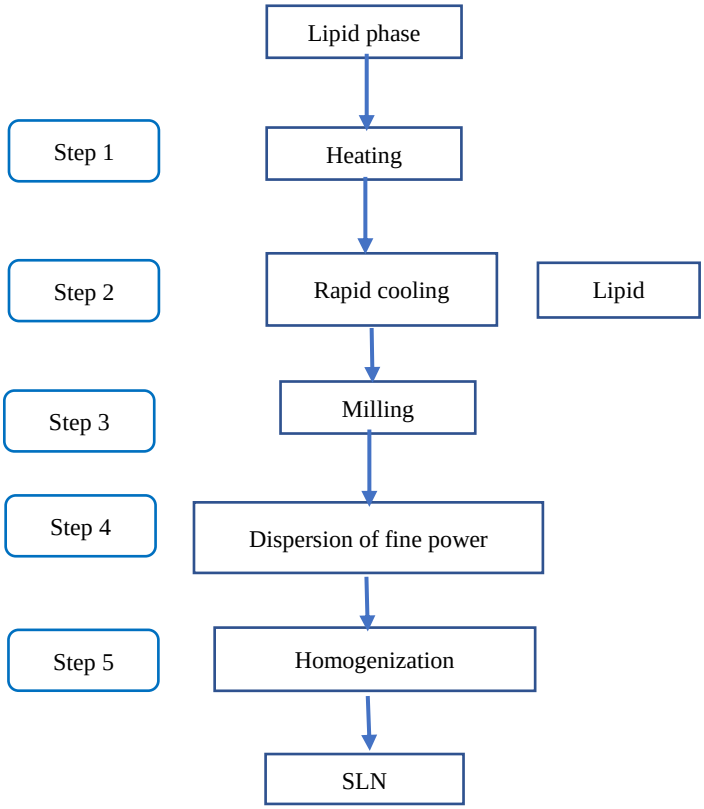

Figure 5: Cold homogenization technique[11]

1.3.2 Ultrasonication/high speed homogenization

SLNs can also be prepared using ultrasonication or high-speed homogenization techniques. For smaller particle sizes, a combination of ultrasonication and high-speed homogenization is required. Potential metal contamination and physical instability, such as particle formation during storage, are the main drawbacks of this approach.[8]

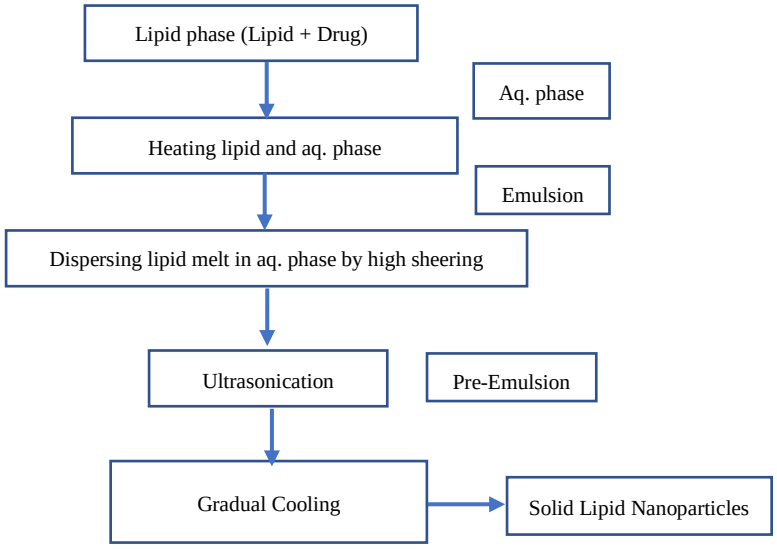

Figure 6: Ultrasonication/high speed homogenization [36]

1.3.3 Solvent Evaporation emulsification technique.

SLNs are also made using the solvent evaporation method. Precipitating in o/w emulsions can be used to create nanoparticle dispersions. The lipophilic material dissolves in an organic solvent that is water-immiscible (such as cyclohexane) in an emulsified aqueous phase. When the solvent evaporates, the lipid precipitates in the aqueous medium, creating a dispersion of nanoparticles with a mean size of 25 nm. Furthermore, solid lipid nanoparticles

with a size range of 30 to 100 nm were obtained by dissolving tripalmitin in chloroform. This solution was emulsified in an aqueous phase using high pressure homogenization. The organic solvent was extracted from the emulsion by low pressure (40–60 mbar) evaporation.[18]

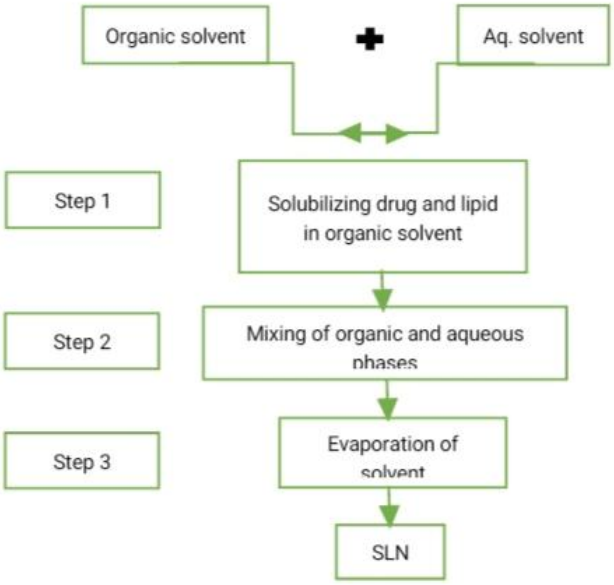

Figure 7: Solvent Evaporation emulsification technique [11]

1.3.4 Solvent Diffusion/Emulsification Method

For the production of NPS, the solvent diffusion/emulsification process is a commonly employed technique. Below is a diagrammatic illustration of the nanoparticle manufacturing process. [19–20]

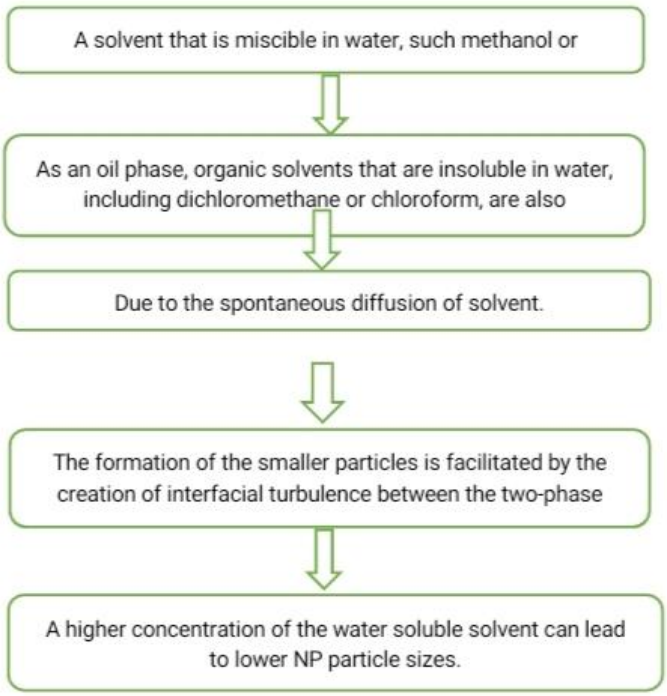

Figure 8: Solvent Diffusion/Emulsification Method [19]

1.3.5 Supercritical fluid method:

This is a different method that uses particles from gas-saturated solutions (PGSS) to create solid-liquid nanoparticles (SLNs). Many advantages of this process include: (i) obtaining particles as a dry powder instead of suspensions; (ii) avoiding the need for solvents; and (iii) using low pressure and

temperature. By employing particles from gas saturated solutions (GSS) to produce SLNs, solvent-free processing has the advantage of being more advantageous. SLN can be set up using the supercritical carbon dioxide solution's quick expansion.[21] With the help of GSS, the lipid material melts and dissolves under pressure in the supercritical fluid (SCF). Saturated solutions expand when sprayed through nozzles or atomizers, enabling the SCF to swiftly escape and leaving the little, dry lipid particles behind. The broad range of lipid miscibility and the absence of organic solvents make SCF a beneficial solution.[22]

1.3.6 Microemulsion based method

The decrease in microemulsion concentration by Gasco and associates served as the foundation for the creation of SLN preparations. There are the external and internal media that comprise these biphasic microemulsions. This mixture consists of water, low melting fatty acids (such as stearic acid), co-emulsifiers (such as butanol and sodium mono cetyl phosphate), and emulsifiers (such as polysorbate 20, polysorbate 60, and soy phosphatidylcholine). In 2-3°C of cold water, a warm microemulsion is dispersed. The combination of microemulsions can influence the dilution process. This method achieves the submicron size without the need for further energy. In order to produce nanoparticles, two main conditions must be met: firstly, more lipophilic solvents must be used to obtain larger particle sizes; secondly, certain solvents must disperse rapidly into the aqueous phase. This method's main advantage is that it requires little to no mechanical energy input. [11,23]

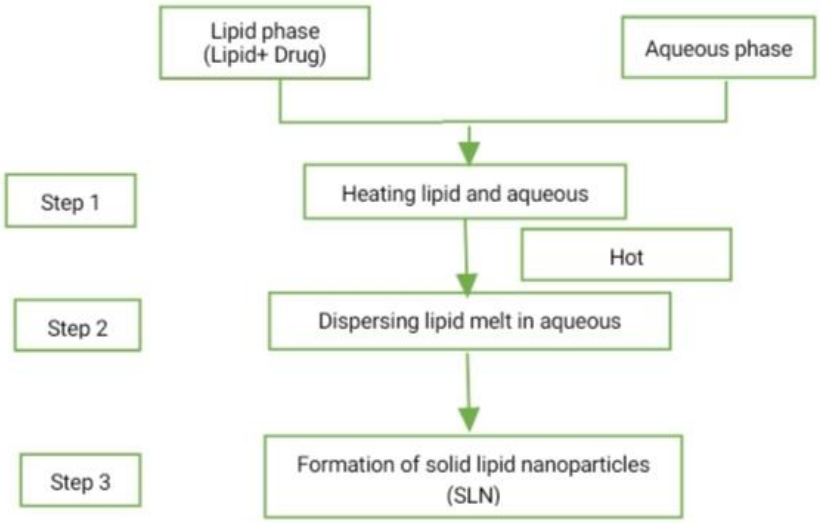

Figure 9: Microemulsion based method [25]

1.3.7 Spray drying method

The method used to transform an aqueous dispersion into a medicine is distinct from lyophilization. It is less expensive than lyophilization in contrast. Lipids having a boiling point higher than 70°C are suggested to be selected for spray drying due to the likelihood of particle gathering, as well as the increased temperature shear pressures and incomplete melting of the particles. The best results were obtained by spray drying with a 1% SLN concentration in a trehalose in water solution or a 20% SLN concentration in ethanol–water combinations (10/9v/v).[24]

1.3.8 Double emulsion method

For SLNs including hydrophilic active medicinal components and peptides, the double emulsion technique is suitable. In a melting lipid combination, the primary W/O emulsion is formed by emulsifying an aqueous drug solution and stabilizing it with suitable excipients. The hydrophilic emulsifier's aqueous solution is used to spread the primary W/O emulsion to create a double W/O / W emulsion. After that, the double W / O / W emulsion is isolated and continuously stirred using filtering. In contrast, large particles are obtained using this approach.[25]

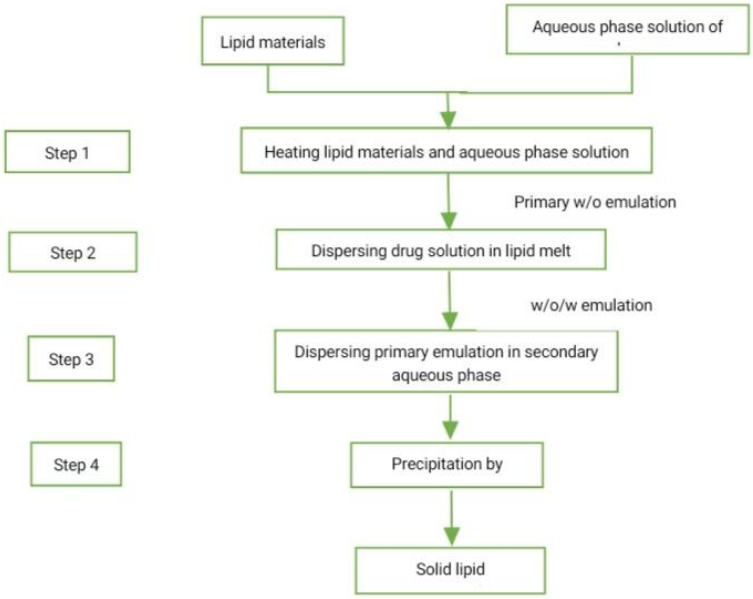

Figure 10: Double emulsion method [25]

1.3.9 Precipitation technique

The precipitation approach, which requires solvents, is another way to create solid lipid nanoparticles. An aqueous phase will be used to emulsify the solution after the glycerides have been dissolved in an organic solvent (such as chloroform). A precipitate of lipid will create nanoparticles once the organic solvent has evaporated. [26-27]

1.3.10 Solvent injection technique

Water-miscible solvent is used to dissolve the solid lipid. A stirred aqueous phase is injected with or without surfactant containing the lipid solvent mixture. To get rid of extra fat, the dispersion was lastly filtered. When preparing and evaluating SLNs for the subcutaneous delivery of Hepatitis B surface antigen vaccination, emulsion in the aqueous phase aids in the formation of lipid droplets at the injection site and stabilizes the SLNs until solvent diffusion is finished.[28]

1.3.11 Membrane contractor method

This study looks into a novel method for producing SLN on a big scale by employing a membrane contactor. The procedure is depicted schematically in little droplets can form when the lipid phase is forced through membrane pores at a temperature higher than the lipid's melting point. As droplets form at the pore outputs, the aqueous phase sweeps them away as it circulates inside the membrane module. The preparation is cooled to room temperature to generate solid liquid nitrogen (SLN). It is examined how process variables (membrane pore size, aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity, and lipid phase pressure) affect the SLN size and lipid phase flux. Additionally, vitamin E-loaded SLN are made, and their stability is shown. [26,29]

1.3.12 Film-ultrasound dispersion

A lipid film was created by the addition of the medication and the lipid to appropriate organic solutions. The aqueous solution containing the emulsions was then added after the organic solutions had rotated, decompressed, and evaporated. The SLN with the small and uniform particle size is generated by using the ultrasound with the probe to diffuser in the last step.[21]

1.4 APPLICATIONS:

1.4.1 SLNs as Gene Vector Carrier

Gene vector formulation can make advantage of SLN. By adding a diametric HIV-1 HAT peptide (TAT 2) to the SLN gene vector, the gene transfer was optimized in one study. SLN carrying genetic/peptide components, including DNA, plasmid DNA, and other nucleic acids, has been reported in

multiple instances recently. When the organic solvent was removed, stable, uniformly sized lipid-nucleic acid nanoparticles (between 70 and 100 nm) were produced from a liquid nanophase that contained water and a water miscible organic solvent in which the lipid and DNA were individually dispersed. Genospheres is the term for it. When an antibody-lipo polymer conjugate is inserted into the particle, it is specifically targeted.[30]

1.4.2 SLNs for topical use

SLNs and NLCs have been applied topically to provide a variety of medications, including antifungals, imidazole, vitamin A, isotretinoin, ketoconazole, flurbiprofen, and glucocorticoids. Epidermal targeting is the result of podophyllotoxin-SLN penetrating both the skin's surface and the stratum corneum. Glyceryl behenate can be used to create vitamin A-loaded nanoparticles. The techniques work well to increase penetration when used in conjunction with prolonged release. The lipid nanoparticles coated with isotretinoin were designed to administer the medication topically. The hot homogenization procedure for this uses Tween 80 and soy lecithin. The rise in isotretinoin's cumulative absorption in skin makes the methodology valuable. The synthesis of SLN gel loaded with flurbiprofen for topical administration presents prospective benefits in that the medication will be delivered directly to the site of action, resulting in higher tissue concentrations. This kind of SLN gel was prepared using polyacrylamide, glycerol, and water. [30–31]

1.4.3 Stealth Nanoparticles

This gives the immune system a quick way to eliminate drugs in a novel and exceptional way. Specific cells could be targeted by such nanoparticles. Stealth SLNs containing medication and marker particles have been successfully tested for a number of animal models. The antibody known as "stealth lipobodies" has an unexpectedly elevated distribution to target tissue's inaccessible locations. In animal models, medicines and marker molecules have been effectively tested with stealth SLNs. [30,32]

1.4.4 SLNs for Potential Agriculture Application

Compared to emulsions, the essential oil extracted from Artemisia arborescent could slow down the rate of evaporation when mixed with the SLN, and these systems were employed as suitable carriers of ecologically safe pesticides in agriculture.[30]

1.4.5 Nanoparticles for brain delivery

The blood-brain barrier is one of the obstacles that medications, such as antibiotics, anti-neoplastic medicines, and various neuroplastic therapies, must overcome medication delivery to the brain via nanoparticles is one way to get over this obstacle. Hexapeptide dalargin is one medication that has been effectively used to target the brain with nanoparticles**.** Many possibilities are considered for the improved delivery of medications to the brain with the use of nanoparticles:

1. A greater concentration gradient at the blood-brain barrier may improve the transport of the drug across the endothelium cell layer, leading to an increase in retention in the brain.
2. The surfactant action of the nanoparticles dissolves the lipids in the endothelial cell membrane, causing membrane fluidization and increased drug permeability across the blood-brain barrier.[33]

1.4.6 SLNs as cosmeceuticals

Certain characteristics of SLN render them attractive candidates as carriers for cosmetic applications:

- It has been demonstrated that labile molecules, such as tocopherol and retinol, are protected from chemical destruction.
- SLN with a drug-enriched core led to continuous release, while SLN with a drug-enriched shell show burst release characteristics allow for regulated release of the active components
- SLN function as occlusives, meaning they can be applied to the skin to raise its water content.
- SLN have the ability to block UV rays, meaning that they can be used alone as physical sunscreens or in combination with molecular sunscreens for enhanced photoprotection. The SLNs have been used as an active carrier agent for UV blockers and molecular sunscreens as well as in the formulation of sunscreens. It has been demonstrated that SLN and NLCs are novel occlusive topicals with regulated release. Glyceryl behenate SLNs have improved vitamin A localization in the higher layers of skin as compared to traditional formulations.[34]

1.4.7 SLN for Nasal Application

Due to its quick absorption, quick start of action, ability to avoid labile drug breakdown in the GI tract (such as peptides and proteins), and adequate transport across epithelial cell layers, nasal administration was a viable alternative non-invasive drug delivery method. Strategies including formulation development and prodrug derivatization have been used to enhance drug absorption through the nasal mucosa. Research teams have suggested SLN as a substitute transmucosal delivery strategy for macromolecular medicinal drugs and diagnostics**.** According to a recent paper, using PEG coating on polymeric nanoparticles as vaccine carriers produced encouraging results. The effective trans mucosal transport of the encapsulated bioactive chemical is attributed to the PEG coating of polylactic acid nanoparticles. For solid lipid nanoparticles, this idea may be helpful.[28]

1.4.8 SLN in Cancer chemotherapy

The in-vitro and in-vivo efficacy of a number of chemotherapeutic drugs that have been encapsulated in SLN have been assessed within the past 20 years. For breast cancer patients, tamoxifen, an anticancer medication, has been added to SLN to extend the drug's release after intravenous injection. SLN loaded with medications like methotrexate and camptothecin has proved successful in achieving tumor targeting. For the purpose of treating lymph node metastases and breast cancer, metoxantrone SLN local injections were developed with the goal of lowering toxicity while enhancing safety and bio-efficacy. [28,35]

1.4.9 Oral SLN in antitubercular chemotherapy

Antitubercular medications, like isoniazid, pyrazinamide-loaded SLN systems, and rifampsin, have the ability to lower dosage frequency and increase patient compliance. Solvent diffusion technology was utilized to manufacture SLNs loaded with antitubercular medicines.[28]

CONCLUSION

The SLN is a desirable technology for transporting colloidal medications due to its exceptional physical qualities, prospective integration of active chemicals, and associated advantages.SLN stand for low-toxicity formulations that can incorporate hydrophilic or lipophilic medicines and have controlled release capabilities. Since poorly soluble compounds improve intestine absorption and shield encapsulated medications, SLN is delivering poorly soluble molecules orally. The benefits of polymeric nanoparticles and fat-based emulsions are combined in SLN as a colloidal drug carrier. These systems have a number of advantages, including reasonable physical stability, ease of inclusion of lipid- and water-soluble medications, affordability, and ease of manufacturing. SLNs support sustained release in addition to efficient medication targeting. LNs have already demonstrated their worth as effective formulations for enhancing medicinal therapies and cosmetics, among other disciplines.

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