



A Comprehensive Study on Solid Lipid Nanoparticles

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ABSTRACT

In the emerging scientific world nanotechnology is now an innovative technology for upcoming generations. Drug delivery technology has a wide spectrum, which is continuously being upgraded at a stupendous speed. Drugs having poor water solubility and pharmacokinetic parameters it is the best emerging Nano formulation to deliver at target sites. In nanotechnology formulations, solid lipid nanoparticles play a prominent role they usually consist of active drug molecules along with solid lipids, surfactants, and/or co-surfactants' SLNS carry some potential features such as Nano-size, surface with a free functional group to attach ligands, and as well they prove safe homing for both lipophilic as well as hydrophilic molecules. Different methods employed in preparing Solid lipid nanoparticles are hot pressure homogenization, ultra-sonification high-speed homogenization, a solvent evaporation method, solvent emulsification-diffusion method, spray drying method, double emulsion method, precipitation method, etc. Moreover, they are characterized by different methods for determining various parameters like particle-size, polydispersity-index, surface morphology, Differential scanning calorimetry, X-ray diffraction, etc. Solid lipid nanoparticles show good stability as well as the ability for surface tailoring with the specific ligand, which makes them a suitable candidate in the therapy of numerous illnesses, especially in the targeting of cancers.

Keywords: homogenization, ultra-sonification, targeting sites

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INTRODUCTION

Nanoparticles are formulated to overcome certain issues like

1. To avoid rapid metabolism and elimination.
2. To enhance the solubility of poorly soluble drugs.
3. To avoid drug toxicity in anti-cancer studies.¹

several systems including micelles, liposomes, polymer nanoparticles, solid dispersions, and nano -capsules, have been developed. SLNs are colloidal carrier system composed of a high melting point lipid as a solid core coated by aqueous surfactant and the drugs used are of BCS Class II and IV since the beginning of the 19th century by professor R.H MULLER from Germany and professor, M. GASCON from Italy considered lipid nanoparticles as a drug delivery system. lipids used in these formulations are completely compatible biologically and tolerated by the human body like triglycerides, fatty acids, steroids, and waxes. By using the combination of emulsifiers, we could obtain a stable formulation. Lipid nanoparticles have many advantages in comparison to other particulate systems

such as the ease of largescale production, biocompatible and biodegradable nature of the materials, low toxicity potential, the possibility of controlled and modified drug release, drug solubility enhancement and the possibility of both hydrophilic and lipophilic drug incorporation. lipid nanoparticles differ from microemulsions thermodynamically by their clarity these are stable dispersions of oil and water which are stabilized by surfactants and emulsifiers.²

The most important parameters in lipid nanoparticles characterizations are particle size and size distribution, zeta potential, polymorphism, degree of crystallinity, drug loading, entrapment efficiency, and drug release. Drug release from lipid nanoparticles is mostly dependent on matrix type and location of the drug in the matrix formulation. The composition of lipid matrix, surfactant concentration, and manufacturing parameters, such as temperature and stirring rate, can also affect drug release profiles. The most important reason for using nanoparticles are ease of large-scale production and their low toxicity potential compared to previous polymeric nanoparticles. Colloidal frameworks are scattering of particles (extremely huge atoms or particle totals) of moderate size between atoms in arrangement and particles in coarse suspension, and it has been very nearly a long time since a colloidal size scope of 1–1000 nm was proposed (le Chatelier, 1919), which is as yet acknowledged today (McNaught and Wilkinson, 1997).³



Advantages of Solid Lipid Nano Particles

SLN combines the advantages and avoid the disadvantages of other colloid carriers. Advantages includes

- ✓ Control and or target drug release.
- ✓ Improve stability of pharmaceuticals.
- ✓ High and enhanced drug content.
- ✓ Feasibilities of carrying both hydrophilic and lipophilic drugs.
- ✓ Most lipids being biodegradable. SLNS have excellent biocompatibility.
- ✓ Water based technology.
- ✓ Easy to scaleup and sterilize.
- ✓ More affordable easier to validate and gain regulatory approval.⁴

DISADVANTAGES OF SOLID LIPID NANOPARTICLES: -

- ✓ Particle growth.
- ✓ Unpredictable gelation tendency.
- ✓ Unexpected dynamics of polymeric transitions
- ✓ Sometimes burst release⁵

METHOD OF PREPARATION OF SOLID LIPID NANOPARTICLES

- High pressure homogenization
- Ultrasonication/high speed homogenization
- Solvent evaporation method
- Solvent emulsification-diffusion method
- Super critical fluid
- Micro emulsion-based method
- Double emulsion method
- Precipitation method
- Film ultrasound dispersion

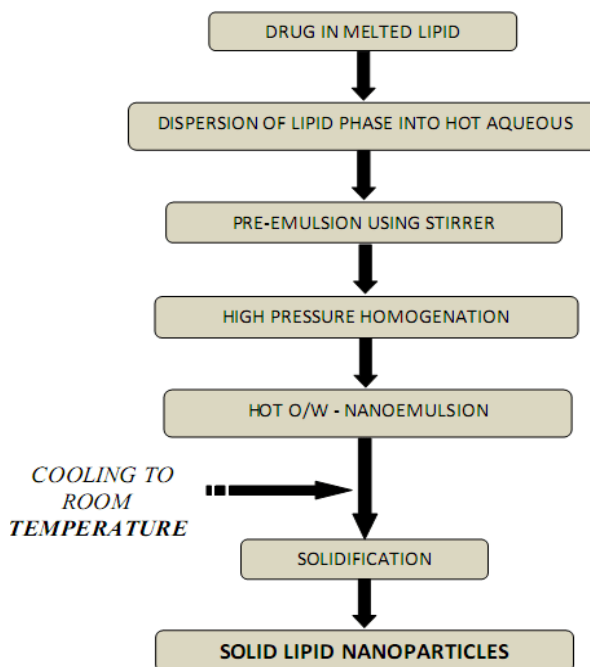
High-Pressure Homogenization (HPH)

It is a most used technique used for the production of solid lipid nanoparticles by using high-pressure *Homogenizers* which pushes a liquid with high pressure (100-2000 bar) through a narrow gap. Fluid gets accelerated at a high speed at over 1000 km/h. High shear stress and cavitation forces derange the particles to the sub-micron range. In general, 5-10% of lipid content is used, but recent studies show that up to 40% of lipid are also being used.

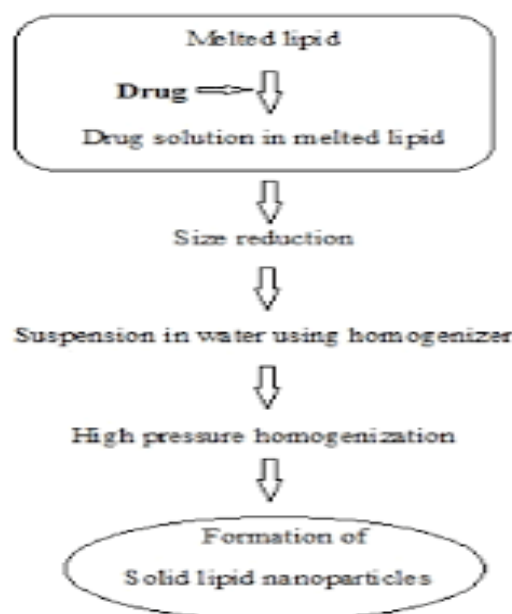
There are two general approaches of HPH work on the same principle

1. hot homogenization method
2. cold homogenization method⁶

Hot Homogenization Method⁷



Cold Homogenization Method



Ultrasonication/High Speed Homogenization

This is the other method for the production of solid lipid nanoparticles. The major advantage of this method is that the equipment used in this method is available at a lab scale. The drawback of this method is that border size distribution ranging inside the micrometre range with potential metal contaminations. This method is having a problem of physical instability problems and particle growth upon storage.⁸

Solvent Evaporation Method

For the generation of solid lipid nanoparticle dispersion by evaporation in o/w emulsions lipid is liquified in a water-immiscible organic solvent which is emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticle dispersion is formed by the precipitation of the lipid in the aqueous medium. Obtained mean diameter of the particles should be in the range of 25 nm with cholesterol acetate as a drug and soya lecithin/sodium glycocholate blend as an emulsifier. The result was confirmed by Siekmann and Westesen (1996), who produced the cholesterol acetate nanoparticles of mean size 29 nm.⁹

Super Critical Fluid Method

This is comparatively a new technique for the production of SLNs which holds an advantage of solvent-less processing. SLNs can be prepared by a rapid expansion of supercritical carbon dioxide (99.99%) solutions which is a good choice for this method.¹⁰

Micro Emulsion Based Method

Gasco et al. (1997) advanced SLNs primarily based at the dilution of microemulsions [eight]. This approach is based totally on the dilution of microemulsions. As microemulsions are -section systems composed of an internal and outer section (e.g., o/w microemulsions). they're made with the aid of stirring an optically obvious mixture at 65-70 °C, which normally composed of a low melting fatty acid (e.g., Stearic acid), an emulsifier (e.g., polysorbate 20), co-emulsifiers (e.g., butanol) and water. the new microemulsion is dispersed in bloodless water (2-3 °C) underneath stirring [four]. in keeping with De Labouret et al. the particle size is severely decided by way of the speed of the distribution approaches. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous segment (acetone), while large particle sizes had been received with greater lipophilic solvents.¹¹

Double Emulsion Method

In the double emulsion technique, the drug (in particular hydrophilic drugs) became dissolved in an aqueous solution, after which changed into emulsified in melted lipid. This number one emulsion become stabilized by adding a stabilizer (e.g., gelatin, poloxamer-407). Then this stabilized number one emulsion was dispersed in the aqueous section containing a hydrophilic emulsifier (e.g., PVA). Thereafter, the double emulsion was stirred and become remoted with the aid of filtration. The double emulsion technique avoids the necessity to melt the lipid for the education of peptide-loaded lipid nanoparticles and the surface of the nanoparticles will be modified for you to sterically stabilize them by way of approach of the incorporation of a lipid/-PEG by-product. Sterically stabilization appreciably improved the resistance of those colloidal systems in the gastrointestinal fluids. This

approach is mainly used to encapsulate hydrophilic drug (peptides).¹²

Precipitation Method

The greater effective and quicker step system changed into developed for the production of SLNs, particularly semisolid formulations. The method is accomplished by melting a lipid after dispersing it in a heated surfactant solution whose temperature is 10 degree Celsius above its melting factor and rotated at 9500 rpm for 1 min. 3 cycles of dispersion are then performed at 85°C and 500 bar strain. And the of the entirety of the rest cycle, the dispersion turns into viscous and is similarly used for the final two cycles. subsequently, the hot viscous nano emulsion is cooled at room temperature. The lipid droplets recrystallize and shape a gel community, and consequently, the SLNs end up semi-strong well matched. A 30–50% w/v lipid attention is needed for this process. The conversion of liquid lipid nanoparticles right into a stable play a pivotal function in enhancing the stability and secure garage of drug shipping structures. besides spray drying, lyophilization is also suitable for converting nano lipid dispersions into dry, solid debris. among those techniques, spray drying is value-powerful and can be used basically for massive-scale functions. Spray drying of lipid nanoparticles is a very touchy technique given that low melting temperature lipids are used within the method. Some studies^{36,41} validated the use of an organic solvent to reduce the processing temperature and facilitate the drying of heat-sensitive substances. The elimination of organic solvents from the lipid nanoparticle matrix are exposed to excessive temperatures, which isn't always successful.¹³

Evaluation Tests

Measurement of Particle Size and Zeta Potential

Photon relationship spectroscopy (PCS) and laser diffraction (LD) are the first methods for routine estimations of molecule size. PCS (likewise alluded to as powerful light dissipating) measures the vacillation of the force of the dispersed light which is brought about by molecule development. This strategy covers a size range from a couple of nanometres to around 3 microns' is a decent instrument to describe nanoparticles. Be that as it may, it cannot distinguish bigger microparticles. Electron microscopy gives, as opposed to PCS and LD, direct data on the molecule shape. The actual steadiness of streamlined SLN scattered is for the most part over a year. ZP estimations permit expectations about the capacity steadiness of colloidal scattering.¹⁴

Invitro-Drug Release

Dialysis Tubing

In vitro drug delivery could be accomplished utilizing dialysis tubing. The strong lipid nanoparticle scattering put in pre-washed dialysis tubing, which can be airtight fixed. The dialysis sac at that point dialyzed against a reasonable disintegration medium at room temperature; at fitting



stretches, the examples removed from the disintegration medium, utilizing an appropriate scientific strategy. Centrifuged and broke down for the medication content.

Reverse Dialysis

In this method, a few little dialysis sacs containing 1ml of disintegration medium set in SLN scattering. The SLNs at that point dislodged into the medium.

Franz Diffusion Cell

The SLNs scattering put in the giver office of the Franz dissemination cell fitted with a cellophane layer. The circulation at that point examined against a reasonable disintegration medium; the examples removed from the disintegration medium at suitable spans and broke down for drug content utilizing fitting techniques like spectroscopy and HPLC strategies.

Atomic Force Microscopy

In this strategy, a test steer with nuclear result sharpness is re-established across an example to deliver a topological guide dependent on the powers at play between the tip and the surface. The test can haul across the model (contact mode) or permitted to drift simply above (noncontact mode), with the specific idea of the specific power utilized serving to recognize among the sub-strategies. That ultrahigh goal is possible with this methodology, which closes by the ability to plan an example steady with properties furthermore to estimate, e.g., colloidal fascination or protection from distortion, makes AFM a significant apparatus.

Electron Microscopy

Strong lipid nanoparticles were seen by transmission microscopy. The trial of SLN was debilitated to ten times and after that mounted on a gold plate. The mounted plates were dried and examined under a transmission electron amplifying instrument without using such a stain. The CCD camera a sensitive picture system was used with the transmission electron amplifying instrument to imagine SLN.

Differential Scanning Calorimetry (DSC)

It is a broadly utilized strategy that estimates contrasts in the measure of warmth needed to expand the temperature of an example contrasted with a reference. Varieties in the warmth stream might be positive or negative and introduced as a component of the virus. Stage progress, there are contrasts in the example contrasted with the reference. the pace of crystallinity utilizing DSC assessed by examination of the liquefying enthalpy/g of the mass material with the softening enthalpy of the scattering.¹⁵

Determination of Incorporated Drug

The measure of medication consolidated in SLNs impacts the release attributes consequently it's indispensable to live the amount of joined medication. The measure of medication typified per unit wt. of nanoparticles is

resolved after the partition of the free medication and strong lipids from the watery medium and this detachment should be possible by ultracentrifugation, centrifugation filtration, or gel saturation chromatography. The medication is regularly tested by a standard insightful procedure like spectrophotometer, spectrofluorophotometry, HPLC, or fluid glimmer tallying.

Route Of Administration

Oral Organization

Oral association of SLN is possible as watery dispersing or then again after change into a customary estimation shape, for example tablets, pellets, holders or powders in sachets. For the age of tablets the liquid SLN dissipating can be used instead of a granulation Fluid in the granulation cycle. Kinds of SLNs arranging which are given by oral course are liquid scatterings SLNs stacked portion shape, for instance, tablets, pellets and case. The microclimate of the stomach favours. Particle combination in view of the causticity and high ionic quality. It isn't strange that sustenance will have large influence SLN execution.¹⁶

Parental Administration

SLNs generally coordinated intravenously to animals. Movement of SLN were found to have higher drug obsessions in lung, spleen and cerebrum, while the course of action incited to more scattering into liver and kidneys. SLN exhibited higher blood levels conversely with a business quiet course of action after intravenous. For parenteral association, SLN scatterings should be sterile. The mean molecule so sterile filtration is un reasonable in these cases.¹⁷

TRANSDERMAL APPLICATION

The tiniest Particle sizes are looked for SLN scatterings with low lipid content (up to 5%). Disadvantages of the dermal association are a low gathering of the dissipated lipid and the low thickness. The joining of the SLN dissipating in treatment or gel is significant in order to achieve an arrangement which can be controlled to the skin

Rectal Organization

Standard rectal transport of prescriptions is as regularly as conceivable used for paediatric patients on account of the straightforward application. Right when the practical pharmacological effect is needed, in a couple of conditions, the parenteral or rectal association is supported. The plasma levels and accommodating amplexness of rectally coordinated meds were represented to be unmatched differentiated and those given orally or intramuscularly in the practically identical estimation. A couple of reports are open on the rectal medicine association through SLN in the composition. Concentrated the circuit of diazepam into SLN for the rectal association to give a quick movement. They thought that the lipid network which is Solid at internal heat level is certifiably not a beneficial structure for diazepam rectal transport. They made plans to use



lipids that disintegrate around the internal heat level in their next tests. Stake covering is apparently a sure methodology on rectal transport and subsequently, improvement of bioavailability.¹⁸

Drug Delivery to Brain

Cerebrum focusing on not just expands the cerebrospinal liquid the grouping of the medication yet additionally diminishes the recurrence of dosing and results. The significant points of interest of this organization course is the evasion of the primary pass digestion furthermore, quick beginning of activity when contrasted with oral organization. LNC (for example NLC) of this age are considered to be one of the significant techniques for drug conveyance with no alteration to the medication particle on account of their quick take-up by the cerebrum, bio acceptability, and biodegradability. Further, the practicality in scale-up and nonattendance of burst the impact makes them additional promising transporters for drug conveyance. Moreover, NLC further upgraded the intranasal drug conveyance of duloxetine in the cerebrum for the treatment of significant burdensome issue. Bromocriptine (BC) a dopamine receptor agonist has been likewise joined in NLCs for controlled conveyance of the medication to give dependable helpful impacts perhaps broadening BC half-life in vivo for the treatment of Parkinson's illness intravenous conveyance of the medication with uninvolved focusing on capacity and simple abolishment. Another revealed model is NLCs of artemether (Nanoject) that offers a huge improvement in the counter malarial action and length of activity when contrasted with the customary injectable plan. The

undertaking can be considered as a reasonable option in contrast to the current injectable intramuscular (IM) definition (Joshi et al. 2008, Joshi and Müller 2009). Bufadienolides a class C-24 steroid additionally end up being powerful regarding upgraded haemolytic action and cytotoxicity with decreased results when joined in NLCs.¹⁹

CONCLUSION

SLN comprises an appealing colloidal medication transporter framework because of the effective fuse of dynamic mixes and the unrelated benefits. The current survey has zeroed in on expanding mindfulness about the nanotechnological field in medication conveyance with the development of a few promising methodologies like strong lipid nanoparticles, nanostructured lipid transporters, lipid drug forms, and so on SLN as a colloidal medication transporter consolidates the benefit of polymeric nanoparticles, fat emulsions, and liposome; because of different positions, including the plausibility of joining of lipophilic and hydrophilic medications, improved actual strength, ease, simplicity of scale-up, and producing. SLNs are set up by different progressed methods. Disservices incorporate low medication stacking limits, the presence of option colloidal structures (micelles, liposomes, blended micelles, drug nanocrystals), the unpredictability of the actual condition of the lipid (change between various alterations), and the chance of supercooled liquefies which mess security up during stockpiling or organization (gelation, molecule size increment, drug removal).

Drugs and Their Biopharmaceutical Application

Drug	Lipid used	Biopharmaceutical application
5-Fluoro uracil	Dynasan 114 and Dynasan 118	Prolonged release in simulated colonic media
Apomorphine	Glycerylmonostearate, polyethylene glycol monostearate	Enhanced bioavailability in rats
Calcitonin	Trimyristin	Improvement of the efficacy of proteins
Clozapine	Trimyristin, Tristearin and Tripalmitin	Improvement of bioavailability
Cyclosporin A	Glycerylmonostearate and glycerylpalmitostearate.	Controlled release
Gonadotropin release hormone	Monostearin	Prolonged release
Ibuprofen	Stearic acid, Trilaurin and Tripalmitin	Stable formulation with low toxicity
Idarubicin	Emulsifying wax	Delivery of oral proteins
Insulin	Stearin acid, octadecyl alcohol, cetylpalmitate, glycerylpalmitostearate, glyceryltripalmitate, glycerylbehenate and glycerylmonostearate.	Potential for oral delivery of proteins.
Lopinavir	Campritrol 888 ATO	Bioavailability enhanced
Nimusulide	Glycerylbehanate, palmitostearate, glyceryltristearate	Sustained release of drug
Progesterone	Monostearin, stearic acid and oleic acid	Potential for oral drug delivery
Repaglinide	Glycerylmonostearate and tristearin	Reduced toxicity
Tetracycline	Gycerylmonostearate and stearic acid	Sustained release

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