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Solid Lipid Nanopaticles As Novel Drug Delivery.

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ABSTRACT

Solid lipid nanoparticles were developed in early 1990. A new type of colloidal drug carrier for intravenous administration. Aqueous dispersion of solid lipid or dry powder with ranges between 50 – 1,000 nm and rapidly developed nanotechnology with potential applications in various field of pharmaceutics cosmetic, clinical medicine research mainly focused on drug targeting site and hydrophilic lipophilic carrier and various lipid and surfactant are used phospholipids and poloxamer 188 and triglycerides are used.SLN offer unique properties such as large surface area, small size, high loading.

Keywords: Nanotechnology, Drug Carrier, Surfactant, Solid-lipid, Phospholipids.

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INTRODUCTION

The current formulations utilize nanotechnology that is preparation of Nano sized. In novel drug delivery system mainly developed nanotechnology principle for Nanoemulsion, nano suspension, solid lipid nanoparticles, nano crystals. The main aim of solid lipid nanoparticles control drug released and to reach the target site. Hydrophilic lipophilic drug carrier used for preparation of solid lipid nanoparticles. It is alternating carrier system to liposomes, emulsion and polymeric nano particles. Unique properties compare with polymer nanoparticles and liposome, emulsion systemic toxicity, low cytotoxicity, low sustained release possible and improve the pharmaceutical approach. SLN mainly offer unique properties such as small size, large surface area, high drug loading and also potential to improve performance of pharmaceuticals.

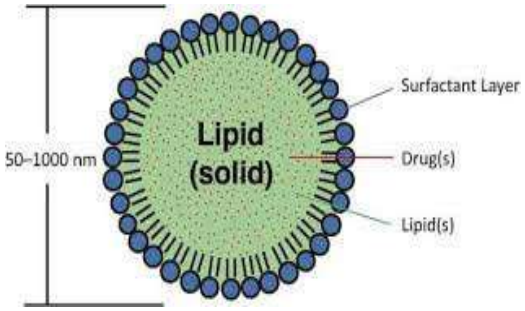


Figure 1: Structure of solid lipid nanoparticles (SLN)

Need for developing solid lipid nanoparticles

- Site-Specific action at the desired rate and dose.
- To control particle size.
- Surface properties of SLN.
- Sustained release of drug (active drug) moiety and diagnostic agents.

Advantages of SLN

- Small size and relatively narrow distribution.
- For site specific drug delivery to provide the biological opportunities.
- Controlled release.
- Excellent Biocompatibility.
- Relatively cheaper and stable.
- Solid lipid nanoparticles spray dried as well as lyophilized.
- Well control over release kinetics of encapsulated compounds.
- The carrier lipids are biodegradable and safe.

- Protection of drugs sensitive and liable for photochemical, chemical or oxidative degradation.
- Enhanced bioavailability of entrapped bio active compounds.

Disadvantages of SLN

- Low capacity of hydrophilic drugs during production process.
- Poor drug loading capacity
- Particle growth.
- Polymeric transitions occur.
- Relative high water content

History and concept of SLN's [1]

Nanosized drug delivery classifications have been developed to overcome one or several of the following problems

- Low or highly variables drug concentrations after per oral administration due to poor absorption, rapid metabolism and elimination.
- Low drug solubility which includes i.v injections of aqueous drug solutions.
- Drug delivery to other tissue combined with high toxicity. (e.g.: Cancer drugs). Several systems, including micelles, liposomes, polymer nanoparticles, nanoemulsion, solid dispersion and nanocapsules have been developed. A promising strategy to overcome these problems

Aims of SLNs.[2,16]

- Opportunity of controlled drug release.
- Opportunity of controlled drug release and drug targeting.
- Increased drug stability and high drug payload.
- Incorporation of lipophilic and hydrophilic drugs feasible.
- No biotoxicity of the carrier.
- Avoidance of organic solvents.
- No harms with respect to large scale manufacturing and sterilization.

Comparison different method of Sold Lipid Nano Particles

Method of SLN	Advantages	Disadvantages
High Pressure Homogenization	Very Low Cost At Lab Scale Possible	At Lab scale possible but damage Bio-molecule. Polydisperse distribution. Energy intensive and

		unproven scalability.
Ultra-sonication /High speed homogenization	To reduced shear stress	Particle growth on Storage. Potential Metal Contamination.
Solvent Evaporation	Continuous Process Scalable Commercially Demonstrated	Energy intensive process Damage biomolecule
Solvent Emulsification	Voidance of heat during the production procedure	-
Microemulsion based method	Low Mechanical energy input Theoretical Stability	Low concentrations of Nano Particles. Extremely sensitive to change.
Super Critical Fluid Method	Avoidance of the use of solvents Particles are obtained a dry powder instead of suspension Carbon dioxide is good choice of solvent in SCF method.	Very expensive method

Lipids & Surfactant Used in Solid Lipid Nanoparticles Production

Lipids	Surfactants
Triglycerols	Phospholipids
Tricaprin	Soy lecithin
Trilaurin	Egg lecithin
Trimyristin	Phosphatidylcholin
Tripalmitin	Ethylene
Tristearin	Oxide/Propylene Oxide
Glycerol	Poloxamer 188
Monostearate	Poloxamer 182
Stearic Acid	Sodium Cholate

SLNs PREPARATION TECHNIQUES (PRIMARY) .[2, 4, 15]

1. High pressure homogenization technique.

- Hot homogenization technique.
- Cold homogenization technique.

2. Microemulsion based technique.

3. Ultrasonication /high speed homogenization technique

4. Precipitation technique.

5. Film-ultrasound dispersion technique.

6. Double emulsion technique.

7. Solvent Injection Technique.

8. Membrane Contractor technique

9. Solvent emulsification-diffusion technique.

10. Supercritical fluid technique

11. Membrane Contractor technique.
12. Emulsification solvent evaporation technique.
13. Solvent emulsification-diffusion technique.
14. Supercritical fluid technique**.**

SECONDARY PRODUCTION STEPS

1. Sterilization
2. Lyophilization
3. Spray drying

1. High pressure homogenization technique

Hot homogenization technique.

Hot homogenization is passed out at temperatures more than the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A preemulsion of the drug loaded lipid melt and the aqueous emulsifier phase (similar temperature) is obtained by high shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, elevated temperatures result in lesser particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also speed up the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bars). In most cases, 3–5 homogenization cycles at 500– 1500 bar are sufficient. Increasing the homogenization pressure or the number of rotations often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The major product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the minor particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months.

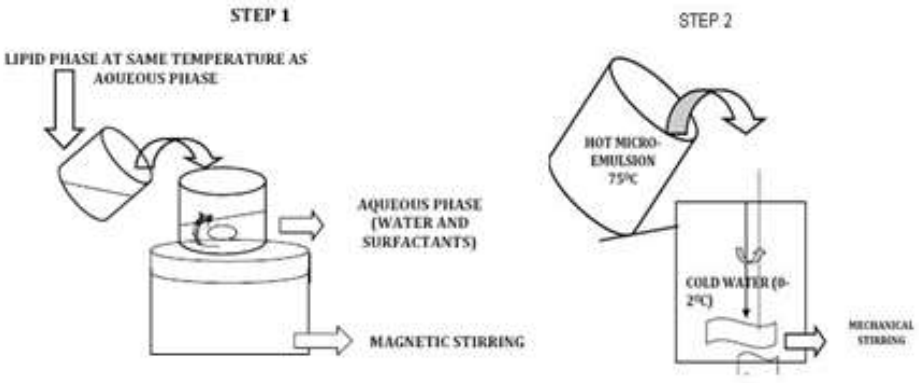
Cold homogenization technique

Cold homogenization method has been carried out to omit the following problems of the hot homogenization technique like temperature mediated drug and carrier degradation acceleration and consequently release of drug into the aqueous phase during homogenization. First stage in cold homogenization is the same with hot homogenization method but the next steps are different. The drug loaded lipid melt is cooled quickly by ice or liquid nitrogen for distribution of drug in the

lipid matrix. The acquired particle sizes are in the range 50- 100 microns for this method. Disadvantages of cold homogenized samples are larger particle sizes and a broader size distribution. However, this method reduces the thermal exposure of the sample.

2. Microemulsion based technique.

This method is based on the dilution of Microemulsion. Microemulsions are two-phase systems composed of inner and outer phases (e.g. o/w Microemulsion). They are prepared by stirring an optically clear mixture at 65-70°C, which typically 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 hot Microemulsion is discrete in cold water (2- 3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients help fast lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the High pressure homogenization based formulations.



3. Ultrasonication /High speed homogenization technique

SLNs are also organized by Ultrasonication or high speed homogenization techniques. For smaller particle size mixture of both Ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used.

4. Precipitation technique.

The lipid is dissolved in an organic solvent (e.g., chloroform) and the solution is emulsified into an aqueous phase. After evaporation of the organic solvent, the lipid is precipitated and forms nanoparticles.

5. Film-ultrasound dispersion technique

The lipid as well as drug are added to appropriate organic solutions, and after decompression, rotation and evaporation of the organic solutions, a lipid film is produced. The aqueous solution containing emulsifier is added to lipid film and, using probe sonication, SLNs are produced. Oleanolic acid SLNs have been produced using soybean phospholipid as a carrier using the film-ultrasound technique.

6. Double emulsion technique.

Double emulsion technique is used mainly for hydrophilic drugs. The drug was dissolved in aqueous medium and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration .After evaporation of organic solvent by rotary; SLNs were recovered by centrifugation at 12000 ×g for 30 min at 4°C.

7. Solvent Injection Technique.

It is a new concept to prepare SLN, which has following advantages over other production methods like use of pharmacologically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. It is based on lipid precipitation from the dissolved lipid in solution. In this method the solid lipid was dissolved in water-miscible solvent (e.g., acetone, isopropanol, and ethanol) or a water miscible solvent mixture. This lipid solvent mixture was inserted through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. The occurrence of emulsifier within the aqueous phase helps to make lipid droplets at the site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent.

8. Membrane Contractor technique.

It is a new technique to prepare the SLN. In membrane contactor technique the liquid point was compelled at a temperature above the melting point of the lipid through the membrane pore swallowing the formation of small droplets. The aqueous phase was stirred constantly and circulates tangentially inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLNs were produced by the cooling of the preparation at the room temperature. Here both the phases were placed in the thermostated bath to keep the required temperature and nitrogen was used to create the pressure for the liquid phase. The influence of various process parameters (aqueous phase cross flow velocity, the lipid phase pressure, aqueous and lipid phase

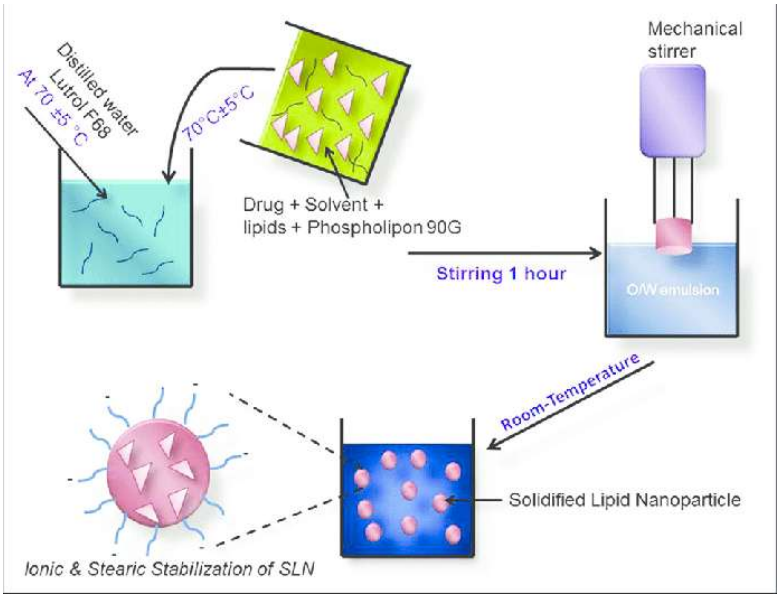
temperature, lipid phase amount and membrane pore size) were studied. This technique is also used for the preparation of polymeric nanoparticles, by means involving a polymerization of dispersed monomers (interfacial polymerization method) or a dispersion of preformed polymers (nano precipitation method). The advantages of this process of SLN preparation using a membrane contactor are shown to be its facility of use, the control of the SLN size by an appropriate alternative of process parameters and it's scaling up ability.

9. Emulsification solvent evaporation technique.

Lipophilic compound is dissolved in water immiscible organic solvent such as cyclohexane, while this technique is based on SLN dispersions by precipitation in oil/water emulsions. This is emulsified in an aqueous phase. SLN dispersion is formed by precipitation of the lipid in the aqueous medium after evaporation of the solvent. The mean diameter of 25 nm with cholesterol acetate as model drug and lecithin/sodium glycol Cholate mixture as emulsifier has been reported for the prepared SLN. The reproducibility of the result was verified by Siekmann and Westesen, who produced the cholesterol acetate SLN with mean size of 29 nm.

10. Solvent emulsification-diffusion technique.

SLNs can also be prepared by solvent emulsification diffusion techniques. The average particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with mean diameters of 30- 100 nm can be obtained by this technique. prevention of heat during preparation is the most important benefit of this technique. In this method, the lipid matrix is dissolved in a water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure, resulting in a nanoparticulate dispersion formed by precipitation of the lipid in aqueous medium.



11. Supercritical fluid technique .

This is a novel technique which newly applied for the production of SLNs. A fluid is capable as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not probable to liquefy a gas by raising the pressure. The supercritical fluid has unique thermo physical properties. As the pressure is raise, the density of the gas increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. A vapor may have small ability to dissolve a compound under ambient condition can completely dissolve the compound under high pressure in supercritical range. Therefore, its solvation power is altered by careful control of changes in temperature and pressure. Many gases like, ethane, ammonia, carbon dioxide and CH2FCF3 were tried, but carbon dioxide is the best option for SCF technique because, it is generally regarded as safe, easily accessible critical point (31.5ºC, 75.8 bar), does not causes the oxidation of drug material, leaves no traces behind after the process, is inexpensive, non-inflammable, environmentally acceptable an easy to recycle or to dispose of. In this method generally use organic solvents (e.g. DMSO, DMFA) because they are fully miscible in SCF-CO2. This technology comprises several processes for nanoparticles production such as Rapid Expansion of Supercritical Solution (RESS), Particles from Gas Saturated Solution (PGSS), Gas/Supercritical Anti-solvent (GAS/SAS), Aerosol Solvent Extraction Solvent (ASES), and Solution Enhanced Dispersion by Supercritical fluid (SEDS), Supercritical Fluid Extraction of Emulsions (SFEE). Mainly SAS and PGSS were used for SLN preparation.

SECONDARY PRODUCTION STEPS

Sterilization

SLNs product should be sterilizes for parenteral application that can be achieved by autoclaving, filtration, gamma irradiation and aseptic production. Sterilization by autoclaving is very common and popular but the problem associated with this is its high temperature and coalescence, as there is no applied shear. Increased temperature will result in melting of lipid particles and formation of o/w emulsion. Schwarz found that lecithin is an appropriate surfactant for steam sterilization, because only a minor increase in particle size was observed.

Lyophilization

Lyophilization stretches long term constancy for a product containing hydrolysable drugs or appropriate product for pre-oral administration. Change into the solid state would avoid the Oswald ripening and avoid hydrolytic reactions. In condition of freeze drying of the product, all the lipid matrices used, form higher solid lipid nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. The state of the freeze drying technique and the removal of water promote the aggregation among SLNs. A sufficient amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process.

Spray drying

It is a substitute and cheaper method to the lyophilization process. This recommends the use of lipid with melting point more than 70° C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture. The addition of carbohydrates and low lipid content favor the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol–water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures.

Composition of SLNs. [1, 3]

Mainly three excipients are used in preparation of solid lipid nanoparticles: Lipids and stabilizer (surfactant) and water**. LIPIDS**: The lipid is the main constituent of lipid nanoparticles that influence their drug loading capacity, their stability and the sustained release behavior of the formulations.

Selection criteria for lipids: Important point to be considered in the selection of drug carrier system (lipid) is its loading capacity and also the intended use.

- Lipids that form highly crystalline particles with a perfect lattice cause drug expulsion.
- More complex lipids containing fatty acids of different chain length form less perfect crystals with many imperfections.

These imperfections provide the space to accommodate the drugs. **Compritol ATO 888** most preferred excipients for SLN, Glyceryl mono stearate & glyceryl mono oleate are mostly preferred in cosmetics products, Stearic acid, palmitic acid, tetra decanoic acid are used for reparation of SLN, Bees wax and carnauba wax was used for preparation but the GRAS (Generally Recommended As Safe) status lipids used to prepare SLNs.

Influence of the lipids.

In hot homogenization it can be seen that average particle size of SLN dispersion is increasing with higher melting lipids and this is because of higher viscosity of dispersed phase.

- Some unusual parameters are specific for every lipid like lipid crystallization, lipid hydrophilicity and shape of lipid crystals.
- Chemically most lipids are mixtures of various compounds so their composition can vary from different suppliers and also from batch to batch but these small differences affect the quality of SLNs to a great extent (e.g. by changing the zeta potential, retarding crystallization processes etc.).
- Increasing the lipid content over 5% to 10% result in larger particles and broader particle size distribution in most cases.

Role of Co-emulsifier

- Due to small mobility of the phospholipid particles, sudden absence of emulsifier on the surface of the particle leads the particle aggregation and increase in the particle size of SLNs.
- To avoid this co-emulsifiers are employed.

Influence of emulsifier.

- Reduction in surface tension and particle portioning during homogenization is facilitated by increasing the emulsifier concentration. Reduction in particle size leads to increased surface area.
- During SLN preparation the primary dispersion must contain excessive emulsifier to rapidly cover the new surfaces formed during High Pressure Homogenization; otherwise it will lead to agglomeration of uncovered new lipid surfaces. The addition of few co-emulsifying agent like sodium glycocholate decreases the particle size

Other Ingredients

- **Cryoprotectants**: Glucose, Maltose, Lactose, Trehalose, Polyvinyl pyrrolidone, Gelatin, Glycine.

- **Charge modifiers**: Phosphatidyl glycerol (DMPG), Diacetyl Phosphate, Stearyl amine, Dipalmitoyl Phosphatidyl choline, Dimyristoyl.
- **Stealthing agents**: poloxamer, Polyethylene glycol.

Routes of Administrations. [7, 18]

The in vivo behavior of the SLN particles will mainly depend on the following points: Interactions of the SLN with the biological surroundings including: distribution processes (Adsorption of biological material on the particle surface and desorption of SLN components into to biological (surroundings) and enzymatic processes.

Various administration routes are

Parenteral administration

Peptide and proteins drugs are usually available for parenteral use in the market. For conventional oral administration is not possible due to enzymatic degradation in GI tract. Parenteral use of SLN reduces the possible side effects of drug incorporated with the increased bioavailability. These systems are very suitable for drug targeting.

Oral administration

Controlled release behavior of SLNs is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa .However, the estimation of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration.

Rectal administration

When quick pharmacological effect is required, in some circumstances, parenteral or rectal Administration is preferred. This route is used for pediatric patients due to easy.

Nasal administration

Nasal route is chosen due to its fast absorption and rapid onset of drug action also avoiding degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers. Respiratory delivery Nebulization of solid lipid particles carrying anti-tubercular drugs, anti-asthmatic drugs and anticancer was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary action.

Ocular administration

Biocompatibility as well as muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting.

Topical administration

SLN are identical attractive colloidal carrier classifications for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Principles of drug release from SLN. [1]

Drug release is affected by particle extent, where tiny particles have bigger surface area, therefore, the majority of the drug associated would be at or close to the particle surface, leading to rapid drug release. Whereas, greater particles have bulky cores which permit extra drug to be encapsulated and gradually diffuse out. It is a task to formulate nanoparticles with the smallest size possible and with maximum stability. The mutual ideology of drug release from lipid nanoparticles is as follows.

- There is different association between drug release and the partition coefficient of the drug. Greater surface area due to smaller particle size in nanometric range gives high drug release.
- When the drug is homogenously dispersed in the lipid matrix, slower drug release can be achieved. It depends on group of drug entrapment model of SLN.

Different models have been described in the literature for how active molecules can be incorporated into SLN [5, 9]

The type of SLN depends on the chemical nature of the active ingredient and lipid, and the solubility of actives in the melted lipid, nature and concentration of surfactants, types of production and the production temperature.

Influences loading capacity of a drug in lipid are

- Solubility of drug in lipid melt
- Miscibility of drug melt and lipid melt,
- The Chemical and physical structure of solid matrix lipid
- Polymorphic state of lipid material

Three different types can be described as:

1. SLN Type I or Homogeneous matrix model or Solid solution model.
2. SLN Type II or - enriched shell model.
3. SLN Type III or enriched core model.

SLN Type I:

The SLN Type I equals to a homogeneous matrix model where the lipid and active ingredient are solidified (or crystallized) simultaneously and uniformly. In this model, the drug is molecularly dispersed in the lipid matrix when the particles are produced by the cold homogenization technique and using no surfactant or no drug solubilizing surfactant.

SLN Type II:

The SLN Type II or drug- enriched shell model is achieved when SLN are produced via the hot HPH technique and the active ingredient concentration in the melted lipid is low. The enriched shell model is considered by drug selectively locating at the interface, either by fast solidification of the matrix lipid or by successful competition of the drug for the interface. Drug discrete by such a model might exhibit a successful burst effect during drug. According to the drug-enriched shell model of drug incorporation, a solid lipid core forms when the recrystallization temperature of the lipid is reached .A typical example of an active-enriched shell model is the incorporation of coenzyme.

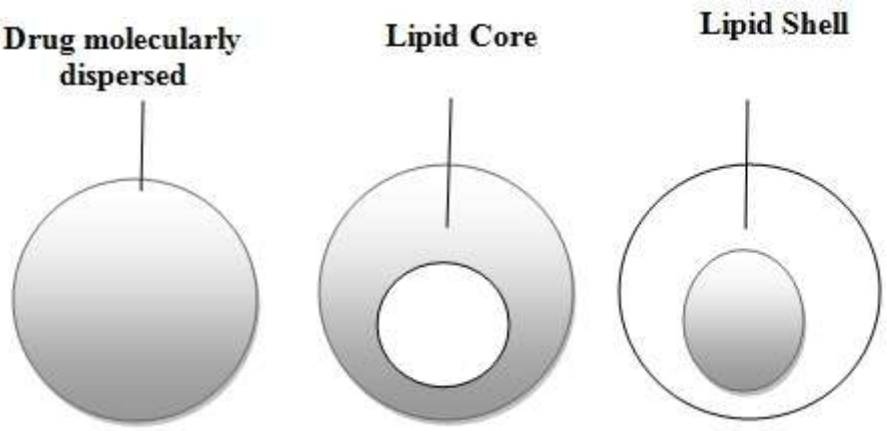
SLN Type III:

The SLN Type III or drug-enriched core model can take place when the active ingredient concentration in the lipid melt is high and at or relatively close to its saturation solubility. This model is characterized by drug selectivity located at the core of the solid lipid nanoparticles, perhaps due to more rapid solidification of the drug relative to the matrix material. According to the drug-enriched core model of drug incorporation, cooling the nano-emulsion leads to a super saturation of the drug which is dissolved in the lipid melt at or close to its saturation solubility and the drug precipitates prior to lipid recrystallization.

Drug Release from SLN [8]

Depending upon the drug solubility and drug / lipid ratio, method of preparation, the drug is located in the core of the particles, in the shell or molecularly dispersed throughout the matrix. There are chiefly three drug incorporation models which describe the incorporation of drug into SLN.

1. Homogenous matrix model.
2. Drug enriched shell, core shell model.
3. Drug enriched core, core shell model.



a. Solid solution **b. Drug enriched Shell** **c. Drug enriched core**

MODELS OF INCORPORATION OF ACTIVE COMPOUNDS INTO SLN

(a) Homogeneous matrix, (b) Drug enriched shell with lipid core, (c) Drug enriched core with lipid shell

The above three models are the function of formulation, combination of solid lipid, active ingredients, surfactants and sometime co-surfactant and of the production techniques (hot *vs.* cold homogenization)

Homogenous matrix model: In this, the drug is molecularly detached in the lipid matrix when the atoms are produced by cold homogenization technique and no surfactant or no drug solubilizing surfactant is used. In this, drug has powerfully definite interactions with the lipid.

Drug Enriched Shell Model: In this model of drug incorporation, a solid lipid core forms when the recrystallization temperature of lipid is reached. On dropping the temperature of this dispersion, drug concentrates in the still liquid outer shell of solid lipid nanoparticles.

Drug Enriched Core model: In this model of drug incorporation, cooling the nano emulsion leads to the super saturation of the drug which is dissolved in the lipid and melt at or close to its saturation solubility and the drug participates prior to the lipid recrystallization and finally needs further cooling to the recrystallization of the lipid surrounding the drug as a membrane

Characterization of SLN[2, 6 10, 18]

Evaluation of the SLNs is necessary for its quality control. However, characterization of SLN is a challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system.

1. **Measurement of Particle Size and Zeta Potential:**

The physical stability of SLNs depends on their size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most effective techniques for determination of particle size. PCS also

known as dynamic light scattering measures the variation in the intensity of the scattered light, which is occurred by particle movement. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3 nm to 3 μm and by laser diffraction in size range of 100 nm to 180 μm. Although PCS is a good device to characterize nano-particles it is capable for the detection of larger microparticles.

2 Zeta potential

Zeta meter is used to measure the zeta potential. Before measurement, SLN dispersions are diluted 50 times with the original dispersion preparation medium for size determination and zeta potential measurement. A high charge of zeta potential may prime to de-aggregation of particles in the absence of other complicating factors such as hydrophilic surface appendages or steric stabilizers. Zeta potential measurements can be useful for predictions about the storage stability of colloidal dispersions.

a. Electron Microscopy:

Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM) provide way to directly observe nanoparticles. However, SEM is better for morphological examination. TEM has a small size limit of detection

b. Dynamic Light Scattering (DLS):

DLS also known as PCS or quasi- elastic light scattering (QELS) the most popular technique determine the size distribution of particles in submicron region and records the variation in the intensity of the scattered light on the microsecond time scale. The various types of samples that can be characterized are nanoparticles, emulsions, Microemulsion, colloidal dispersion, proteins, polymers, micelles, vesicles.

c. Static Light Scattering (SLS) / Fraunhofer Diffraction:

SLS is a collective method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

d. Acoustic Methods:

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

e. Nuclear Magnetic Resonance (NMR):

NMR can be used to determine both the size and qualitative nature of nanoparticles.

f. Atomic Force Microscopy (AFM):

A probe tip with atomic scale quickness is raster across a taster to produce a topological map based on forces at play between the tip and the surface.

Measurement of Crystallinity and Lipid Modifications:

The X-ray Deflection (Powder X-ray Diffraction) and Differential Scanning Calorimetry (DSC): The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the previous to be resolute thus permitting the degree of Crystallinity to be assessed. DSC can be used to control the nature and the speciation of Crystallinity within nanoparticles through the measurement of glass and melting point temperature. Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates decrease in the following order is that

Super cooled melt < α-modification < β9-modification < β-modification.

Entrapment Efficiency:

The entrapment efficiency of the drug is resolute by measuring the concentration of free drug in the dispersion medium.

The Ultra-centrifugation was approved by using Centrisart, which consist of filter membrane (molecular weight cutoff 20,000 Da) at the base of the sample recovery chamber. The SLNs along with encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber. The quantity of the drug extant in the aqueous phase is resolute by HPLC or UV spectrophotometer.

% Entrapment efficiency = [(Initial drug weight–weight of free drug) / Weight of initial drug] × 100%

***In-vitro* drug release:**

In-vitro drug release studies are used for quality control studies as well as for the prediction of *in-vivo* kinetics. In this SLN's due to very small size of the particles, the release rate observed *in-vivo* can differ greatly from the release obtained in buffer solution. Hence in-vitro release studies remain useful for quality control as well as for evaluation of influence of process parameters on release rate of active components.

Dialysis Tubing:

In vitro drug release can be reached using dialysis tubing. The SLNs dispersions are placed in prewashed dialysis tubing which can be hermetically sealed The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the tasters are withdrawn from the medium at appropriate intervals, centrifuged and analyzed for drug content using a suitable method (U.V. spectroscopy, HPLC *etc).* The maintenance of sink condition is essential.

Reverse Dialysis: In this technique, a number of Small dialysis sac containing 1 ml of dissolution medium are placed in SLN dispersion. The SLNs are then placed into the dissolution medium. The direct dilution of the SLNs is possible with this method; however the rapid release cannot be quantified using this method

Franz Diffusion Cell:

The SLNs diffusion is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The diffusion is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals and analyzed for drug content using a suitable method (U.V. spectroscopy, HPLC *etc*.). The maintenance of sink condition is essential.

Drug Release from SLN:

Depending upon the drug solubility and drug / lipid ratio, method of preparation, the drug is located in the core of the particles, in the shell or molecularly dispersed throughout the matrix. There are mostly three drug incorporation models which describe the incorporation of drug into SLN.

APPLICATIONS OF SLN [2, 6, 17]

- **Cancer chemotherapy**

From the last twenty years many anticancer agents have been formulated into SLN system that resulted in improvement of efficiency with significant decrease in associated side effects. Such chemotherapeutic agents when encapsulated into SLN system has augmented stability and pharmacokinetics with reduced toxicity which proved the SLN to be a suitable carrier for delivery of such agents. Not only small anticancer molecules but also macro molecules like antisense oligo nucleotides have been delivered to liver cancer cells by lipid coated particles. 70 SLN was also employed as a targeted carrier for anticancer drugs to solid tumor, as exemplified by Tamoxifen SLN prolonged the release of drug after IV administration in breast cancer. The advantage of using SLN containing anticancer drug is passive

Targeting property due to enhanced permeability and retention (EPR) effect in which particles are shielded by surface coating using poly ethylene glycol/oxide (PEG/PEO) system which enhances the circulation time. Other drugs used in the similar manner are methotrexate and camptothecin similar fashion, SLN have been employed in treatment of colorectal and lung cancer. Doxorubicin and paclitaxel were loaded in SLN and evaluated for colorectal cancer treatment however doxorubicin is not an ideal drug candidate for the same cancer.

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- **Brain drug delivery**

Extremely fine particles of SLN with diameter less than 50 nm offer compensation in drug targeting drugs to brain this could be attributed to enhance the drug penetration through blood brain barrier especially SLN coated with polysorbate surfactants demonstrated increased transport of drugs. SLN system also favors reduced uptake by reticuloendothelial system which leads to lower cytotoxicity and enhanced drug loading ability thus making them preferred over polymeric nanoparticles. SLN offers high capacity to load the drugs and at the same time avoids drug degradation and releases the impassive drug within tumor cells which is due to the lipid components used for surface coating. Though nanotechnology gained momentum in targeting drugs to brain, several formulations showed reduced presence of drugs in brain which is attributed to swift clearance from reticuloendothelial system. This clearance from reticuloendothelial system consists of opsonization, phagocytosis and reuptake. This could be overtaken by inserting hydrophilic groups at the surface of particles. Such modifications in the formulations of SLN for targeting brain tumor aided to deliver drugs including peptides, cytokines, antibodies and ferromagnetic agents.

- **Parasitic diseases**

SLN and nano-structured lipid carriers (NLC) are particulate in nature and inherent structure exhibit good potential in the treatment of parasitic infections. With esteem to encapsulation capacity and target ability, it requires extensive investigations on these systems to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.

- **Ultrasonic drug and gene delivery**

Ultrasonic drug and gene delivery by nano carriers has remarkable potential because of the wide variety of drugs and genes could be delivered to targeted tissues by fairly noninvasive means. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes in vitro and in vivo.

- **Pulmonary disorders**

Nano particles with their special characteristics have several merits in targeted drug delivery compared with other systems. Targeted nanoparticle delivery to the lungs is a talented area of interest. SLN powders can be used in dry powder inhaler form by spray-drying with lactose as an excipient.

- **Topical applications**

In future, it is estimated that SLN replace other carriers for tropical formulations, SLN are usually prepared from well tolerated excipients and possess adhesive properties which helps in the formation of film on the skin due to their small particle size which may assist the drug penetration through stratum corneum. SLN and NLC have been used for topical applications for various drugs such as Tropolide and glucocorticoids. Numerous hydrophilic and hydrophobic drugs including corticosteroids and anticancer agents like doxorubicin and paclitaxel have been delivered through SLN. In the treatment of eczema, SLN formulations consisting glucocorticoids and calcineurin inhibitors were tried, in the similar lines, glucocorticoids were formulated in lipid nanoparticles which showed skin atrophy in long term use. The existing clotrimazole creams though treated effectively the topical fungal infections but upon discontinuation of the clotrimazole application, dermal fungal reinfection was observed. This defect of such formulations has been overcome by incorporating clotrimazole in SLN and NLC. Encouraged by such developments in antifungal drug delivery, SLN has also reduced the toxicity of few antifungal drugs, to exemplify this ketoconazole which is potent antifungal agent, developed as SLN for tropical fungal infections, minimized the adverse effects of ketoconazole and also provided control release. SLN's aid in achieving better localization, occlusiveness, controlled release and increased skin hydration in topical formulations.

- **Cosmeceuticals** [3, 19]

SLN have been applied in the preparation of sunscreens. SLN & NLC have proved as controlled release innovative occlusive topical. It has been reported that, 31% increase in the skin hydration upon addition of 4% SLN to a conventional cream. Better localization of vitamin A with glyceryl behenate SLN was reported in comparison to conventional formulations.SLN show a UV-blocking potential, i.e. they act as physical sunscreens on their own and can be combined with molecular sunscreens in order to achieve improved photo protection. Many features of SLNs are advantageous for dermal application of cosmetic products have been reported, e.g. occlusive properties, increase in skin penetration and avoidance of systemic uptake.

- **Agriculture application.** [6]
- Essential oil is extracted from Artemisia arboreseens L. incorporated in SLN were able to reduce the rapid evaporation compared with emulsion and system have been used in agriculture as safe pesticide.

Stability and storage

- Stability testing is an integral part formulation development. it generates the information on which to base proposals for the shelf life of drug substances and products and their

recommended storage conditions. Stability data also a part of the dossier submission to regulatory agencies for licensing approval.

- Stability testing ensures that drug substance will be safe and effective throughout the shelf life of the products become increasingly complex and diverse.
- The physical properties of SLNs during prolonged storage can be determined by monitoring changes in drug content , zeta potential , particle size , appearance and as the function of time . External limitations such as temperature and light seem to be of primary importance for long-term stability.

The most favorable conditions for long term stability.

Most favorable storage temperature.

Long term storage did not result in drug loaded SLN aggregation.

A rapid growth of particle size was observed.

CONCLUSION

SLN create an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. The review paper has focused on increasing awareness about nano technological field in drug delivery with several approaches and improving therapeutics. SLNs have already been proven as good formulations in Cosmeceuticals, other fields; they must occupy a considerable place in the pharmaceutical market.

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