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# A Review on Solid Lipid Nanoparticles

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**ABSTRACT**

The study assesses the original conceptions and ideas reach a mature level in the golden era of pharmacological nanocarriers. The present question is how to improve nano-formulations to guarantee that they are safe, efficient, and scalable, so that they may be produced at an industrial level and move to clinical usage. There is little doubt that nano-formulations are incredibly important tools for drug delivery applications. Lipid nanoparticles have gained traction in this context because they are often viewed as formulations that are non-toxic, biocompatible, and simple to make. Lipid nanocarriers are being used increasingly in the pharmaceutical industry to carry and deliver a variety of therapeutic agents, from biotechnological products to tiny medication molecules. Beginning with a short description of the properties of solid lipid nanoparticles, this paper next highlights the need of conducting methodical preformulating investigations. The primary uses and benefits of this class of nano vehicles in certain therapeutic contexts are explored. The next section discusses pharmacokinetic elements, including routes of administration, absorption after oral administration, distribution in the body, and elimination procedures. Concerns of toxicity and safety are also addressed. By using descriptive statistics from the most recent solid lipid nanoparticle studies, our study offers a unique perspective on the biopharmaceutical characteristics of these nanovehicles. All of the results, trends, graphs, and discussions that are shown here are based on a thorough (and repeatable) search of the literature that only looked at original papers on the topic over a 7-year period (from 2013 to the present), which accounts for more than 60% of all publications on the subject in the major bibliographic databases and search engines. The therapeutic use areas, absorption and distribution procedures, and current initiatives for the translation of lipid-based nanoparticles into clinical practise were the main points of emphasis. In order to comprehend the reasons behind the small number of solid lipid nanoparticles undergoing clinical trials, the presently ongoing clinical studies on lipid nanoparticles were examined, along with a short discussion of what successes or milestones are yet to be achieved.

## INTRODUCTION:

It is advised to use solid lipids nanoparticles (SLNs), a pharmaceutical that is water soluble, as an effective carrier technique for rectifying effective treatment. Nanoparticles are characterised by sizes between 10 and 1000 nm for colloidal molecules. These are made from synthetic, distinctive polymers with the goal of improving medicine delivery and lowering mortality.[1]

They have created a flexible replacement for lipid nanoparticles as a means of medication delivery. They are ideally suited to maximise sedate delivery and decrease lethality since they are produced from synthetic or special polymers.[2]

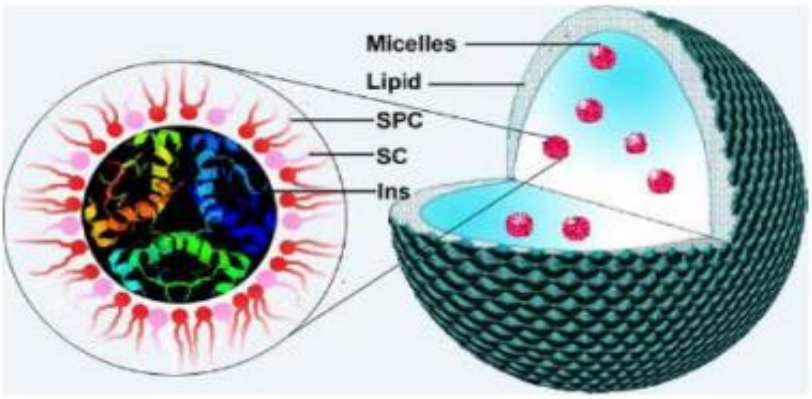


**Fig. 1: Structure of Solid Lipid Nanoparticles**

SLN are attractive for their ability to improve the implementation of medicines and have intriguing qualities including small size, large surface zone, high medicament mounting, and stages interacting at the interface.[3]

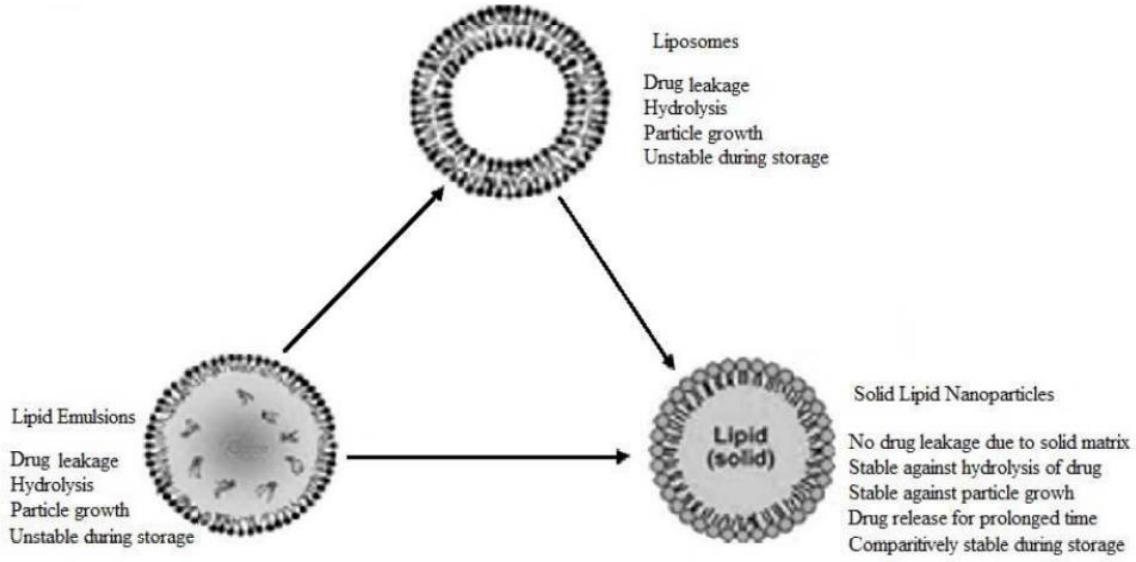


**Fig.2: Diagrammatic representation on SLN over emulsions and liposome**

SLNs are a cutting-edge colloidal carrier system that may be used as an alternative to an oil-in-water emulsion for parenteral delivery. But an SLNs has taken the place of the emulsion's liquid lipid.[4]

### 1.1 Advantages of SLNs[5]

- Powdered detailing may be shaped after being stop dry.
- Dynamic medicine can be introduced gradually over a lengthy period of time.
- Outstanding biocompatibility
- Enhance medications' stability.
- Excellent repeatability using as the readiness process a clever high-weight homogenization procedure.
- Significantly increased drug content.
- The possibility of combining drugs that are both hydrophilic and hydrophobic.
- The biodegradable nature of the transporter lipids provides protection. staying away from natural solvents atoms that are only partially soluble in water have increased bioavailability.

- Strategies for avoiding natural solvents are in place.
- Possibility of mass production and clean-up.

**1.2 Disadvantages of SLNs:**[7,8,9.]

- Sedative stacking limit is poor.
- Drug ejection following a polymeric motion in a crowded area.
- Variable tendency for gelation.
- The inability to combine hydrophilic drugs due to apportioning effects during the production process.

**2. Aim of SLNs:**[10,11]

- Possibility of administering banned substances and drugs that target
- Moderate (less expensive than transporters based on polymers or surfactants).
- It is possible to include both lipophilic and hydrophilic medicines.
- Steer clear of organic solvents.
- Issues with large scale creation and sanitization
- Enhanced tranquillizer security.
- Since most lipids may be broken down by biodegradation, the transporter has little biotoxicity.
- Increasing the bioavailability of bioactive mixtures that are caught.

**3. Method of Preparation of Solid Lipid Nanoparticles:**[12]

The SLNs preparation method includes the use of high shear homogenization, ultrasonication, microemulsion-based SLNs design, supersonic fluid innovation, splash drying, soluble emulsification/vanishing, soluble infusion technology, and soluble emulsification-dissemination.[13]

Recently, lipid nanoparticles have also been produced using this technique13. This process is driven by the precipitation of organised fragmented lipids. This technique allows for simultaneous soluble elimination and lipid synthesis. Dissolvable ejection is crucial and may be performed by refining or another way if it is not finished within the prescribed circumstances. Lipid nanoparticle organisation occurs after the naturally existing water-immiscible dissolvable has disappeared. The quantity of admixture, the lipid concentration, the temperature, the blending methodology, the type of natural dissolvable, and the emulsifier are just a few of the variables that affect particle size.[14] SLNs are produced from fat, emulsifiers, and water dissolvable using multiple techniques, and they are classified under.

### 3.1 High pressure homogenization:

This technique is being used to create SLNs for the first time, and it is reliable and efficient. High pressure homogenizers (100–2000 bar) drive a fluid through a narrow orifice (in the range of a few microns). The fluid accelerates to a very high velocity (above 1000 km/h) over a very short distance. The particles disintegrate into submicron sizes as a result of cavitation pressures and very high shear stresses. However, lipid content of up to 40% has also been studied, 5–10% lipid content is frequently used.

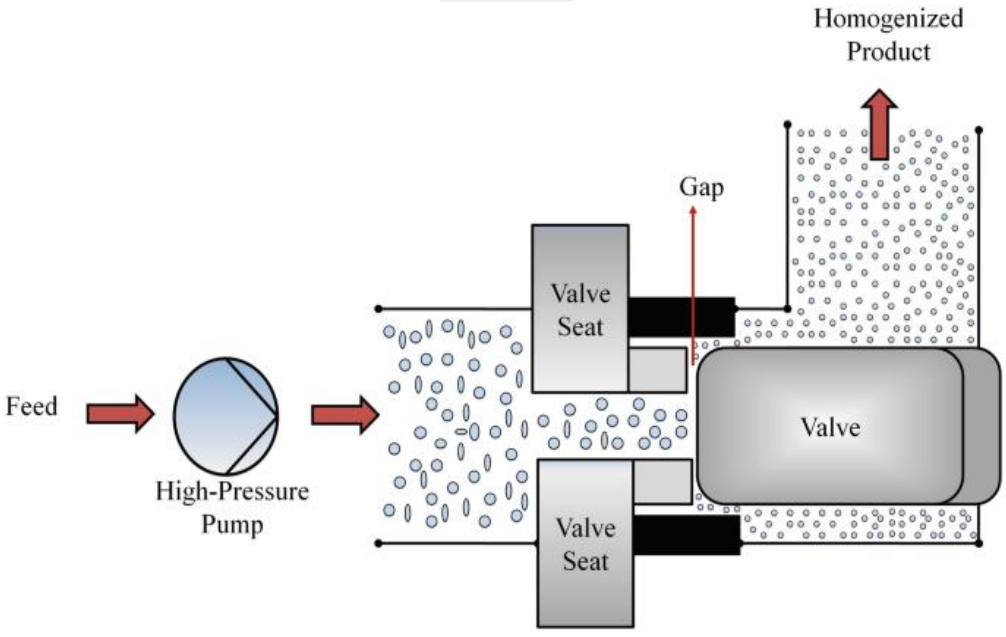


**Fig.3: Diagrammatic representation of HPH**

Cold homogenization and hot homogenization are the two forms of HPH. In both situations, a preliminary phase entails the medication being dissolved in the fat melt in order to be incorporated into the bulk lipid.

**A. Hot Homogenization:**

Hot homogenization, which is done at temperatures above the lipid's melting point, is also referred as "emulsion homogenization." Using a high-shear mixing apparatus, the drug-loaded lipid melt and the aqueous emulsifier phase are combined to create a pre-emulsion at the same temperature. Since the quality of the pre-emulsion greatly affects the quality of the finished product, it is preferable to achieve droplets that are just a few micrometres in size. Smaller particle sizes typically arise because increasing temperatures cause the inner phase's viscosity to drop.

High temperatures, however, can expedite the degradation of drugs and carriers. The homogenization procedure may be repeated several times. Never forget that the temperature of the sample increases during high pressure homogenization. 3-5 homogenization cycles between 500 and 1500 bar are often enough. The high kinetic energy of the particles causes particle coalescence, which results in an increase in particle size when the homogenization pressure or cycle count are increased. The major outcome is a nano-emulsion, that solidifies upon cooling at room temperature due to the lipid's liquid state. Due to the small particle size and the presence of emulsifiers, lipid crystallisation may be significantly slowed down, and the sample may remain in the form of a super-cooled melting for many months.[16]

**B. Cold Homogenization:**

In contrast, the cold homogenization involves grinding a suspension at higher pressure while using a solid fat. Because of a rise in temp. during homogenization, effective temperature management and regulation are required to guarantee the lipid is in an unmolten form.

The following three drawbacks of the hot homogenization method have led to the development of cold homogenization.

1. Equipment that can degrade drugs due to temperature.

2. During homogenization, drug dispersion into the aqueous medium

3. The nanoemulsion's complex crystallisation process, which can result in multiple alterations or super-cooled melt pressure.

### 3.2 Ultra-sonication and high-speed homogenisation

SLNs can also be made using high-speed homogenization or ultrasonication methods. It is necessary to combine ultrasonication and high-speed homogenization for lower particle sizes. Although it lowers shear stress, there are several drawbacks, including the possibility of metal contamination and physical instability such particle development during storage. It uses a bath sonicator or a probe sonicator. 16,18.

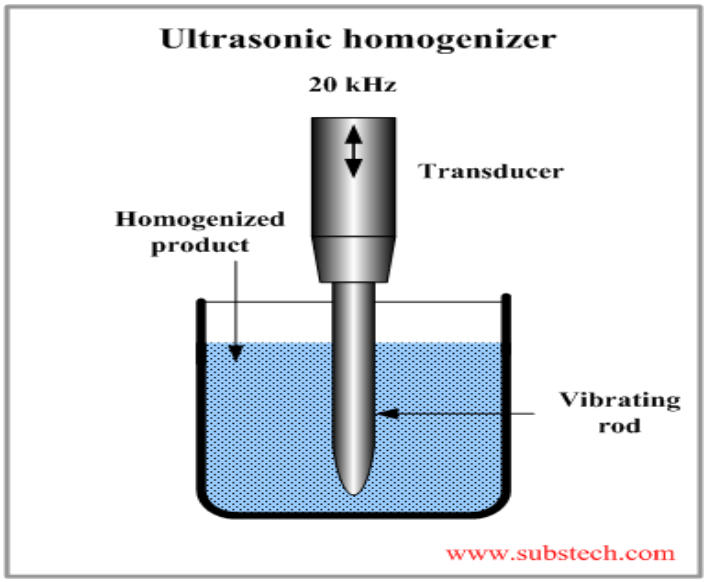


**Fig.4. Ultrasonic homogenizer**

### 3.3 Solvent evaporation method

The lipid soluble substance is dissolved in an aqueous phase of an organic solvent that is water-immiscible (such as cyclohexane). After the solvent has evaporated, lipid precipitates as nanoparticles with a mean size of 25 nm, giving rise to a dispersion of nanoparticles. The solution has been homogenised under high pressure and emulsified in a water phase. Under lower pressure, the organic solvent was evaporated out of the emulsion. 16,17,18,19.

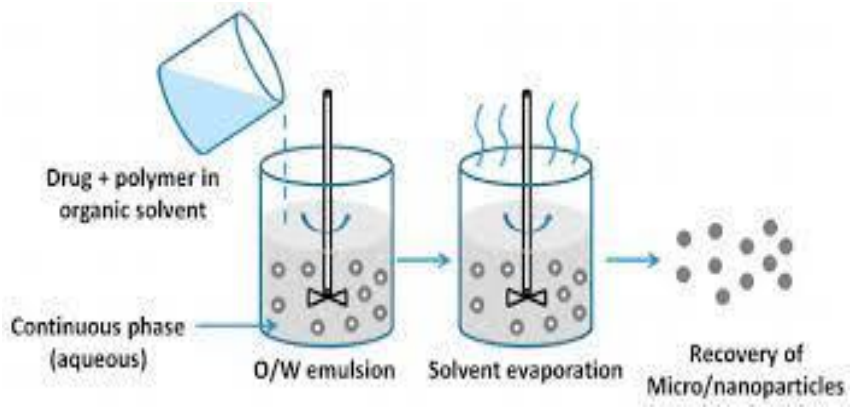


**Fig.5: Diagrammatic representation of solvent evaporation method**

### 3.4 Solvent emulsification diffusion method

This technique allows for the production of particles with typical diameters between 30 and 100 nm. The absence of heat throughout formulation is the major benefit of this method. In this methodology, the fat is usually dispersed in the organic phase in a steam bath warmed to 50 °C, and the zeta potential is changed by an acidic aqueous phase to produce coacervation of SLN. Centrifugation is then used to easily separate the two phases. The SLN suspension had been created swiftly. After centrifuging it, the entire dispersed system may be re-dissolved in distilled water. (16)

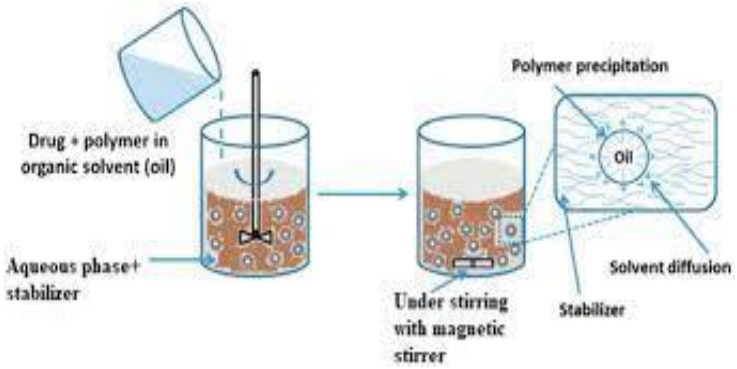


**Fig.6: Diagrammatic representation of Solvent emulsification diffusion method**

### 3.5 Supercritical fluid method

This procedure of producing SLN is very fresh and offers the benefit of processing without the use of solvents. This platform technology for the creation of powder and nanoparticles comes in a variety of forms. The rapid expansion of supercritical carbon dioxide solutions

technique can be used to make SLN. It was wise to use carbon dioxide (99.99 percent) as the solvent in this approach. (16)

### 3.6 Microemulsion based method

Techniques for SLN preparation that Gasco and colleagues created are based on diluting microemulsions. Low melting fatty acid, co-emulsifier (sodium mono-octyl phosphate), emulsifier and water are generally used to create an optically clear combination. The warmed microemulsion is dispersed in ice water (2–3 °C) while being stirred. Based on the research, since the micro-emulsion already has a droplets form, no power is required to create particles with a diameter of less than one micron. Fessi produced polymer particles by adding water to polymer solutions. According to De Labouret et al., the velocity of the distribution processes is crucial in defining the particle size. Only acetone, a solvent that diffuses into the water phase relatively quickly, may form nanoparticles; more lipophilic solvents provide bigger particle sizes. Similar to how acetone forms polymer nanoparticles, the hydrophilic co-solvents of the microemulsion aid in the production of lipid nanoparticles. (20,21)

### 3.7 Double emulsion-based method

It is possible to create double w/o/w microemulsions in two steps. A drug-containing aqueous solution is first applied at a temp close to the fat melting point to a combination of melted lipid, detergent, and co-surfactant to produce a transparent system. In the second stage, water, surfactant, and cosurfactant are combined with the created w/o microemulsion to create a clear w/o/w system. Warm micro double emulsions can be cleansed with dispersion medium using an ultrafiltration machine, then dispersed in cold water to create SLNs. The internal aqueous droplets inside the oil phase coalesce as a result of the coalescing oil droplets, and the layer on top of the internal droplets rupturing, multiple emulsions exhibit intrinsic instability. In order to produce SLNs, the transparent double microemulsions must be stable for a short period of time, which can be achieved between their formation and their quenching in cold aqueous media. (16)

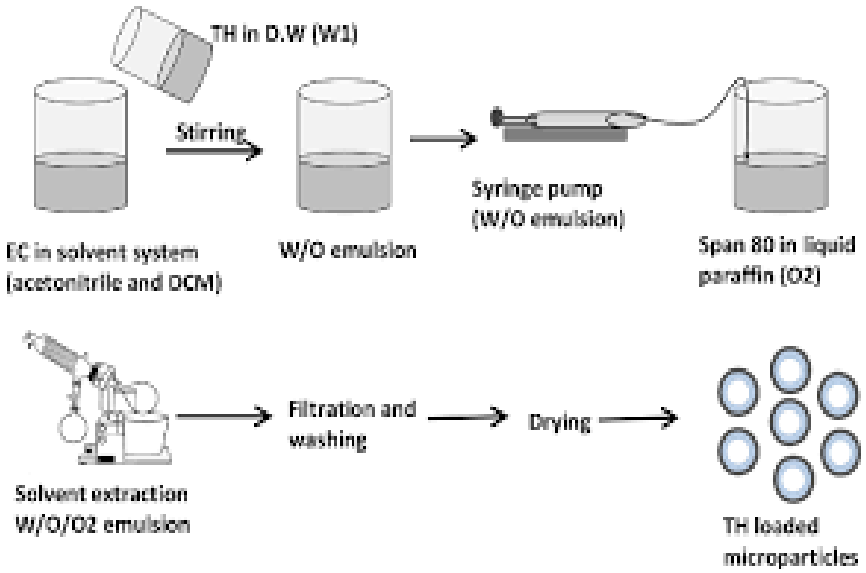


**Fig.7: Diagrammatic representation of double emulsion-based method.**

### 3.8 Precipitation technique

Another way of producing solid lipid nanoparticles is through precipitation, which is distinguished by the requirement for solvents. An organic solvent (like chloroform) will be used to dissolve the glycerides, and an aqueous phase will be used to emulsify the result. 16

### 3.9 Film ultrasound dispersion

After adding the lipid and the medication to the appropriate organic solutions, which were then rotated, decompressed, and evaporated to create a fat film, the watery mixture consisting the emulsions was then included. Finally, the formation of the SLN with the small and homogeneous size of particles using ultrasound with the probe to diffuser.

### 3.10 Solvent injection technique

It is a revolutionary method for making SLN that has the benefits listed below over previous production techniques: use of an organic solvent that is pharmacologically acceptable, simple handling, and a quick manufacturing process without the need for technical equipment. Its foundation is the precipitation of lipid from a mixture of dispersed lipids. This method involved dissolving the solid lipid in a water-miscible solvent (such as ethanol, acetone, or isopropanol) or a combination of water-miscible solvents. Then, with or without the addition of a surfactant, an injecting needle has been used to introduce the mixture of lipid solvents into the agitating aqueous phase. The resultant dispersion was then filtered through paper to

remove any excess fat. The emulsifier in the water phase helps to produce fat drops at the site of injection and remains stable SLN until solvent dispersion is finished by reducing the surface tension between water and solvent. (16,22,23,24)

### 3.11 Membrane contractor method

In order to enable large-scale production, the current work examines a novel method for producing SLN utilising a membrane contactor.

Small droplets are created when the lipid phase is forced through the membrane pores at a temperature higher than the lipid's melting point. The droplets that develop at the pore outputs are swept away by the aqueous phase as it circulates inside the membrane module. The formulation is subsequently cooled to room temperature to create SLN. On the size of the SLN and on the lipid phase flux, it is explored how the process variables affect these variables. (25)

## 4. Characterization of Solid Lipid Nanoparticles (SLNs)[26]

Due to the tiny size of the particles and intricacy of the framework, characterising solid lipid nanoparticles is a true test. Particle size, Measurement of transportation energy (zeta potential), degree of fat and crystallinity change (polymorphism), interaction with other colloidal structures (micelles, liposomes), duration of circulation operations, tranquillize, in vitro release of drug, and surface morphology are the critical parameters that should be assessed for the SLNs. The following are some criteria that must be taken into account while characterizing anything.

### 4.1 Particle Size and Zeta Potential[27,28]

Several techniques, including photon-connection spectrometry, TEM, and SEM, as well as SEM combined with energy dispersive X-Beam spectrometry can determine the size of nanoparticles. Between them, PCS and electron microscopy techniques are the most frequently used methods. SEM and TEM are quite beneficial for morphology and fit as a fiddle of lipid nanoparticles. They also provide for assurance of particle size and dispersion. Nuclear drive microscopy is another advanced small technique used to characterise nanoparticles. This is an additional tool for visualising the particles' initial, undisturbed form and surface characteristics. The drive in this method between the surface and the inspection

tip results in a spatial determination of up to 0.01 m. This method determines the size range from 3 nano-meters to 3 microns based on the variation in the strength of the scattered light produced by particle development.

### 4.2 Determination of Incorporated Drugs[29]

Following the completion of the separation process by ultracentrifugation, which involves removing the free medicine and solid fats from the liquid medium, the amount of medication fused is determined. Additionally, tranquillizer material may be particularly resolved by taking the drug out with the proper dissolvable under perfect circumstances, followed by an examination of the resultant item in SLNs.

Models have been put up to illustrate how the number of drug atoms in SLNs is limited. The enhanced shell model is characterised by medicine particularly positioned at the interface, either via rapid network lipid hardening or by efficient medication competition for the interface. Such a model's sedative dispersion may have a positive burst effect during medicine release. Medication is distributed evenly across the lattice in the homogeneous framework paradigm, much like a Solid arrangement. Medication selectivity located in the centre of Solid lipid nanoparticles, maybe as a result of the medication hardening more quickly than the grid material, describes the advanced centre model.

### 4.3 In-vitro Drug Release Studies[30]

Research on in-vitro tranquillizer delivery is often useful for quality assurance and for predicting in-vivo energy. Medication discharge profiles can be conducted with or without dialysis tubing. The SLNs scattering is introduced into prewashed dialysis tubing during dialysis, which is followed by hermetically sealing the tubing before dialyzing against a disintegration medium at a constant temperature with constant mixing. Tests were performed under different conditions, centrifuged, and measured for medication. Another technique that relies on switch dialysis and avoids the fenced-in region of the colloidal drug carrier in a dialysis sac was reported by Impose and Benita in 1990. This method is insufficiently delicate to characterise the colloidal transporter's rapid medicine discharge rate.

### 4.4 Storage Stability[31,32]

The structural firmness of the SLNs throughout deferred accumulating can be controlled by keeping an eye on variations in particles estimate, tranquillizer ingredient, appearance, and viscosity. Additionally, TLC ought to be capable of accomplishing this.

For long-term stability, external factors like temp. and light seem to be of the utmost significant. For a scattering to continue to be physically stable, the zeta potential should typically be higher than - 60mV.

The best stockpiling temperature is 4°C.

20°C- Long-term storage had no effect on the amount of medicine stacked in SLNs or on drug loss. 50°C - A rapid increase in particle size was observed.

### 4.5 Crystallization Tendency and Polymorphic Behaviour of SLNs[33,34]

Paid that lipid crystallisation is associated with drug fuse and discharge rates, uncommon consideration must be given to this phenomenon. The solid state of the particles is extremely important since it reduces the mobility of combined drugs, preventing drug leakage from the carrier. Warm research and X-beam diffraction are fundamental techniques to establish the physic-substance condition of particles. The most often used techniques in warm investigation are differential warm evaluation and differential filtering calorimetry.

### 5.1 Route of Administration

SLNs are provided by following the institution's procedure.

### 5.2 Oral Organization[35,36,37]

SLN can be administered orally in the form of a watery dispersion or, alternatively, after being changed into a conventional measurement form, such as tablets, pellets, containers, or powders in sachets. In the granulation procedure for making tablets, SLN scattering can be employed in place of a granulation fluid. Fluid scatterings are one of the types of SLNs planning that are covered in the oral course. SLNs come in stacked dosage forms such pills, pellets, and cases. The causticity and high ionic quality of the stomach's microenvironment encourage Particle aggregation. It is not unusual for nutrition to have a significant impact on SLN performance.

### 5.3 Parenteral Organization[37,38]

SLNs are often administered intravenously to animals. In contrast, the arrangements led to increased drug dissemination into the liver and kidneys. Conveyance of SLN was discovered to have higher drug fixations in the lung, spleen, and brain. In comparison to a business sedate setup after intravenous, SLN showed greater blood levels. SLN scatterings must be sterile for parenteral organisation. In these situations, the mean particle size makes sterile filtering unfeasible.

### 5.4 Transdermal Application[39]

The SLN scatterings with minimal lipid content in the fractal diameters are the newest ones to be on the lookout for (up to 5 percent). The thinness and poor clustering of the distributed lipid are drawbacks of cutaneous organisation. To get a plan that can be controlled to the skin, the SLN scattering must be combined with a therapy or gel.

### 5.5 Pulmonary Administration[41,42]

A highly intriguing application appears to be the SLN's aspirational organisation. Because the SLN powders' particles are too small and will be exhaled, it is impossible to direct them to the lung. The fluid SLN scatterings are aerosolized, which is a very simple method. The crucial aspect is that the SLN shouldn't completely during aerosolization. By colliding an airborne mass of beads with a mass of glass in a measuring glass, the vaporised beads were collected.

### 5.6 Rectal Organization[43,44,45.]

For paediatric patients, the usual rectal route of administration is used as much as feasible due to its ease of usage. When compared to drugs given orally or intravenously, the plasma levels and beneficial adequacy of rectally administered drugs were shown to be superior. Through SLN, a few reports on the rectal medicine organisation are available. Diazepam was concentrated into SLN for rectal organisation in order to provide a quick response. They focused on the fact that lipid networks, which are solid at body temperature, are not an effective method for delivering diazepam through the rectal route. They decided to use lipids that dissolve at body temperature in their upcoming experiments. PEG coating is unquestionably a reliable method for rectal delivery, improving bioavailability.

## CONCLUSION:

The last 10 years have seen a lot of interest in SLNs and nano-structured phospholipid transporters as prospective DDS. The utilisation of environmentally safe, biodegradable ingredients and processing techniques may be their main benefit. The majority of nano systems in this class come into the lower risk category (class I) of the nanotoxicological categorization system proposed by Keck and Müller due to their size and biodegradable nature. It should be underlined, however, that before progressing these systems to extensive manufacturing and commercialization, comprehensive clinical and environmental safety evaluation must be carried out. Both the corresponding regulatory framework and the creation of standardised methods to evaluate possible dangers of exposure to nanoparticles are urgently required.

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