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AN OVERVIEW ON SOLID LIPID NANOPARTICLES

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ABSTRACT

In order to replace well-established colloidal carriers such emulsions, liposomes, and polymeric micro- and nanoparticles, solid lipid nanoparticles (SLN) were first created in late 1991. In the rapidly expanding field of nanotechnology, solid lipid nanoparticles are at the vanguard and have several potential applications in clinical therapy, drug delivery, and research, as well as in a wide range of other sciences. Due to their unique size-dependent properties, lipid nanoparticles have the potential to develop innovative therapeutics. The ability to incorporate pharmaceuticals into Nano carriers has given medicine delivery a new prototype; this prototype could be used for secondary and tertiary levels of drug targeting. This paper examines a variety of solid lipid nanoparticles and discusses their advantages, disadvantages, and potential remedies. Solid lipid nanoparticles can be produced in a variety of ways and for a variety of purposes on a large scale. Aspects of biodistribution and solid lipid nanoparticle dosage are also discussed.

Keywords: homogenization, TEM, PCS, biodistribution, solid lipid nanoparticles (SLN), colloidal drug carriers, and targeting

INTRODUCTION

Solid lipid nanoparticles (SLN) were initially made available as an alternative to conventional colloidal carriers for the delivery of medications in December 1991. This system is made up of spherical stable lipid cells with nanometer-sized diameters that are typically dispersed in liquid surfactant or water arrangements **[1]**. SLNs are colloidal carrier systems comprised of a high melting point lipid as a solid core coated by aqueous surfactant. The medications used in SLNs are of BCS Classes II and IV **[2]**. SLNs have solid lipid in place of the liquid lipid that is present in other colloidal carriers. A well-known example of the use of solid lipid as a matrix material for drug administration is the use of lipid pellets for oral medication delivery **[3]**. An undeniable advantage of SLN is the fact that the lipid matrix is made up of physiological lipids, which lowers the risk of both acute and long-term toxicity **[4]**.

In addition to having the advantages of polymeric nanoparticles, lipid emulsions, and liposomes, SLN also has a number of other advantages, such as good biocompatibility, non-harmfulness, stability against mixtures, sedate spillage, hydrolysis, biodegradability, physical table, and utility as a drug carrier for lipophilic substances. But there are several differences and discrepancies between lipid emulsion and liposomes **[3]**.

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Their size range of around 40 to 1000 nm can be studied using TEM (Transmission electron microscopy) and SEM (scanning electron microscopy) **[6]**. SLNs are composed of 0.1 to 30 (% w/w) of solid fat dispersed in an aqueous phase. Surfactants are used in concentrations ranging from 0.5 to 5% to increase stability. The particle size, long-term storage stability, drug loading, and release properties can all be affected by the lipids and surfactants used **[7]**.

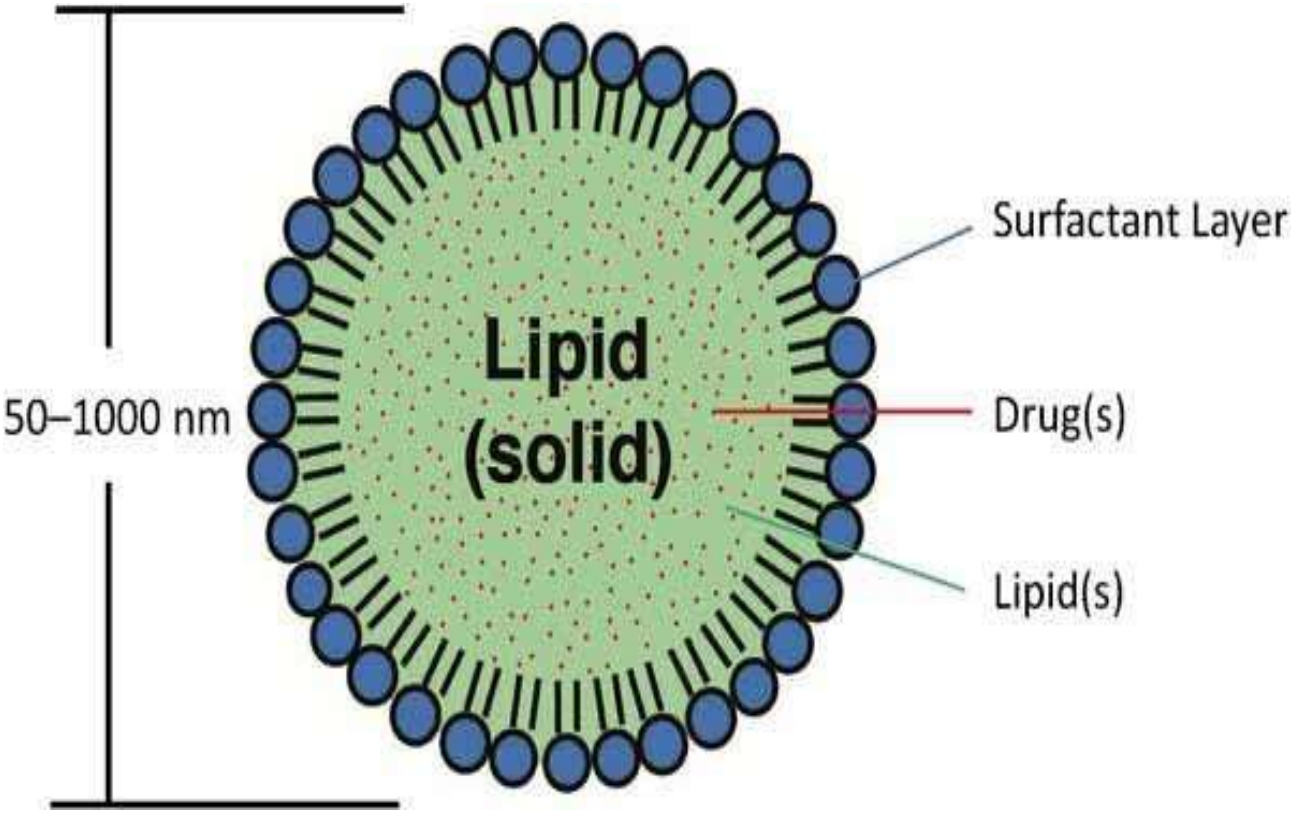


Figure 1: Structure of Solid Lipid Nanoparticles

Advantages

- It increases the bioavailability of poorly water-soluble compounds.
- It improves medicine absorption into the skin by using a technique known as site-specific distribution of pharmaceuticals.
- It regulates both drug targeting and the possibility of drug release.
- It shields fragile molecules from the outside environment as well as chemically labile reducing agents in the intestine.
- SLNs are more stable than liposomes, in comparison.
- It promotes the integrated labile chemical synthesis compound and trapping bioactive bioavailability.
- Achieved with high attention on functional compound.
- Lyophilization is an option **[8]**

Disadvantages

- Medication exclusion due to polymeric change during storage; limited medicine packing capacity; relatively large dispersed water volume (7099.9%); and medication exclusion following polymeric change.
- Due to partitioning effects, the loading of water-soluble medicines throughout the manufacturing cycle is limited **[29]**.
- Gelation propensity. Incredible polymeric transition motion **[8]**

Methods of Preparations:

1) High Pressure Homogenization.
   a) Hot homogenization
   b) Cold homogenization
2) Ultrasonication/high speed homogenization a) Probe ultrasonication
b) Bath ultrasonication
3) Solvent evaporation method
4) Solvent emulsification diffusion method
5) Supercritical fluid method
6) Micro emulsion-based method
7) Spray drying method
8) Double emulsion method
9) Precipitation technique
10) Film ultrasound dispersion

1.High pressure homogenization:

HPH technology is a tried-and-true technique for generating lipid nanoparticles. This approach to the mass production of LNs is an improvement over earlier approaches. There have been both hot and cold homogenization procedures created. The medicinal ingredient is dissolved or dispersed in the melted lipid prior to the HPH in both techniques. High pressure (100–2000 bar) is used to drive the fluid through the homogenizer's tiny gap. Particle sizes are typically in the sub-micron range. Homogenization has many advantages, including large-scale production, the absence of organic solvents, greater product stability, and improved drug loading. However, due to particular high pressure and temperature circumstances, its application is troublesome **[9] [10]**.

a) Hot homogenization:

Emulsion homogenization is a common name for hot homogenization, which is carried out at temperatures over the melting point of the lipid. The drug-loaded lipid melt and the aqueous emulsifier phase are mixed together form a pre-emulsion using a high-shear mixing device at the same temperature (Ultra-Turrax). Because the quality of the pre-emulsion greatly affects the quality of the finished product, it is ideal to obtain droplets in the range of a few micrometers. Because the inner phase's viscosity is decreased at higher temperatures, smaller particle sizes are often the result.

However, high temperatures also expedite the rate of degradation of both the drug and the carrier. The homogenization process may be repeated numerous times. It must always be restrained. 3-5 homogenization cycles between 500 and 1500 bar are frequently adequate. The high kinetic energy of the particles causes particle coalescence, which leads in an increase in particle size when the homogenization pressure or cycle count are increased. The major outcome is a nano emulsion, which solidifies upon cooling at room temperature because of the lipid's liquid condition. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be significantly slowed down, and the sample may remain a super-cooled melt for several months **[11]**.

b) Cold homogenization:

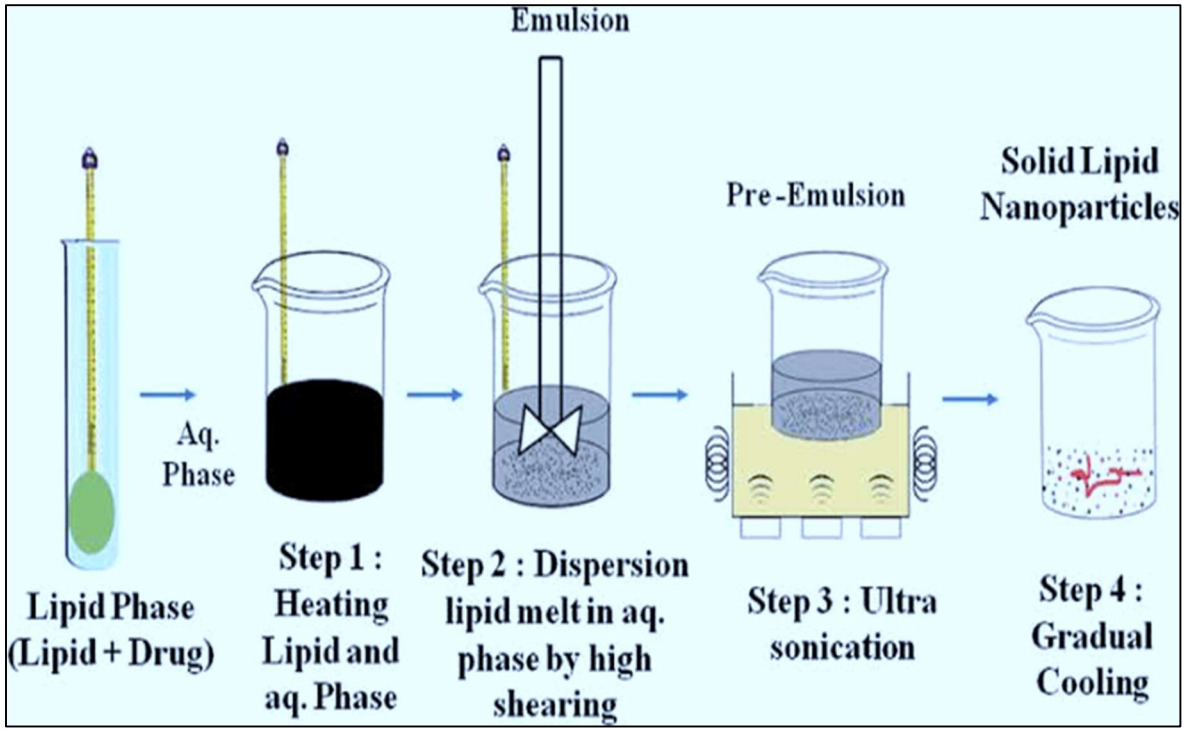
The cold homogenization, on the other hand, entails the high-pressure grinding of a suspension while utilizing a solid lipid. Effective temperature management and regulation are necessary to ensure the lipid is in an unmolten condition because a rise in temperature occurs during homogenization. The following three shortcomings of the hot homogenization method are what gave rise to cold homogenization. 1. Equipment that can

degrade drugs due to temperature. 2. During homogenization, drug dispersion into the aqueous phase 3. The nano emulsion's complex crystallization process, which can result in several alterations or super-cooled melt pressure. The drug must first be solubilized or dispersed in the bulk lipid melt, which is the same as heat homogenization in the first step. The drug-containing melt cools quickly, promoting uniform drug distribution throughout the solid matrix. Lipids become more brittle at low temperatures, which leads to particle comminution. The solid lipid microparticles are dispersed using a cold emulsifier solution. The pre-suspension is subjected to high pressure homogenization at or below room temperature. In general, greater particle sizes and a wider range when compared to heat homogenization **[11]**.

2.Ultrasonication/High speed homogenization:

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. Use of a bath or probe Sonicator is made in this situation **[9] [12]**.

Figure 2: Ultrasonication/High speed homogenization method



3. Solvent evaporation method:

In this method, the lipid is dissolved in an organic, water-immiscible solvent. The next step is the creation of an emulsion in a surfactant-containing aqueous phase. Under low pressure, the solvent is evaporated out of the emulsion. Evaporation is responsible for the dispersion of nanoparticles in the aqueous phase (using lipid precipitation process in the aqueous phase). Unlike cold homogenization, this method won't be subject to heat stress, however its usage of an organic solvent has disadvantages. Particle size might vary depending on the solid lipid and surfactant **[13] [14]**.

4.Solvent emulsification diffusion method:

This technique involves dissolving the medication and lipid in an organic solvent (such as cyclohexane, dichloromethane, toluene, or chloroform) before using high-speed homogenizers to emulsify them in an aqueous procedure. The coarse emulsion was quickly passed through a microfluidizer to increase the efficiency of emulsification. Mechanical mixing at room temperature and low pressures (e.g., rotatory evaporators) removes the naturally solubilized content, leaving SLNs lipid precipitates **[15]**.

5.Supercritical fluid method:

SFEE is a relatively recent technique for making SLN. This method uses a supercritical fluid, such as carbon dioxide, to extract the solvent from oil-water emulsions. Despite the fact that carbon dioxide is a great substitute, many drugs cannot be dissolved by it. So, a method that can be utilized in place of SFEE is supercritical antisolvent precipitation (SAS) **[16] [17]**.

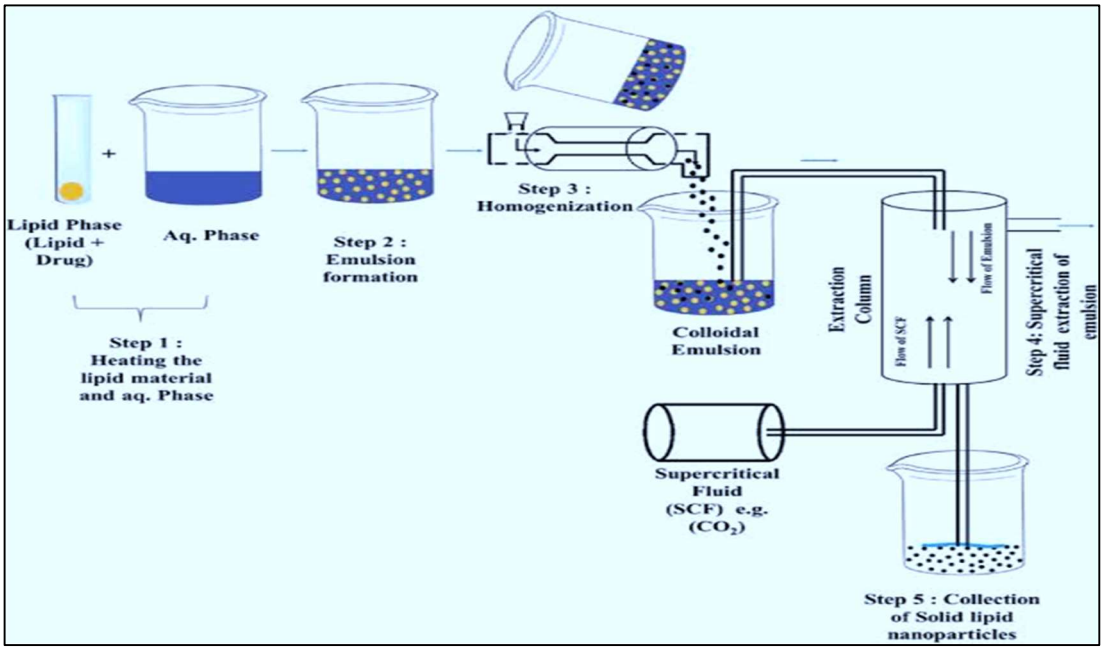


Figure 3: Diagrammatic presentation of Supercritical fluid method

6. Microemulsion based method:

In this method, microemulsions are diluted. Because microemulsions (like o/w microemulsions) are two-phase systems composed of an inner and an outer phase. They are formed by stirring a liquid that is optically transparent and typically contains water, an emulsifier (like polysorbate 20), a low melting fatty acid (like stearic acid), co-emulsifiers (like butanol), and an emulsifier (such as polysorbate 20). The hot microemulsion is dispersed in cold water (2–3°C) while being stirred. When the particle content is low, too much water must be removed in order to turn the SLN dispersion into solid goods (tablets, pellets) through the granulation process. High temperature gradients promote rapid lipid crystallization and inhibit aggregation. Due to the dilution stage, the achievable lipid levels are much lower than for formulations based on HPH **[18]**.

7.Spray drying method:

The lyophilization process, which creates medicinal goods from an aqueous SLN dispersion, is replaced by this technology. Spray drying is not widely used for the synthesis of lipids, despite being a more economical method than lyophilization. due to the particle aggregation that this method's high temperatures and shear pressures create. According to past studies, lipids having a melting point greater than 70 °C are suitable for spray drying **[5]**.

8. Double emulsion method:

It is possible to create double warm/o/w microemulsions in two steps. A drug-containing aqueous solution is first added to a mixture of melted lipid, surfactant, and co-surfactant at a temperature just above the melting point of lipid in order to form a transparent system. The second stage involves combining the created w/o microemulsion with water, surfactant, and cosurfactant to create a transparent w/o/w system. Warm micro double emulsions can be cleansed with a dispersion medium using an ultrafiltration machine, then dispersed in cold water to create SLNs. Numerous emulsions show inherent instability as a result of the oil droplets coalescing, the internal aqueous droplets within the oil phase coalescing, and the layer on top of the internal droplets rupturing. The transparent double microemulsions must be ready to be quenched in cold aqueous medium for a few minutes in order to form SLNs, which is doable **[9][19]**.

9.Precipitation technique:

Precipitation is a different method of generating solid lipid nanoparticles and is distinguished by the need for solvents. The glycerides will be dissolved in an organic

solvent (such as chloroform), and the solution will then be emulsified in water. Following the evaporation of the organic solvent, lipid will precipitate out and create nanoparticles **[9]**.

10. Film ultrasound dispersion:

The aqueous solution containing the emulsions was then added after the lipid and the drug were added to the appropriate organic solutions, which were then rotated, decompressed, and evaporated to produce a lipid film. Finally, utilizing ultrasound with the probe to diffuser, the SLN with the small and uniform particle size is produced.

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES:

Several parameters which have to be considered in characterization are as follows:

1.Partical size & Zeta potential:

The kind and quantity of emulsifying agents and lipids, as well as the matrix's composition, all have an impact on particle size. It has been asserted that increasing the emulsifier lowers the mean diameter of the bulk **[18]**. The zeta potential calculates the charge on the particles. This facilitates the design of particles with reduced reticuloendothelial uptake. To divert SLNs away from the RES, the particle surface should be hydrophilic and charge-free **[18]**.

2.In vitro drug release studies:

Studies on drug release in vitro are most useful for predicting in vivo kinetics and quality control. It is possible to carry out drug release profiles with or without dialysis tubing. Prewashed dialysis tubing receives the SLNs dispersion during dialysis, which is followed by hermetically sealing and dialyzing against a dissolving media at a constant temperature while being constantly agitated **[20]**.

3.Determination of incorporated drugs:

The amount of drug integrated is determined after the free drug and solid lipids have been removed from the aqueous medium via centrifugation filtration, ultracentrifugation, or gel permeation chromatography. Under ideal circumstances, the drug can be extracted using a suitable solvent, and the resulting product can be examined in SLNs to determine the drug content directly **[3]**.

4.Storage stability:

It is possible to determine if the SLNs will maintain their physical stability throughout prolonged storage by keeping an eye on changes in particle size, drug content, appearance, and viscosity. This can also be done via thin layer chromatography **[21]**.

5.Crystallization tendency and Polymorphic behavior:

Since it impacts the incorporation and release rates of medications, lipid crystallization

needs to be taken into particular consideration. The solid state of the particles is essential because it decreases the mobility of the drugs they carry, preventing drug leakage from the carrier. Fundamental techniques for figuring out the physic-chemical state of particles include thermal analysis and X-ray diffraction **[18]**.

ROUTE OF ADMINISTRATION AND THEIR DISTRIBUTION:

Parenteral route:

SLN has been intravenously administered to animals. Doxorubicin incorporated into SLN produced blood levels after intravenous injection in rats that were higher than those of a commercial medication solution. It was found that SLN enhanced drug concentrations in the brain, spleen, and lung whereas solution increased distribution to the liver and kidneys in terms of drug distribution throughout the body. Parenteral applications for SLN can be used in a variety of situations. Subcutaneous injection of drug-loaded SLN can be utilized, for example, to deliver interferon or erythropoietin for commercial purposes (EPO). Additional alternatives include intra-articular and intra-peritoneal passages. Intraperitoneal administration of drug-loaded SLN will prolong the release due to the application location. Additionally, the medication's absorption into the SLN may minimize irritation compared to injecting drug microparticles **[11]**.

Oral route:

Oral SLN delivery techniques involving aqueous dispersions or conventional dosage forms, like pills, pellets, or capsules, are also appropriate. Particle aggregation is promoted by the high ionic strength and acidity of the stomach. As is to be expected, food will unquestionably have a big impact on SLN performance. The plasma levels and body distribution following administration of CA-SLN suspension as contrasted to a CA solution were evaluated (CA-SOL). Two plasma peaks were seen after CA-SLN was delivered. The first peak could be attributed to the presence of free drug; the second peak can be attributed to the controlled release of SLN or potential gut uptake **[9]**.

Topical route:

The ability of the SLN to stop the breakdown of chemically labile medications and the occlusion effect brought on by film formation on the skin are the main advantages of topical products. Many chemicals, especially those used in the cosmetics industry, lack the required chemical stability to be added, such as vitamin C or retinol. Retinol integration is only possible when appropriate packaging materials are utilized, along with specific

protective procedures during manufacture (such noble gassing) (e.g., aluminum) **[22]**.

Ophthalmic route:

Numerous research has looked into the use of nanoparticles for sustained drug delivery to the eye. The main problem with ophthalmologic formulations is rapid removal from the eye, which demands medicine transportation through the nose following application. It may be proven that nanoparticles' enhanced adhesiveness causes larger medication concentrations at the site of action **[23]**.

Respiratory route:

SLN powders cannot be administered to the lung because they must be breathed and because their particles are too tiny. Aqueous SLN dispersions can be easily aerosolized using this method. It is essential that the SLN do not mix during aerosolization. The aerosol droplets were collected by causing the aerosol to strike the glass wall of the beaker. In essence, this shows that SLN are suitable for lung administration. Once the medication has been localized in the bronchial tube and the alveoli, it can be released from the lipid particles under carefully controlled circumstances **[9]**.

CONCLUSION:

Due to its favorable physical characteristics, promising incorporation of active chemicals, and related advantages, the SLN is a desirable system for delivering colloidal medicines. The objective of the current study was to advance understanding of the use of nanotechnology in pharmaceutical delivery in light of the emergence of various types of literature on the design and operation of solid lipid nanoparticles, nanoparticle transporters, lipid drug comparisons, etc. SLNs have already shown their value as potent formulations for boosting therapies in industries like cosmetics and medicine. In order to maximize effectiveness and reduce negative effects on tissues other than the target, SLNs provide a patient-friendly, economical way to distribute drugs through a variety of channels. The application of SLN occasionally appears to be more advanced after more than two decades of research. In parenteral formulations, many drugs with limited vapor solubility, short half-lives, and poor chemical stability will have additional options thanks to them.

DECLARATIONS:

1. Ethics approval and consent to participate

Not applicable

2. Consent for publication

Not applicable

3. Availability of data and materials

Data will not be shared; authors permission was not given for sharing of data.

4. Competing interest

Not applicable

5. Funding

Not applicable

6. Authors contributions

AJ- writing original draft, Review administration

R.P., P.K., P.M. – Resources, visualization, data curation, writing review and editing

"All authors have read and approved the manuscript".

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