IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Solid Lipid Nanoparticle : A Novel Approach For Delivery Of Poorly Water Soluble Drug

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Abstract

The GI tract's numerous enzymatic barriers make it difficult to administer medications with low water solubility orally. Solid matrix-based lipid nanoparticles have gained attention as a promising drug delivery method to increase the bioavailability and absorption of various medications, particularly lipophilic compounds. According to reports, the most promising technology for oral administration is solid lipid nanoparticles (SLN), which offer a number of benefits over traditional dosage forms, including improved solubility, stability, permeability, and bioavailability with negligible side effects. Physiologically biocompatible lipids are used to create solid lipid nanoparticles. SLNs have been used to deliver various medications orally, parenterally, transdermally, intranasally, ocularly, and in the lungs, with improved safety, bioavailability, and overall therapeutic effects. In this review we have highlighted composition of SLNs, detail method of preparation of SLNs , Routes of Administration & Recent work of SLNs. We have also summarizes the API localization within SLNs, Advantages & limitations of SLNs, Features of Methods, Evaluation of SLNs & Application of SLNs.

Index Term : Nanocarrier, Solid Lipid Nanoparticles, Components, Preparation Method, Routes of Administration

1.INTRODUCTION

Schizophrenia is a significant global public health issue, Although advancements in the field of neurology, schizophrenia remains a significant global public health issue that impairs the personal, social, educational, and occupational functioning of its individuals[1].Schizophrenia is a long-term mental illness that can be identified by a variety of symptoms, including delusional behaviour, speech and behaviour disorientation, hallucinations, and cognitive impairment. Furthermore, because of its early onset and chronic character, schizophrenia is seen as a disabling condition for both patients and those who care for them because of its negative and cognitive symptoms[2,3]. Ziprasidone is used in schizophrenia. A derivative of benzo-thiazolyl piperazine, ziprasidone (ZP) is an antipsychotic. ZP Is a type 2 dopamine (D2) blocker, a selective monoaminergic inhibitor with affinity for the type 1 and type 2 adrenergic receptors, the H1 histaminergic receptor, and serotonin type 2 (5HT2) [4,5].Because they are unable to penetrate the brain, many neurotherapeutics are ineffective in treating illnesses of the central nervous system

(CNS)[6].Drug transport to the brain is hampered by numerous factors, even though cerebral blood flow is comparatively high. The brain and its blood supply are separated by two physiological barriers that control drug delivery: the blood–cerebrospinal fluid barrier and the blood–brain barrier (BBB)[7].Ziprasidone belongs to BCS Class II[8].As it is belong to BCS Class II it have the poor solubility & high permeability. It is poor water soluble drug, which required a method which can enhance it's solubility. Targeted delivery of poorly soluble drugs is greatly aided by nanotechnology. Nanotechnology-based nanodrug delivery systems, vesicular drug delivery systems, solid lipid nanoparticulate drug delivery systems, and so on are examples of nanotechnology-based drug delivery systems[9]. Preventing undesirable side effects, maintaining an optimal amount of medicine at the tissue of interest to create better therapeutic outcomes, and minimising premature drug degradation are the key goals of creating an efficient drug delivery system. Conventional medication administration methods have a number of drawbacks, including a higher likelihood of skipping a dosage, unstable drug levels, low bioavailability, undesired side effects, low patient compliance, fast metabolism, and toxicity. Target-specific nanocarrier systems, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), niosomes, liposomes, ethosomes, bilosomes, transferosomes, colloidosomes, pharmacosomes, herbosomes, layerosomes, sphingosomes, and ufosomes, can be used to get over those limitations[10].Nanoparticles are colloidal particles with sizes between 10 and 1000 nm. They are made of natural and synthetic polymers and are perfectly suited to minimise toxicity and enhance drug delivery. They have become a viable alternative to liposomes as drug carriers over time. The effectiveness of using nanoparticles for administering drugs relies on their capacity to pass through various anatomical barriers, release their contents continuously, and remain stable at the nanoscale. However, the widespread application of nanoparticles to clinical practice has been constrained by the lack of safe polymers with regulatory approval and their prohibitive cost [11].Lipids have been proposed as an alternative carrier to avoid the drawbacks of polymeric nanoparticles, especially for lipophilic drugs. Solid lipid nanoparticles (SLNs), also known as lipid nanoparticles, are attracting significant interest among formulators worldwide[12].As an alternative to the current conventional carriers (emulsions, liposomes, and polymeric nanoparticles), SLNs are colloidal carriers that were developed in the past decade. These are a new kind of submicron-sized lipid emulsions in which a solid lipid has been used in place of the liquid lipid, or oil. SLN are appealing due to their ability to enhance the performance of pharmaceuticals, nutraceuticals, and other materials. They have special qualities such very small size, large surface area, high drug loading, and the interaction of phases at the interfaces [13].

2.COMPOSITION OF SLNs

2.1.Lipid

The primary ingredient in the formulation, lipids control the loading, stability, release, and encapsulation of any API. Thus, choosing the right lipids is essential to a successful formulation. Biocompatible/physiological, biodegradable, and generally recognized as safe (GRAS) lipids with a melting point greater than 40°C to ensure a solid state at both room temperature and body temperature are the best options for SLN formulation, which lowers the risk of toxicity[14].

Table 1 : examples of lipid used in solid lipid nanoparticle [15]

Triglycerides	Partial glycerides	Fatty acids
Glyceryl trilaurate/Trilaurin	Glyceryl palmitostearate	Myristic acid
Glyceryl tricaprate/Tricaprin	Glyceryl behenate	Decanoic acid
Glyceryl tribehenate/Tribehenin	Glyceryl distearate	Palmitic acid
Glyceryl trimyristate/Trimyristin	Glyceryl monostearate	Behenic acid
Glyceryl tripalmitate/Tripalmitin		Stearic acid
Glyceryl tristearate/Tristearin		

2.2.Surfactant

Generally , surfactants are essential to the production of lipid nanoparticles because they help disperse the lipid melt in the aqueous phase and stabilize the lipid nanoparticles in dispersions after cooling[16].When using surfactants to prepare SLN, the most important factors to take into account are their safety, compatibility with other excipients, ability to produce the desired size with the least amount of consumption, and ability to cover the surfaces of the SLNs with enough stability[17]. These carriers' surfactants have the ability to break down cell membranes and increase epithelial permeability, which helps get around restrictions on drug absorption[18].

Table 2 : examples of surfactant used in SLNs [15]

Non-ionic	Anionic	Cationic
Polysorbate 20	Sodium lauryl sulphate	Cetrimonium bromide
Polysorbate 60	Sodium dehydrocholate	Chlorhexidine salts
Polysorbate 80	Sodium taurodeoxycholate	Dimethyldiocta-decylammonium bromide
Polysorbate 85	Sodium taurocholate	
Poloxamer 182	Sodium glycocholate	
Poloxamer 188	Sodium taurocholate	
Poloxamer 407	Sodium cholate	
Poloxamine 908		

2.3.Other agent

Lipid nanoparticle formulations may include additional ingredients, such as charge modifiers and the surface, cryoprotectants utilized in SLN drying methods like lyophilization and spray drying, and other ingredients in addition to lipids and surfactants. It is possible to decrease the absorption of lipid nanoparticles by the reticuloendothelial system (RES) by altering their surface with surface modifiers like hydrophilic polymers[19].Coating with a biocompatible polymer, like poly (ethylene) glycol (PEG), can delay the rapid absorption of SLNs and lengthen the time that blood circulates[20].

Table 3 : other agent used in preparation of SLNs[21]

Cryoprotective	Load modifiers	Surface modifiers
Polyvinyl pyrrolidone	Diacetyl phosphate	mPEG5000-C-LAA18
Polyvinyl alcohol	Stearylamine	mPEG2000-C-LAA18
Glycine	Ionic polymers	DPPE-PEG2000
Mannitol	Sodium hexadecyl phosphate	SA-PEG2000
Lactose	Mono-decyl phosphate	DSPE-PEG2000
Maltose	Mono-hexadecyl phosphate	
Mannose	Mono-octyl phosphate	

3.API LOCALIZATION WITHIN SLNs

The structural organization of the colloidal lipid systems determines the location of the active molecule. Consequently, three broad and widely recognized classifications arise from the model that corresponds to the basic spherical model for SLN: (i) the active molecule is uniformly distributed along the length of the particle structure (homogeneous matrix); (ii) the API is concentrated within the particle and is encircled by the lipid matrix in a core-shell structure (enriched core); and (iii) the API is concentrated on the particle. surface (enriched coat). The drug's excellent solubility is generally facilitated by a higher temperature in the aqueous medium. This operating condition allows for a significant amount of drug in phase because, in the majority of studies, the temperature used to prepare the granules is usually at least 10° above the melting point of solid lipids. The aqueous phase becomes supersaturated during cooling, causing a decrease in drug solubility. Theoretically, this should cause the active molecules to migrate to the lipid substrate because of their lipophilic nature. When solid lipids have a high melting point and high crystallization temperature, they can crystallize before the active molecule during the nanoemulsion system O/W hot cooling process, housing the active molecule on the particle surface. This results in the formation of the outer shell, or enriched shell structure. This model is inappropriate for prolonged drug release because the concentrated outer shell layer exhibits an explosion effect on drug release[22]. On the other hand, let's say that using fat results in a low melting or crystallization point. If so, the high temperature might persist as a super cooled liquid or as a metastatic crystalline form with additional high temperature particles. Only rotation can contain active elements. Alternatively, when homogenization is applied at high cold pressure, it can stimulate nucleation and become evenly distributed throughout the grain structure or encapsulated within the seed (core-shell structure).By combining lipophilic active molecules into the SLNs using the hot homogenization method and applying the cold homogenization method, it is possible to obtain the homogeneous matrix model. For a uniform drug distribution in SLN, this solidified structure depends on its solid state[23,24].The concentration of the active molecule in the core-shell or enriched core structure is almost at the saturation point in lipid fusion; cooling this highly concentrated lipid reduces its solubility in lipid fusion, causing it to deposit in the centre of the SLN and form an active molecule-enriched nucleus. The sustained release profile is the result of this kind of structure[25,26].

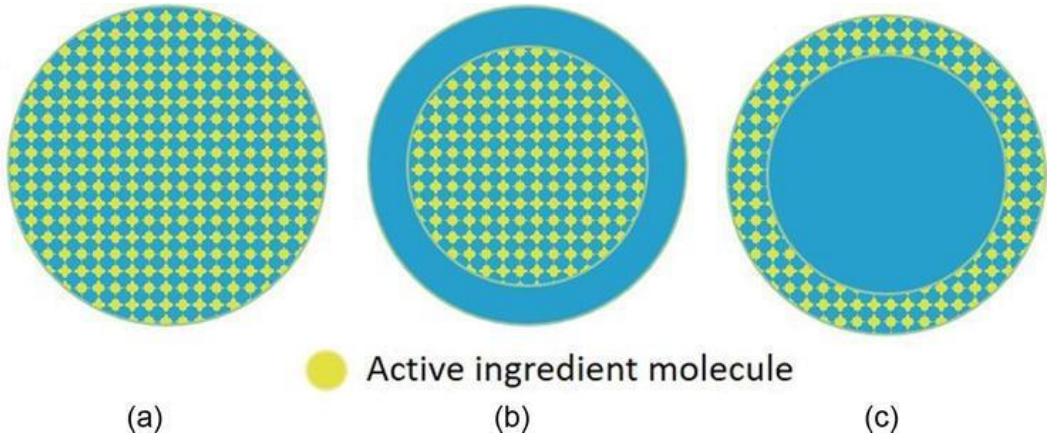


Figure 1 : API location in SLNs [21]

4.ADVANTAGES & LIMITATIONS OF SLNs [15]

4.1.Advantages of SLNs :

1. Improved release control and targeting of encapsulated compounds through size engineering and lipid composition
   - Melting acts as a catalyst.
   - Applying ligand coating or attachment to SLNs.
   - Delivery via injectable route specific to the site.
   - Requires a lower dose quantity and fewer doses overall.
   - A quicker start to the therapeutic effect.

2. The cells in the RES (Reticulo Endothelial System) do not readily absorb SLNs smaller than 120 nm, which allows them to evade the filtration process of the liver and spleen.

3. Using biocompatible/biodegradable lipids reduces both acute and chronic toxicity.

Reduce or eliminate the use of organic solvents during production.

4. Higher drug absorption because: - It is possible to combine hydrophobic and hydrophilic drugs.

   - High payload for drugs.
   - Drug actives are incorporated into labile chemical protection
   - A larger surface area leads to quicker dissolution.

5. Less complicated to produce than biopolymeric carriers since: - No special solvent is needed. Both the standard emulsion manufacturing process and raw materials are applicable.

   - A large variety of safe and biodegradable lipids are available. – Outstanding affordability and repeatability.
   - Large-scale production, lyophilization, and sterilization that are feasible.
   - A high concentration of the functional compound is achievable.
   - Adequate for combining two or more medications for combination treatment.
   - Small dosage form and precise dosage.

6. Improved medication stability in comparison to alternative colloidal carrier systems.
7. Flexibility in application and variety of drug delivery routes.
8. The creation of novel, safe medications.
9. Decrease in fed/fasted variability.

4.2.Limitations of SLNs :

SLNs often have the following drawbacks:

1. Poor drug loading capacity and entrapment efficiency.
2. Drugs may leak out during storage following a polymeric transition.
3. The dispersions have a relatively high water content, ranging from 70-99%.
4. Due to partitioning effects during production, hydrophilic drugs have a poor loading capacity.
5. It is impossible to undo molecular changes made during production.
6. Because nanoparticle production is expensive, the total cost of the product is high.
7. May trigger an immunological response and allergic reaction in the body.
8. Because of their small size and large surface area, they are challenging to handle.

5. METHODS OF PREPARATION OF SLNs

5.1.High Energy Method

Hot homogenization and cold homogenization are two categories for this technique, depending on the temperature at which SLN is produced. This method's benefit is that it produces SLNs with small particle sizes and high entrapment efficiency. High-pressure homogenization involves pumping molten lipid quickly and at a pressure of 500–5000 bar through a small opening. Although up to 40% lipid content has also been studied, typically 5–10% lipid content is used. Hot homogenization and cold homogenization are two common methods of HPH[28-30].

5.1.1.Hot homogenization

The process of the hot homogenization method is done at temperatures higher than the lipid's melting point. Here, the medication and the lipid are mixed together at the same temperature with an aqueous surfactant. The high shear device is used to form a hot pre-emulsion. To produce the SLNs, the hot colloidal emulsion droplets are recrystallized by bringing the emulsion down to room temperature. Higher temperatures generally lead to smaller particle sizes because the internal phase's viscosity decreases. High temperatures, however, can also quicken the drug's and the vehicle's rate of degradation. Three to five homogenization cycles at 500 to 1500 bar are usually adequate[28, 29].Because of their high kinetic energy, increasing the number of cycles or the homogenization pressure frequently results in larger particles, which cause coalescence. The particle size can be as small as 500 nm[29].

5.1.2. Cold homogenization

This method involves cooling the drug-containing lipid melt. Lipid microparticles are formed by grinding solid lipids. Pre-excitation is produced by dispersing these lipid microparticles in a cold surfactant solution. After that, this

hypothetical process is homogenized at room temperature or lower because SLNs can directly absorb lipid microparticles due to gravity[28,29]. This technique typically yields particle sizes between 50 to 1000 nm[28].

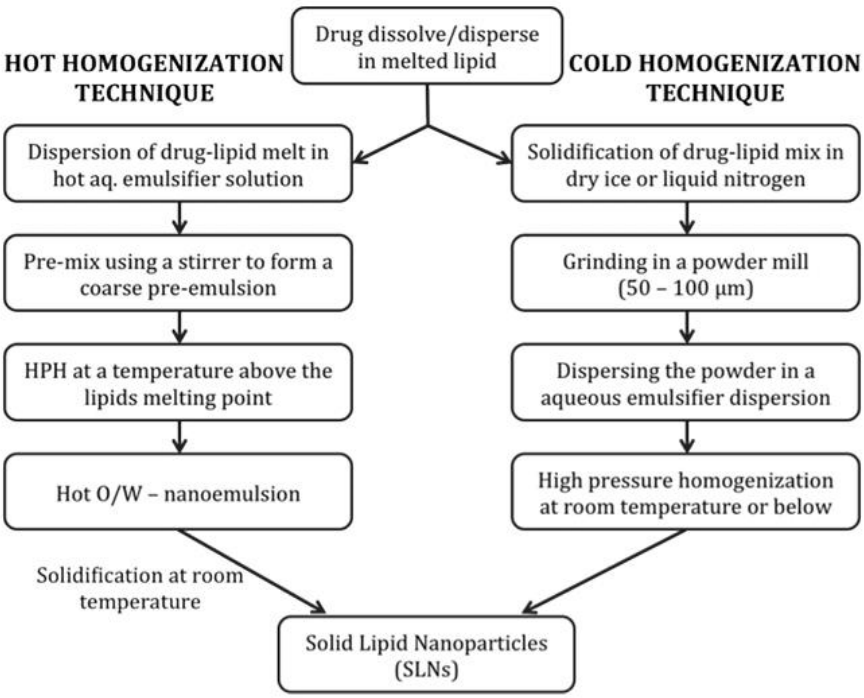


Figure 2 : systematic representation of hot & cold homogenization technique [15]

5.1.3.Ultrasounication Technique/ High Shear Homogenization

Based on the principle of cavitation, the ultrasonication technique is a dispersing method. First, a previously melted solid lipid is mixed with the drug. In the subsequent phase, the melted lipid is mixed with the heated aqueous phase (which has been heated to the same temperature) and blended using a high-speed stirrer or probe sonication. The aqueous phase is then added to the lipid phase drop by drop and stirred magnetically. A probe sonicator in a water bath (at 0oC) is used to ultrasonicate the resultant pre-emulsion. The manufacturing temperature was maintained at least 5°C above the melting point of the lipid to avoid crystallization during the process. After obtaining the nanoemulsion (o/w), contaminants from the ultrasonication process are eliminated by filtering it through a 0.45 µm membrane. Mannitol (5%) can be added to SLNs as a cryoprotector, lyophilization can be used to create freeze-dried powder, and the resulting SLNs are kept at 4°C to improve formulation stability[31,32].

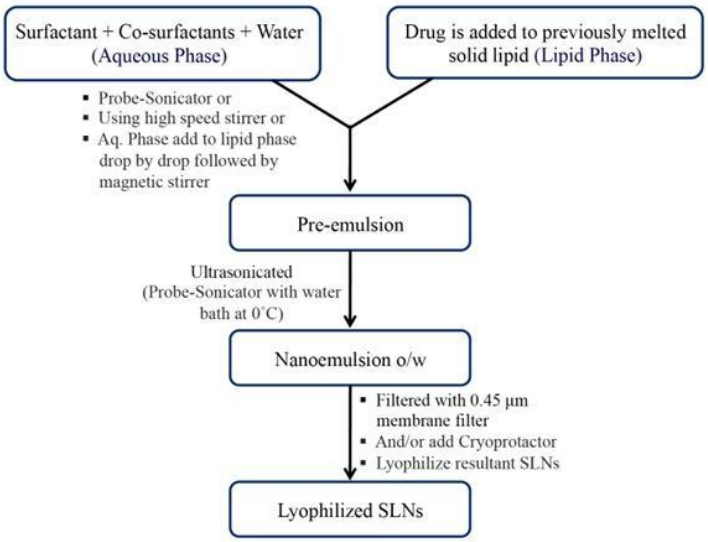


Figure 3 : systematic representation of ultrasonication process [15]

5.1.4.Supercritical fluid-based method

Compounds dissolve more readily in a supercritical fluid (SCF), which is created when a fluid's critical values for temperature and pressure are exceeded. One of the special qualities of supercritical fluid technology is its ability to produce small-sized, irregularly-shaped solids. The special qualities of supercritical fluids (SCF) include high diffusivity, low viscosity, and high compressibility. The most widely used SCF is supercritical CO2 (SCCO2) because it is easily obtainable, non-flammable, and non-toxic. SLNs can be prepared using five primary supercritical fluid extraction (SCF) methods: (i) supercritical fluid extraction of emulsions (SFEE), (ii) particles of gas-saturated solutions/suspensions (PGSS), and (iv) rapid expansion of supercritical solutions (RESS).[33, 34]

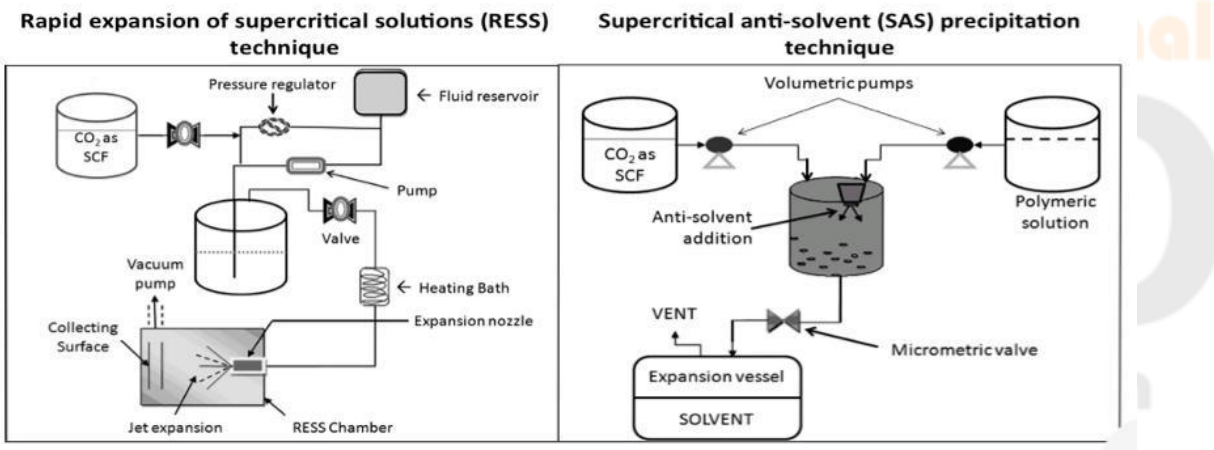


Figure 4 : systematic representation of supercritical fluid-based method [15]

5.2.Low energy methods

Particle size reduction can be achieved with low energy methods, some of which even happen on their own without the need for significant energy consumption. These lower-quality energy techniques rely on the system's characteristics and intricate hydrodynamic interfacial processes. It is thought that the spontaneous curvature of

surfactant molecules changes from negative to positive (o/w) or from positive to negative (w/o), releasing chemical energy during emulsification[35].

5.2.1.Microemulsion Method

The two steps of the microemulsion method are (I) creating a microemulsion and (ii) diluting it. The drug and lipids are combined in the first step at a temperature higher than the melting point of the lipids. To create a microemulsion, an aqueous phase containing surfactant is preheated to the same temperature and added to the lipid phase while gently swirled. The microemulsion is added to a cold aqueous solution in step two while being mechanically stirred. Lipid precipitation causes SLNs to form as a result of this process. This is a simple, repeatable, solvent-free method that can be scaled up. But because it uses a lot of water and surfactant, a water-removal step is necessary[36].

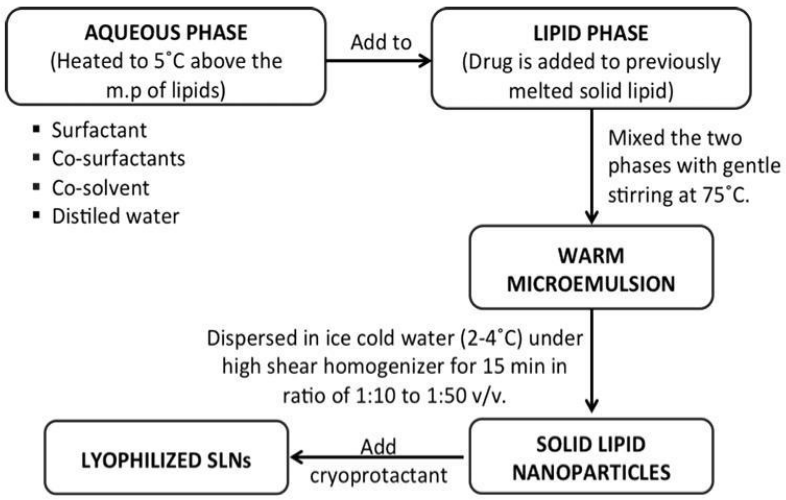


Figure 5 : systematic representation of microemulsion process[15]

5.2.2. Double Emulsion Method

One of the most popular methods for creating nanoparticles encapsulated with hydrophilic active ingredients and stabilized with surfactants or stabilizers is the double emulsion technique. There are three main steps to this method, which is also referred to as the multiple emulsion method: Water-in-oil emulsions (i) form, also known as reverse emulsions; (ii) the W1/O emulsion is added to the aqueous surfactant solution to form a W1/O/W2 emulsion, which is continuously stirred (sonicated or homogenized); and (iii) the solvent evaporates or the multiple emulsions are filtered to form nanoparticles[28].

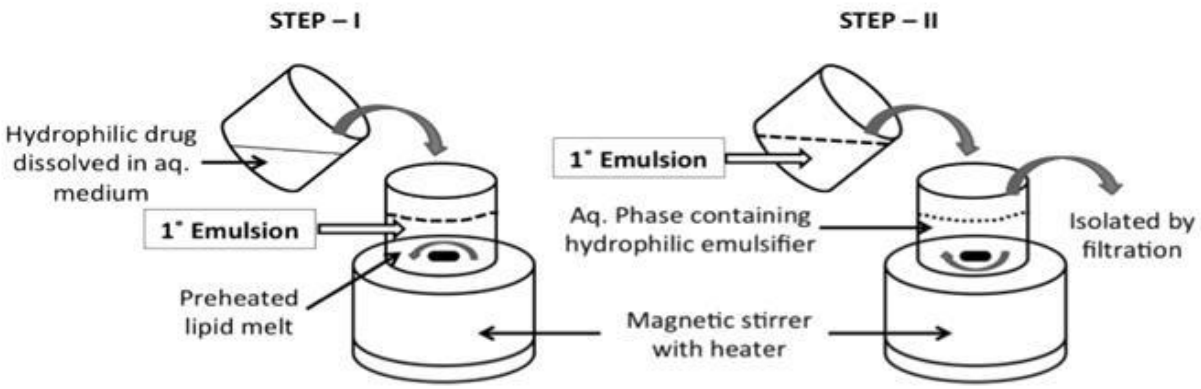


Figure 6 : systematic representation of double emulsion technique [15]

5.2.3.Phase inversion method by temperature (PIT)

Using heating and cooling cycles, the temperature-induced phase inversion technique converts an O/W emulsion into a W/O emulsion and back again until an emulsion is finally achieved. O/W correlation, in which every inversion works to shrink the droplet's size and enable the extraction of nanoparticles through a last dilution step in cold water[24, 25]

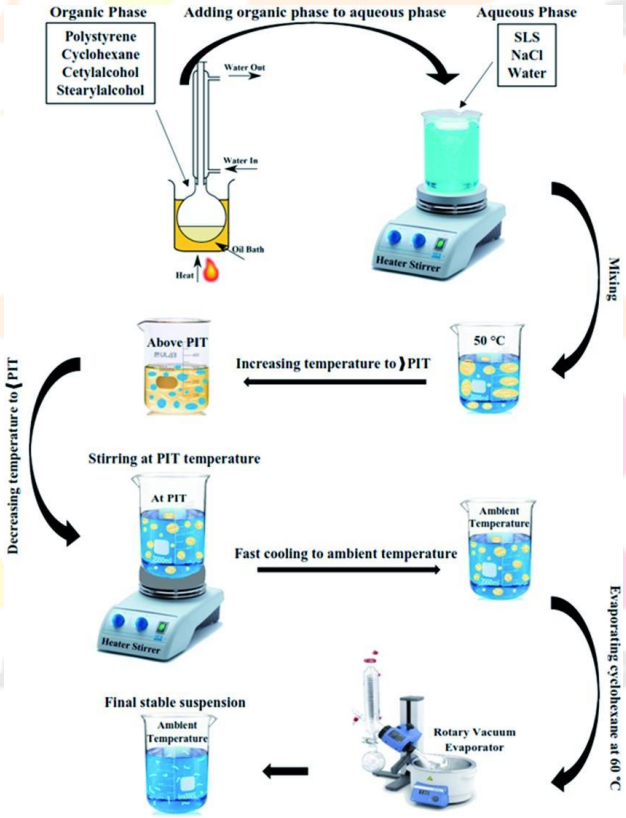


Figure 7 :systematic representation of phase inversion method by temperature [44]

5.2.4.Membrane contactor method

Using this technique, the lipid phase is forced through the pores in the membrane, causing small droplets to form at the outlet of the pores and be removed by the flowing water. After bringing the preparation down to room temperature, SLNs are produced[37].

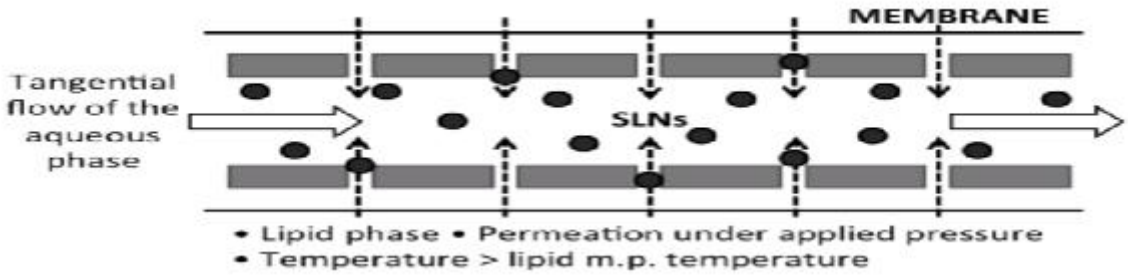


Figure 8 : systematic representation of membrane contactor[15]

5.2.5.Coacervation technique

The precipitation of free fatty acids from their micelles in the presence of a surfactant is the basis of the coacervation method. A fatty acid salt is evenly distributed throughout the stabilizer solution during this procedure. After heating the mixture to the fatty acid salt's Krafft point, it was constantly stirred until a clear solution was achieved. To create a single phase, the API's ethanolic solution is then gradually added while being constantly stirred. In order to obtain the nanoparticle suspension, a coacervation agent or an acidifying solution is then added[38]. The concentration of the micellar solution and the amount of polymer utilized for stabilization determine the particle size of SLN, which can range from 260 to 500 nm[39].

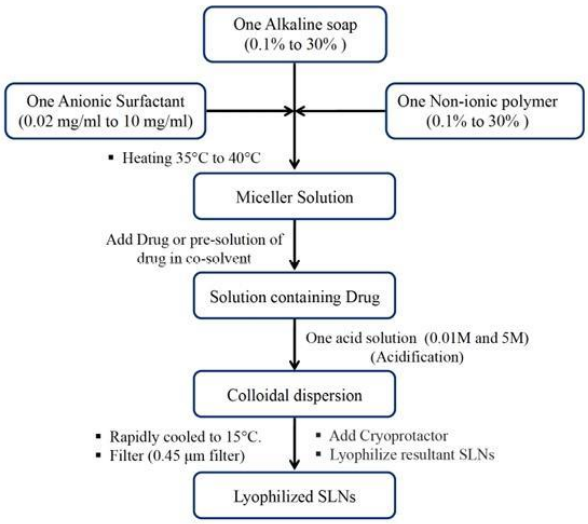


Figure 9 : systematic representation of coacervation technique [15]

5.2.6.Melt Dispersion Technique

This method involves heating the lipid phase above its melting point and using a low HLB surfactant to disperse it in water. In order to encourage the formation of SLN, an aqueous solution of surfactant with a high HLB content is added to the emulsion once more without causing it to form. This double w/o/w emulsion is then poured into cold water and gently stirred[40].

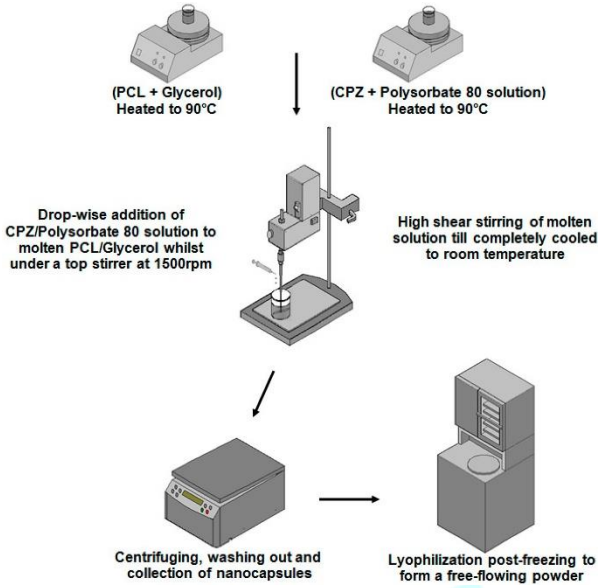
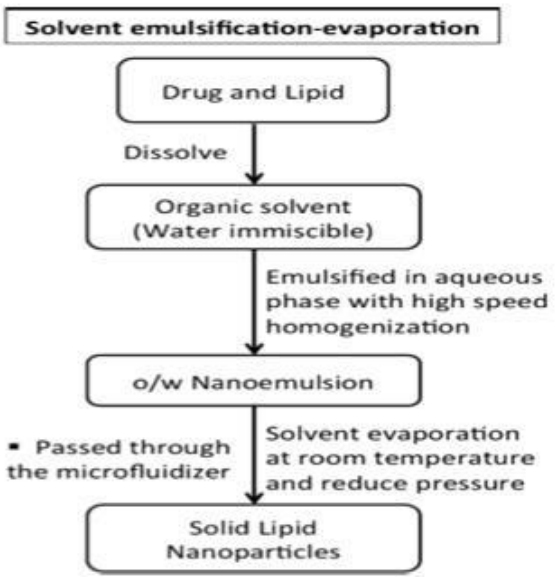


Figure 10 : systematic representation of melt dispersion technique [45]

5.2.7. Solvent evaporation emulsion method

There are three fundamental steps in the solvent evaporation emulsion (SEE) method for creating nanoparticles. To create a clear, homogeneous lipid solution, step (I) involves adding lipid material to a known volume of organic solvent that is immiscible in water and mixing it properly. In step (II), a high-speed homogenizer is used to combine the previously prepared solution with the appropriate volume of a heated aqueous solution containing surfactant above the melting point of lipids to create a thick emulsion. Next, in step (III), the nanoemulsion is produced by means of a high-pressure homogenizer, the high pressure of which turns the coarse emulsion into a nanoemulsion. Since the lipid material will precipitate in the water upon evaporation of the organic solvent, nanodispersion forms thereafter. By passing the lipids through a sintered disk filter funnel, they are separated after they precipitate in an aqueous medium. This method produces nanoparticles with a high trapping efficiency, are not flocculated (a single entity), and are



nanosized. [41].

Figure 11 : systematic representation of solvent evaporation emulsion method [15]

5.2.8.Solvent emulsion and diffusion method

The process relies on the thermodynamic equilibrium and initial saturation of the organic phase with an aqueous phase stabilizer. The drug is dissolved in the saturated solution created by using a homogenizer; an emulsifier is then used to disperse the drug in an aqueous solution to create an o/w emulsion. By adding additional water to the emulsion in the proper ratio while moderately stirring with a magnetic stirrer, the solvent can more easily diffuse into the water, resulting in nanoprecipitation and the formation of SLNs. Using this method, particles with an average diameter of 30,100 nm can be produced[42].

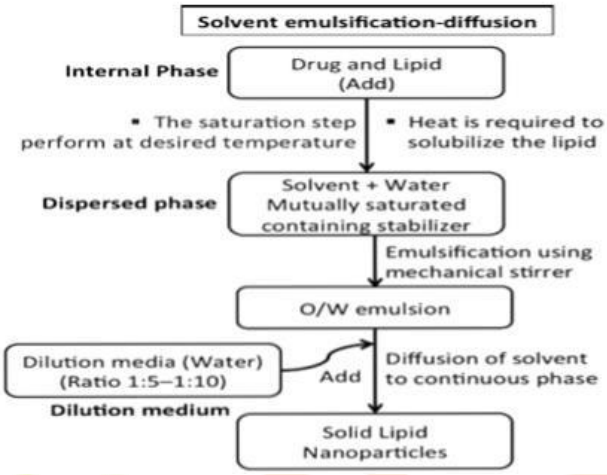


figure 12 : systematic representation of solvent emulsion and diffusion method [15]

5.2.9.Solvent injection technique (or solvent displacement)

This method involves dissolving the lipid and the active component in a solvent that is water soluble. A suspension of lipid nanoparticles is then created by dispersing the mixture with mild mechanical stirring in an aqueous solution of a surfactant; the solvent is then extracted. The distribution process's speed affects the size of the particles. Smaller particles are produced at higher speeds. Greater amounts of lipophilic solvents result in larger particles, which may pose an issue. The method has several benefits, including low temperatures, low cutting pressure, ease of handling, and a quick production process without requiring particularly sophisticated equipment (like a heavy homogenizer)[43].

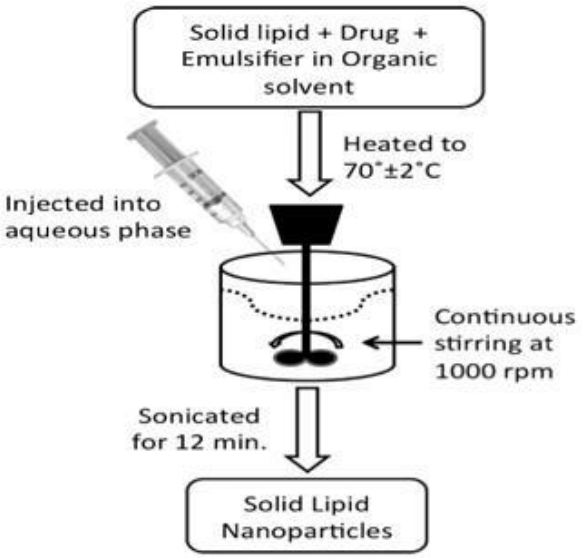


Figure 13 : systematic representation of solvent injection technique (or solvent displacement) [15]

6.FEATURES OF METHODS

Table 4 : feature of various methods [36]

Method	Feature
Hot high-pressure homogenization	Operation free of organic solvents, quick production time, and viability of scaling up Unfit for medications that are hydrophilic or heat-sensitive
Cold high-pressure homogenization	Ideal for drugs that dissolve in water to avoid medication loss Big particles and time-consuming procedures
High-speed stirring and ultra-sonication	Easy implementation and operation without the need for organic solvents Elevated levels of surfactant, medication exposure to elevated temperatures, and metal pollution
Supercritical fluid	Uniform distributions of particle sizes and high extraction efficiencies of solvents Use of costly supercritical fluids and organic solvents
Microemulsion	Easy to scale up, repeatable, solvent-free, and practical large volumes of water and surfactant
Double emulsion	Creating a double emulsion of water, oil, and water Ideal for hydrophilic medications Large particle size and high drug loss
Phase inversion temperature	Based on polyoxyethylated surfactants that are non-ionic low energy consumption, no need for solvents Low stability of the aqueous mixture
Membrane contactor	Use of a particular membrane contactor Scale-up viability and controllability of particle size Complex system and membrane clogging potential
Coacervation	Usage of fatty acid alkaline salts Simple and solvent-free Not suitable for medications that are sensitive to pH; only works with alkaline salt lipids
Solvent emulsification-evaporation	Ideal for medications that are extremely thermolabile, low temperatures, and physical strain Removal of toxic organic solvents
Solvent emulsification-diffusion	Ideal for medications that are highly thermolabile, doesn't require extreme heat or physical strain Removal of toxic organic solvents, a large volume of water, and a low concentration of SLN
Solvent injection	Easy to use, quick production, and no complex equipment Removal of toxic organic solvents

7.EVALUATION OF SLNs[36]

7.1.Partical Size:

A non-essential parameter in the process control and quality assurance of SLNs production is particle size. The total surface area and physical stability of the nanodispersion system are influenced by the particle size. Particle size can be ascertained via laser diffraction and dynamic light scattering (DLS), commonly referred to as photon correlation

spectroscopy . Using the fluctuation of the scattered light intensity brought on by the movement of the particles, DLS calculates the particle size. With a size range of a few nanometers to three micrometers, it is reasonably sensitive and accurate. Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM) these are also used for particle size analysis of SLNs.

7.2.PolydispersityIndex

The size distribution of a nanodispersion is reflected in the polydispersity index (PI).A more monodispersed nanodispersion is indicated by a lower PI value [52].A nanodispersion that has a PI value less than 0.5 is typically homogenous and monodispersed. An API value greater than 0.5 indicates that a nanodispersion is non-homogeneous and polydisperse. Nonetheless, the majority of research indicates that a good size distribution is indicated by a PI value < 0.3 . DLS can be used to measure PI.

7.3.Zeta Potential

The electric potential of NPs resulting from ionization of the NP surface groups or ion adsorption is known as the zeta potential. It is dependent upon both the media that surrounds the NPs and their surface chemistry. DLS is typically used to determine a nanodispersion's zeta potential. One can forecast a nanodispersion's physical stability using zeta potential. Strong repulsion between the NPs is indicated by a high zeta potential, which can stop particle aggregation. However, in a low zeta potential nanodispersion, the attraction between the particles outweighs the repulsion, causing the nanodispersion to coagulate or flocculate. For the stabilization of a nanodispersion, an absolute zeta potential value greater than 30 mV is generally regarded as suitable.

7.5.Entrapment Efficiency

The ratio of the drug entrapped into nanoparticles (NPs) to the total amount of drug used in production is known as entrapment efficiency (EE).

EE% = Amount of drug entrapped/ Total drug amount ×100

In order to maximize EE, various process and formulation parameters are typically adjusted while preparing SLNs. Once the unentrapped drug has been extracted from the SLN dispersions, the amount of the entrapped drug can be ascertained. Currently, a number of techniques are employed, including ultracentrifugation, dialysis, gel filtration chromatography, and filter membrane (MWCO 10–20 kDa). It is possible to extract and quantify entrapped drug SLNs. It is also possible to quantify the drug that is not entrapped, which leads to an indirect calculation of the drug's amount.

7.6.Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD)

The crystallinity and polymorphic behaviour of the constituents of SLNs are frequently studied using DSC and XRD [58]. It is necessary because during storage, a polymorphic transition between the lipid matrix and the drug that is entrapped could cause the drug to expel itself in an unwanted way. The DSC method calculates a sample's heat gain or loss as a function of temperature. It displays how temperature variations have affected the samples' physical and chemical composition. An SLN sample's degree of crystallinity can be ascertained using DSC by comparing the

sample's melting enthalpy/g to that of the bulk material. Based on their crystal structure, XRD can identify particular crystalline compounds. It is predicated on the diffracted angles of the X-ray beam, which are determined by the atomic arrangement and the separation between the planes of the crystals. Every kind of crystalline material has a different XRD pattern, which includes the diffractions' position and intensity. In addition to characterizing the structure of drug and lipid molecules, XRD can be used to predict the phase behaviour and arrangement style of lipid molecules. Typically, DSC and XRD analyses are carried out in tandem to assess the polymorphic behaviour and crystallinity of SLNs.

7.7.Drug Incorporation Models and Drug Release

The lipid matrix of SLNs incorporates drugs using three distinct models: a homogenous matrix, a drug-enriched shell, and a drug-enriched core. The drug and lipid are uniformly distributed in the homogenous matrix model. When using the hot homogenization method to prepare SLNs of highly lipophilic drugs, this kind of drug incorporation is achievable. Furthermore, the homogenous matrix model can also be obtained through the cold homogenization method. According to this model, the drug's release results from both the lipid's degradation and its diffusion out of the solid lipid matrix. For the prednisolone-loaded lipid nanoparticles, this model was considered to be valid.

7.8.Stability and Safety

Lipids in solid-liquid nanoparticles (SLNs) are typically present in a mixture of α and β polymorphs; kinetic energy, such as light and temperature, can transform them to β polymorph with gel formation. The physical stability of SLN dispersions can be assessed by changes in particle size, PI, and zeta potential; increases in these parameters along with a decrease in zeta potential are signs of instability; light and temperature can cause particle growth and lower zeta potential. Storing SLN dispersions at low temperature and shielding them from light will greatly increase their physical stability. For instance, an SLN dispersion gelled after three months of light storage, and the zeta potential dropped (from −24.7 to −18 mV). Zeta potential dropped to -15 mV and the particle size of the SLNs increased at high temperatures. After three months, the SLNs' particle size remained constant in cold environments. According to a number of studies, SLN dispersions remained physically stable for over a year.

8.ROUTES OF ADMINISTRATION

8.1.Oral administration

When used as a carrier in the oral route, SLN enhances drug absorption through the GI tract and increases oral bioavailability of drugs. In one study, SLN loaded with famotidine demonstrated a 2.06-fold increase in oral bioavailability and a prolonged release when compared to a commercial product. Due to its quick first-pass metabolism, the antipsychotic medication aripiprazole's in-vivo effects were lessened when taken orally. Sinha et al. synthesized SLN of aripiprazole by employing sodium taurocholate and tween 80 as surfactants and tristearin as a lipid. By using a dizocilpine-induced schizophrenic model in lace mice, it was discovered that the in-vivo efficacy was increased. Aripiprazole's oral bioavailability was 1.6 times greater in the pharmacokinetic studies of the SLN formulation when compared to Its suspension[46].

8.2.Parenteral administration

Because of their small size, SLN can pass through the vascular system and reduce the negative effects of the medication that is being administered. Parents can safely use SLN to administer lipids that are physiologically well-tolerated. They obstruct the systemic circulation's macrophage uptake. Zhou et al. reported on the targeted delivery of hyaluronic acid coated SLN. In this study, the afflicted joint tissues were targeted with SLN containing glucocorticoid prednisolone, which reduced the level of inflammatory cytokines in the blood and the swelling of the joints[47].

8.3.Topical administration

Applying SLN topically increases drug delivery to the targeted site of action while minimizing side effects. Topical preparations can be applied to achieve systemic, stratum corneum, and surface effects. The anti-inflammatory drug auraptene's low aqueous solubility limits its application as a topical medication. Daneshmand et al. developed the SLN of auraptene for topical delivery, which demonstrated both desirable anti-inflammatory activity and enhanced cutaneous uptake[48]. The most effective method for topical antifungal medication delivery is through SLN. Pityriasis versicolor was treated with fluconazole using an SLN gel. When compared to Candistan® 1% cream, the prepared gel demonstrated superior therapeutic activity against pityriasis versicolor[49].

8.4.Transdermal application

It was reported that the dispersion of SLNs, which is made with a low lipid content of up to 5%, has extremely small particle sizes. Because of the dispersion's low viscosity and low lipid concentration, it is challenging to apply SLNs directly to the skin. It is best to incorporate SLNs into the base of a cream, ointment, or gel to make it easier to apply them to the skin. The concentration of lipids should be raised in order to create a semisolid system that is appropriate for applying directly to the skin for the dispersion of SLNs[50].

8.5 . Rectal administration

Due to its simplicity of use, this approach is recommended for patients who are younger. Comparing rectally administered drugs to oral or intramuscular routes at similar doses, it was reported that the plasma level and therapeutic effectiveness of the former were higher. Din and colleagues created a dual-reverse, thermosensitive hydrogel of flurbiprofen loaded with SLN. Because of its delayed initial burst effect, SLN loaded hydrogel demonstrated higher drug release compared to pure drug and lower drug release compared to hydrogel when compared to the drug and hydrogel[51].

8.6.Nasal administration

For the drug's quick absorption and quick onset of action, the nasal route is recommended. Because it stays out of the GI tract, the medication doesn't deteriorate. When efavirenz is administered intranasally, it has been observed that the drug's SLN increases the concentration of the drug in the brain[52].

8.7.Ophthalmic administration

The primary issue with administering a medication via the eyes is its low bioavailability. After administration, only 5% of the medication can pass through the cornea40. Voriconazole SLN administered ophthalmically demonstrated burst release followed by sustained release in one study. It was noted that the drug had a longer residence time on the surface of the eyes[53].

8.8.Pulmonary administration

Aerosolized SLN dispersions can be administered to the lungs, circumventing the drug's first-pass metabolism and augmenting its absorption even more. When the drug was trapped in SLN, it exhibited controlled release behavior. In a study comparing SLN and liposomes, SLN demonstrated longer lung exposure following pulmonary administration41. This could be helpful in the delivery of some medications. Rosiere et al. developed the paclitaxel SLN for lung tumors. The SLN were administered by pulmonary route after being coated with chitosan and a folate-grafted copolymer of polyethylene glycol. The coated SLN was found to be useful for paclitaxel inhaled therapy and to have a good pharmacokinetic profile and prolonged release of paclitaxel in the lungs[54].

9.RECENT WORK ON SOLID LIPID NANOPARTICLES

9.1.SLN for genetic materials

DNA, miRNA, siRNA, nucleic acids, and other genetic materials may be delivered by SLN. Genetic materials are delivered via unique cationic solid-state nanoparticles (SLN). Catalytic SLN was prepared by Botto et al. The interaction with plasmid DNA was revealed by the thermal analysis of cationic SLN. The outcome showed that the type and quantity of surfactant used in the preparation affects how well gene therapy is delivered[55]. In order to reduce STAT3 overexpression and overcome cisplatin resistance in lung cancer cells, Kotmakci et al. developed cationic solid-state nanoparticles (SLN) for the delivery of RNA-mediating plasmid DNA. Cationic SLN of plasmid DNA complexes reduces cisplatin resistance in cells and downregulates STAT3 expression in resistant cell lines[56].TRPV1-targeting siRNA loaded SLN was created by Sharma et al. without the use of a cationic agent. The effects of PEG600 as a surfactant on endosomal uptake and particle size reduction were demonstrated by the author. It was demonstrated that SLN are efficient at silencing the skin TRPV1 after topical administration of TRPV1-targeting siRNA loaded SLN to rats[57]. To lower the amount of 5-α reductase enzyme, which causes conditions like benign prostatic hyperplasia, prostate cancer, and androgenic alopecia, Ekbaba et al. developed SLN of shRNA-encoding plasmid. It was discovered that the formulation was effective in lowering the 5-α reductase enzyme level in the DU-145 cell line in vitro with the least amount of cytotoxicity[58].

9.2.SLN in tuberculosis disease

Costa et al. prepared isoniazid SLN by functionalizing it with mannose (M-SLN) in a study. Compared to the SLN, the M-SLN displayed higher uptakes on alveolar macrophage cells. It was discovered that the M-SLN was more successful in delivering anti-tubercular medication to alveolar macrophages[59].In a different study, mannose was engineered into SLN surfaces to deliver rifampicin, a medication used to treat tuberculosis. It was discovered that the mannosylated SLN could sustain the drug load prior to entering the macrophage and inducing alveolar macrophage

phagocytosis[60]. Rifampicin SLN coated with chitosan was prepared by Vieira et al. When compared to uncoated SLN, the chitosan coated SLN exhibited greater mucoadhesive qualities in vitro and increased drug release in alveolar epithelial cells A549[61].

9.3.SLN in cancer

SLN have many uses in different kinds of cancer. In one study, tocopheryl polyethylene glycol succinate (TPGS) and Brij 78 were used as co-delivery vehicles to create solid lipid nanoparticles of curcumin and piperine. In vitro experiments on reversing P-glycoprotein-mediated multidrug resistance in A2780/Taxol cells demonstrated the efficacy of SLN. Low intrinsic toxicity tumor cells were selectively killed by curcumin SLN[62]. By altering the surface of solid lipid nanoparticles with N-carboxymethyl chitosan (NCC), the bioavailability of the particles can be enhanced. Through surface modification of SLN with NCC, the intestinal delivery, lymphatic uptake, and cytotoxicity were increased. As the cellular uptake on MCF-7 cells increased, it was discovered that the bioavailability and effect on tumor cells increased as well[63]. Chirio et al.'s study on HCT-116 colon cells demonstrated that the SLN can incorporate a larger dosage of medication and be used to treat cell cultures with low cytotoxicity[64]. To make it tumor targeting, Chuang et al. created pH-sensitive cationic polyoxyethylene SLN of camptothecin (CPTPEG-SLNs+). CPT-PEG-SLNs+ increased the effectiveness of camptothecin against HCC36 or CL1-5 tumors and accumulated over a lengthy period of time (>120 hours) in a variety of tumor types[65].

9.4.SLN in depression

He et al. prepared SLN of dexanabinol and curcumin to examine the antidepressant effect in a corticosterone-induced depression model. SLN improves the antidepressant effect of curcumin while overcoming its low solubility and low bioavailability. The SLN demonstrated that curcumin levels in mice's brains increased and that the drug's antidepressant effects were prolonged[66]. Agomelatine is an antidepressant; Fatouh et al. prepared SLN of it to improve its bioavailability and target delivery to the brain. When it came to brain targeting, intranasal administration of SLN proved to be more successful than intravenous administration. The pharmacokinetic analysis demonstrated that agomelatine SLN had a greater absolute bioavailability than valdoxan oral suspension[67].

9.5.SLN in cosmetics

In general, UV rays are very damaging to skin. SLN are a valuable drug carrier in cosmetics because they exhibit uniform skin dispersion without the need for greasy oil, controlled drug release, and superior UV ray blocking[68]. An antioxidant-rich natural sunscreen ingredient is silymarin. A sunscreen cream was created by preparing and further formulating the silymarin SLN. Following cream evaluation, the sun protection factor in-vitro and in-vivo were 14.1 and 13.80, respectively, and accelerated stability studies revealed no changes. These results demonstrated that silymarin SLN can be used for photoprotective action when formulated as sunscreen cream[69].

9.6.SLN as a carrier for sustain drug delivery

The medication's release from the SLN's matrix can be regulated. Drugs that are lipophilic and hydrophilic can be sustainedly delivered with SLN. Curcumin-loaded SLN demonstrated enhanced antibacterial efficacy and sustained release in a study by Jourghanian et al[70]. Domperidone SLN was developed by Shazly et al. When compared to the

conventional tablet, which showed instantaneous release, the prepared SLN demonstrated sustained release of domperidone for up to 12 hours. The outcomes of pharmacokinetic investigations demonstrated that domeperidone's oral bioavailability was improved[71].

9.7.SLN for brain targeted drug delivery

Since SLN has a particle size of only 50 nm, it can be directed specifically towards the brain. Because of their capacity to cross the blood-brain barrier, SLN are employed in the treatment of CNS illnesses as a means of drug delivery. The ability of ligands to functionalize SLN renders them suitable for targeting brain sites. When compared to drug suspension, TMC (N-trimethyl chitosan) coated SLN improved brain delivery, according to a study by Ramalingam et al. After oral administration, the surface modification with TMC protects them in the stomach environment, allowing a significant amount of medication to enter systemic circulation and pass through the blood-brain barrier[72].A natural remedy for a number of brain conditions, including cerebral ischemia, is andrographolide. However, poor solubility, instability, and low bioavailability are issues related to its delivery to the brain. Andrographolide SLN was created by Graverini et al. for brain delivery. In in vivo experiments, SLN were transferred to the brain parenchyma after passing through the blood-brain barrier and beyond the vascular bed[73].

10.APPLICATION OF SLNs [74]

- SLN as potential new adjuvant for vaccines.
- Solid lipid nanoparticles in cancer chemotherapy.
- Solid lipid nanoparticles for delivering peptides and proteins.
- Solid lipid nanoparticles for targeted brain drug delivery.
- Solid lipid nanoparticles for parasitic diseases.
- Solid lipid nanoparticles for ultrasonic drug and gene delivery.
- SLN applied to the treatment of malaria.
- Solid lipid nanoparticles in tuberculosis disease.
- SLN in cosmetic and dermatological preparations.
- SLN for potential agriculture applications

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