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RECENT ADVANCES OF SOLID LIPID NANOPARTICLES: A REVIEW

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ABSTRACT

Most of the active pharmaceutical ingredients (APIs) under development are poorly water soluble and have poor bioavailability. Nanotechnology is an approach to overcome the challenges of conventional drug delivery systems. Solid Lipid nanoparticles show interesting features concerning therapeutic purposes. The main advantage is that they are prepared with physiologically well-tolerated lipids. Solid Lipid Nanoparticles (SLNs) as novel lipid based nanocarriers with size range between 10 to 1000nm. SLNs were introduced to overcome problems of polymeric nanoparticles. By putting forward physiological safe lipids in place of polymers to prepare lipid nanoparticles, a novel formulation technique came into light. An approach undertaken here is to focus on various production methods for preparation of SLNs, wide pharmaceutical applications of SLNs in drug delivery are explored.

KEY WORDS: Solid lipid nanoparticles; Colloidal delivery system; Oral Bioavilability; Water Insoluble Drugs; Preparation; Characterisation.

INTRODUCTION

Targeted delivery system is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, new challenge have opened for improving drug delivery.[1] Compared to many other materials used as drug carriers, in particular to polymers, lipids are regarded as a more physiological option and a high biocompatibility is expected.[2] From all the different types, Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and

research as well as in other varied sciences. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers.[3]

In system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. It is identical to an oil-in-water emulsion for parentral nutrition but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e. yielding Solid Lipid Nanoparticles. Different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are described.[4] Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system.[5] Basically, SLNs are made of a solid lipid core with a monolayer phospholipid shell. The solid state of the nanoparticulate matrix provides protection to chemically labile drugs and prolongation of drug release.[3] The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics.[6]

SLN encompasses the advantages of polymeric nanoparticles, fat emulsion and liposomes but simultaneously avoid some of their disadvantages. They have many advantages such as good biocompatibility, non toxic, stable against coalescence, drug leakage, hydrolysis, biodegradable, physically table and good carrier for lipophillic drugs. There are major difference between lipid emulsion and liposomes. The basic structure of a lipid emulsion is a neutral lipophilic oil core surrounded by monolayer of amphiphilic lipid.[4] Nanosized drug delivery systems have been developed to overcome the following problems.

a) Low or highly variables drug concentrations after per oral administration due to poor absorption, rapid metabolism and elimination.

b) Poor drug solubility which includes iv injections of aqueous drug solutions.

c) Drug distribution to other tissue combined with high toxicity. (eg: Cancer drugs).[1]

Solid lipid nanoparticles (SLNs) were developed at the beginning of the 1990s as an alternative novel carrier system to liposomes, emulsions and polymeric nanoparticles.

SLNs are sub-micron colloidal carrier of 50-1000nm size range, which are composed of physiological lipid dispersed in water or in an aqueous surfactant solution. They are made of solid hydrophobic core having a monolayer of phospholipid coating. The solid core contains

the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics. lipid particulate DDS about depending on their architecture and particle size. Due to the large number of administration routes available, these delivery systems perform differently depending on the formulation type and route of administration. SLNs offer unique properties such as smaller size, larger surface area, interaction of phases at the interfaces, and these are attractive of their ability to improve performance of neutraceuticals, pharmaceuticals and other materials. The lipid used in SLNs melting point must exceed body temperature.[7]

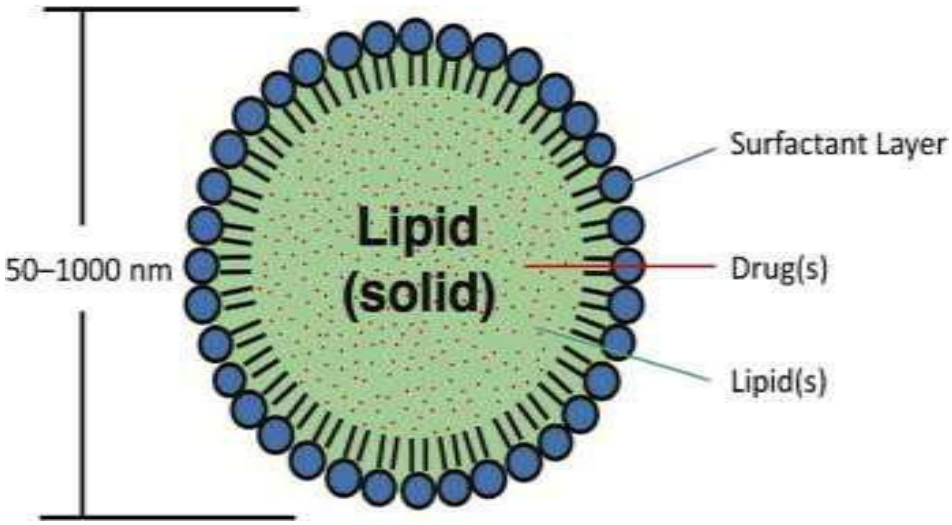

Figure. 1: Structure of SLN.

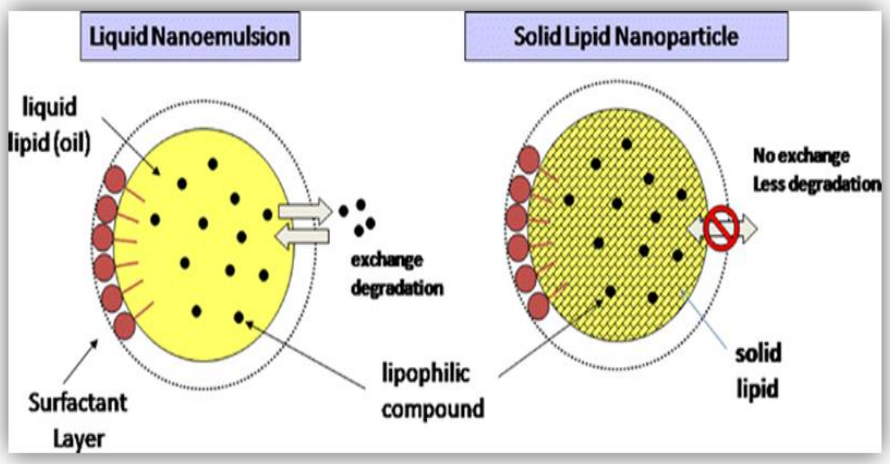

Figure. 2: Structure of Liquid Nano emulsion and SLNs.

History and concept of SLN's[10]

Nanosized drug delivery systems 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.
- Poor drug solubility which includes i.v injections of aqueous drug solutions.
- Drug distribution to other tissue combined with high toxicity. (eg: Cancer drugs).

Several systems, including micelles, liposomes, polymer nanoparticles, nanoemulsions, solid dispersion and nanocapsules have been developed. A promising strategy to overcome these problems involves the development of suitable drug carrier system like solid lipid nanoparticles.

Aims of SLNs[10]

- Possibility of controlled drug release.
- Possibility 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 problems with respect to large scale production and sterilization.

Principles of drug release from SLN[10]

Drug release is affected by particle size, where tiny particles have larger surface area, therefore, the majority of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have bulky cores which permit more drug to be encapsulated and gradually diffuse out. It is a challenge to formulate nanoparticles with the smallest size possible and with maximum stability. The common ideology of drug release from lipid nanoparticles is as follows.There is an opposite association between drug release and the partition coefficient of the drug.

– Larger 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 type of drug entrapment model of SLN.

Advantages of SLNs[7,17]

SLNs combine the advantages of other colloidal particles like polymeric nanoparticles, fat emulsions and liposomes while simultaneously avoiding their disadvantages. The advantages of SLNs including the following such as.

- SLNs can be enhancing the bioavailability of entrapped bioactive
- SLNs particularly those in the range of 120 -200 nm are not taken up readily by the cells present in the RES and thus bypass liver and spleen filtration
- In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity
- It is easy scale up and excellent biocompatibility
- Enhanced bioavailability of entrapped bioactive compounds
- Controlled and targeted release of the incorporated drug can be achieved
- Increased scope of drug targeting can be achieved by coating with or attaching ligands to SLNs
- Drug stability of SLNs for three years has been developed. This is of more importance compared to the other colloidal carrier systems
- Better control over release kinetics of encapsulated compound
- Excellent reproducibility with use of different methods as the preparation procedure
- The feasibility of incorporating both hydrophilic and hydrophobic drugs.
- The carrier lipids are biodegradable and safe
- Avoidance of organic solvents
- Feasible for large scale production and sterilization.

Disadvantages

- Poor drug loading capacity
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions (70-99.9%)
- The low capacity to load water soluble drugs due to partitioning effects during production process.

Potential problems associated with SLN and its Production Technology[11]

- Pay-load for a number of drugs too low Drug expulsion during storage
- High water content of SLN dispersions

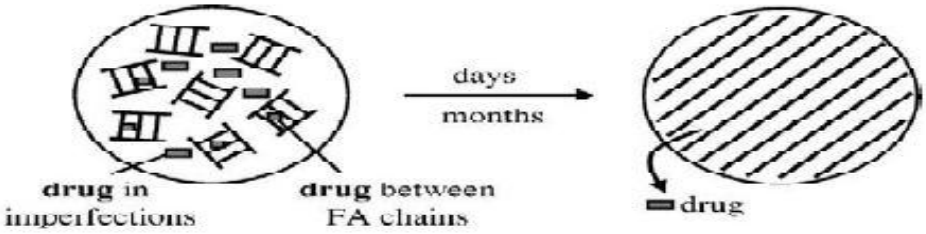

Figure. 3: Mechanism of drug expulsion during storage of SLN dispersions, transition to highly ordered lipid crystal.

A potential problem in SLN is the formation of a perfect crystal, which can be compared to a dense 'brick wall'. Using different molecules, i.e. different 'stones' to build the matrix or 'wall' leaves enough imperfections to accommodate the drug. Drug load in SLN is limited due to the formation of the lipid crystal. Drug expulsion is caused by an ongoing crystallization process towards a perfect crystal.

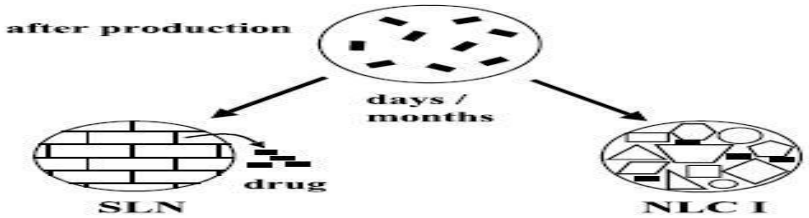

Figure. 4: Crystallisation process during storage to perfect crystal in SLN (left) and unchanged remaining NLC I structure with imperfections.

Factors affecting loading capacity of a drug in lipid are

- solubility of drug in lipid melt.
- miscibility of drug melt and lipid melt.
- chemical and physical structure of solid matrix lipid.
- polymorphic state of lipid material.

Challenges for formulation and delivery[17]

Problems frequently occurring with many drugs are

- Poor solubility
- Insufficient in vitro stability (shelf life)
- Too low bioavailability
- Too short in vivo stability (half-life)

- Strong side effect
- Need for targeted delivery
- Regulatory issues/hurdles
- Lack of large scale production.

Table. 1: Comparative properties of solid lipid nanoparticles, Polymeric nanoparticles, Liposomes, Lipid emulsions.[11]

S. No.	Property	SLN	Polymer Nanoparticles	Liposomes	Lipid Emulsions
1.	Systemic toxicity	Low	>or = to SLN	Low	Low
2.	Cytotoxicity	Low	>or = to SLN	Low	Low
3.	Residues from organic solvents	No	Yes	May or may not	No
4.	Large scale production	Yes	No	Yes	Yes
5.	Sterilization by autoclaving	Yes	No	No	Yes
6.	Sustained release	Yes	Yes	<or = to SLN	No
7.	Avoidance of RES	Depend on size and coating	No	Yes	Yes

Models for incorporation of active compounds into SLNs[7,14]

There are basically three different models for the incorporation of active ingredients into SLN

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

The structure obtained is the function of the formulation composition (lipid drug and surfactant) and of the production conditions.

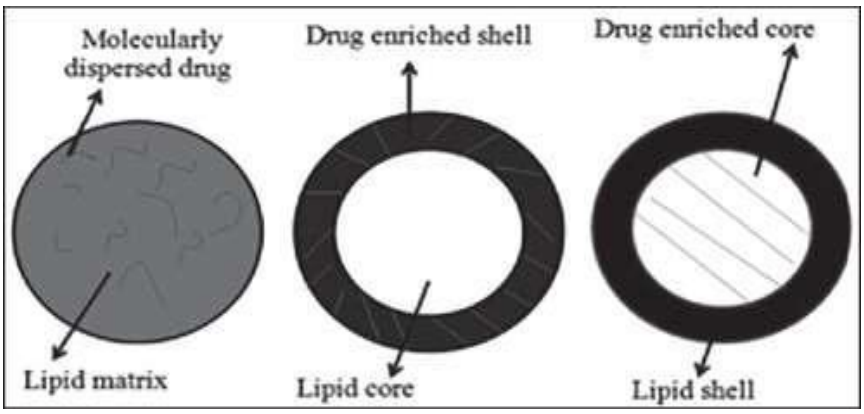

Figure. 5: Models for incorporation of active compounds into SLNs.[17]

Table. 2: Drug incorporation:- different models.

Solid solution model	Core-shell model (drug-enriched shell)	Core-shell model enriched core)
Formation of this model in cold homogenization technique	Formation of this model in hot homogenization technique	Dispersion cooling leads to a super saturation of the drug which is dissolved in the lipid.
Using no drug-solubilizing surfactant	Formation of lipid core at recrystallization temperature of lipid	Precipitation of drug in melted lipid
Drug dispersed in lipid matrix	Cooling of the obtained dispersion leads to repartitioning of the drug to the lipid phase	Finally, further cooling lead to recrystallization of the lipid
There is a strong interaction between lipid and drug	Concentration of drug in surrounding membrane	Formation of drug-enriched core

Composition of SLNs[17,18]

Mainly three excipients are used in preparation of solid lipid nanoparticles: Lipids and stabilizer (surfactant) and water.

LIPIDS: The lipid, itself, is the main ingredient 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 excipient for SLN, **Glyceryl monostearate** & **glyceryl monooleate** are mostly preferred in cosmetics products, **Stearic acid, palmitic acid tetradecanoic acid** are used for reparation of SLN, **Bees wax** and **carnuba 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 peculiar 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 low mobility of the phospholipid molecules, sudden lack 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 some co-emulsifying agent like sodium glycocholate further decreases the particle size.

Lipids	Surfactants and Cosurfactants
Triglycerols Tricaprin Trilaurin Trimyristin Tripalmitin, Tristearin	**Phospholipids** Soy lecithin Egg lecithin Phosphatidylcholine
Acylglycerols Glycerol monostearate Glycerol behenate Glycerol palmitostearate	**Ethylene oxide/propylene oxide copolymers** Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamer 908
Fatty acids Stearic acid Palmitic acid Decanoic acid Behenic acid	**Sarbitan ethylene oxide/propylene oxide copolymers** Polysorbate 20 Polysorbate 60 Polysorbate 80
Waxes Cetyl palmitate	**Alkylaryl polyether alcohol polymers** Tyloxapol
Cyclic complexes Cyclodextrin	**Bile salts:** Sodium cholate Sodium glycocholate Sodium taurocholate Sodium taurodeoxycholate Taurocholic acid sodium salt
Hard fat types Witepsol W 35 Witepsol H 35	**Alcohols** Ehanol Butanol

Table. 3: Other ingredients.

Cryoprotectants	Trehalose, mannose mannitol, polyvinyl, pyrolidone, glucose, maltose, lactose, glycine, gelatin, etc.
Charge modifiers	Stearylamine, diacetyl phosphate, dipalmitoyl phosphatidyl choline (DPPC), dimyristoyl phosphatidyl glycerol (DMPG)
Stealthing agents (agents for improving circulation time)	Poloxamer, polyethylene glycol

Principles of drug release from SLNs[17]

The general standards of medication discharge from lipid nanoparticles are as per the following

1. Higher surface territory because of little molecule measure in nanometer extent gives higher medication

discharge.

2. Slow medication discharge can be accomplished when the medication is homogenously scattered in the lipidframework. It depends on sort and medication entanglement model of SLN.

3. Crystallinization conduct of the lipid carrier and high portability of the medication lead to quick medication discharge.

4. Fast initial drug release in the first 5 min in the drug –enriched shell model as a result of the outer layer of particle due to larger surface area of drug depositon on the particle surface.

5. The burst release is reduced with increasing particle size and prolonged release could be obtained when the particles were sufficiently large, i.e., lipid macromolecules.

6. The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the outer factor which is important, because a low surfactant concentration leads to a minimal burst and prolonged drug release.

7. The particle size affect drug release rate directly depends on various parameters such as composition of SLN formulation (such as surfactant, structural properties of lipid, drug) production method and conditions (such as production time, equipment, sterilization and lyophilization).

1.7. Methods of Preparation of Solid Lipid Nanoparticles.[7,16,18]

1. High pressure homogenization

a. Hot homogenization

b. Cold homogenization

2. Ultra sonication/ High speed homogenization

a. Probe Ultra sonication

b. Bath Ultra sonication

3. Solvent evaporation method

4. Solvent emulsification-diffusion method

5. Super critical fluid method

6. Micro emulsion based method

7. Spray drying method

8. Double emulsion method

9. Precipitation Technique

10. Film-Ultrasound dispersion

High pressure homogenization: It is a reliable and powerful technique, which is used for the production of SLNs.High pressure homogenizer push a liquid with high pressure (100-2000 bar) through a narrow gap (in the range of a few microns).The fluid accelerates on a very short distance to very high velocity(over 1000km/h).Very high shear stress and cavitation forces disrupte the particles down to the sub micron range. Generally 5-10% lipid content is used but upto 40% lipid content has also been investigated work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization: Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. High pressure homogenization of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. The hot homogenization technique can be used for lipophilic and insoluble drugs.

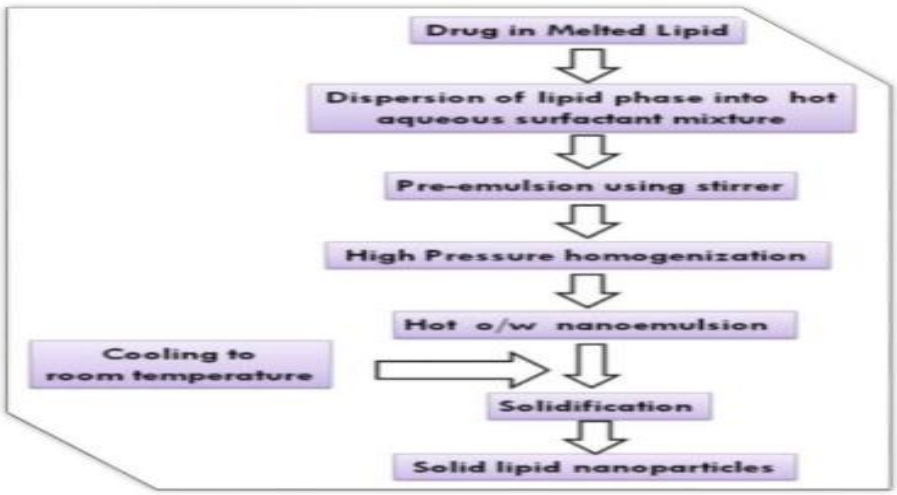

Figure. 6: SLNs Preparation by hot homogenization process.

This technique is not suitable for incorporation of hydrophilic drugs into SLNs because higher portion of drugs in water during homogenization results in low entrapment efficiency.

Cold homogenization

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

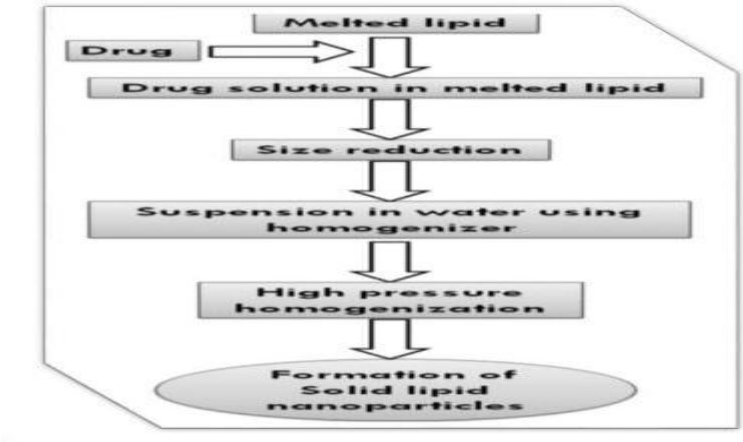

Figure 7: SLNs Preparation by cold homogenization process.

Solvent evaporation method

The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclo hexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure.

Micro emulsion based method

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. microemulsions). They are made by stirring an optically transparent 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 micro emulsion is dispersed 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 facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.

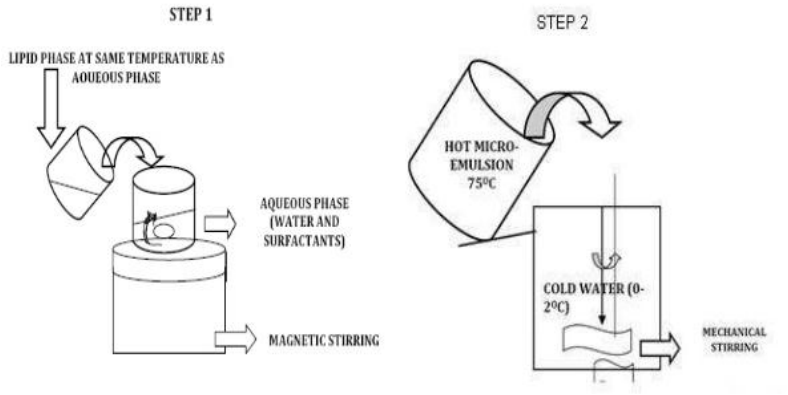

Figure. 8: SLNs Preparation by micro emulsion process.

Solvent emulsification-diffusion technique.[18]

The particles with average diameters of 30-100nm can be obtained by this technique.

In this technique, the solvent used must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid. When heating is required to solubilize the lipid, the saturation step was performed at that temperature.

Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles .Here the both the phase were maintain at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved .Throughout the process constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization.

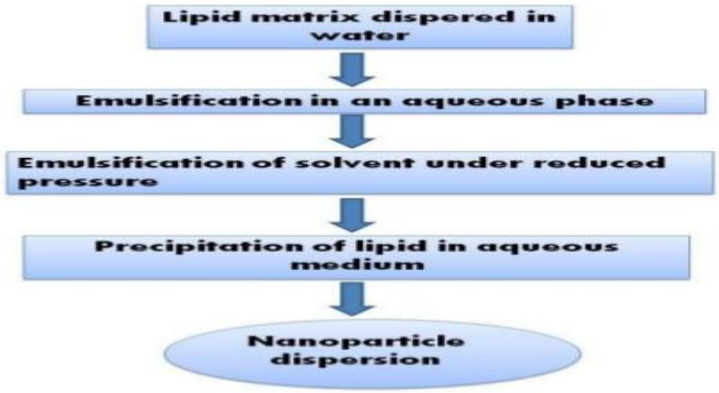

Figure. 9: SLNs Preparation by solvent emulsification diffusion method.

Solvent Injection technique [17]

It is a new approach to prepare SLNs. In this technique, the solid lipid was dissolved in water-miscible solvent (e.g. ethanol, acetone, isopropanol) or a water-miscible solvent mixture. Then this organic solvent mixture was slowly injected through an injection needle in to stirred aqueous phase with or without surfactant. Then the dispersion was filtered with a filter paper in order to remove any excess lipid. The presence of surfactant within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize the formed SLNs until solvent diffusion was complete by reducing the surface tension.

Membrane contactor technique

The liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores allowing the formation of small droplets. SLNs were formed by the cooling of the preparation at the room temperature. Here both the aqueous and organic phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase More recently, a process known as nanotemplate engineering technology (NET) is developed in which "direct cooling" is utilized.

The process consists of three steps.

- Melting a pharmaceutically acceptable matrix comprised of lipids, polymers
- Adding pre-heated water with stirring to form the o/w microemulsion
- Cooling to room temperature with stirring to generate the SLNs.

Double emulsion method: For the preparation of hydrophilic loaded SLNs a novel method based on solvent emulsification-evaporation has been used. Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

Spray drying method: It is an alternative technique to the lyophilization process. This indicates the use of lipid with melting point more than 70^{o}C. The optimum results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

SLN preparation by using supercritical fluid[20]

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

Precipitation technique[21]

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

Film-ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

Secondary production steps[19,20]

Freeze drying

Lyophilization is a promising way to increase the chemical and physical stability over extended period of time. Lyophilization had been required to achieve long term stability for a product containing hydrolysable drugs or a suitable product per oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions.

In case of freeze drying of the product, all the lipid matrices used, form a larger solid lipid nanoparticle with wider size distribution due to presence of aggregates between the particles. The conditions of the freeze drying and the removal of water promote the aggregation of the solid lipid nanoparticles during the freeze drying process.

Sterilization: Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving which is applicable to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it was found to cause a distinct increase in particle size.

Spray drying: Spray drying might be alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method has been used scarcely for SLN formulation, although spray drying is cheaper as compared to lyophilization. The lipids with melting point at temperature greater than 70^{o}C had been recommended for spray drying.

Table. 3: Advantages and Disadvantages of different methods.[18]

S. No	Method	Advantages	Disadvantages
1a	Hot HPH	Versatile, avoid use of organic solvent, easy scalability, Short production time, instruments easily available and no regulatory problems	High temperature lead to degradation, conformational changes in protein, coalescence of particles, burst release due to high emulsifiers
1b	Cold HPH	Minimizes thermal exposure of the drug but does not avoid it completely. Useful in temperature labile drugs or hydrophilic drugs	Higher Polydispersity index
2	Emulsificationsolvent evaporation	Avoidance of heat during production thus useful for thermolabile drugs. Simple procedure	solvent residues
3	Emulsification-Solvent diffusion	Simple procedure, Fast drug release (drawback when slow release is required)	Low lipid content, Low EE and DL, organic solvent residue, Lack of scale up
4	Micro emulsion	No need for specialized equipment and energy for production	high concentrations of surfactants and co-surfactants, presence of large amounts of water in system
5	Membrane Contactor	Simple method, Control of particle size by selection of process parameters, and its scaling-up abilities	-
6	PGSS	one step procedure, no need of organic solvent, low processing temperature conditions	frequent nozzle blockage with hydro-phallic drugs, machinery is costly
7	Multiple emulsion	No need to melt lipids, high loading of hydrophilic drugs, useful for protein loading	Use of solvent and surfactant
8	Solvent injection	no need for high pressure homogenization, easy handling, fast production process, No need for specialized equipment	Use of solvent and surfactant
9	Film Ultra-sonication dispersion	Simple, No need for specialized equipment	Metallic particle contamination, broader particle size
10	Phase inversion	Useful for thermolabile drugs, avoid organic solvent, No need for specialized equipment	-

Characterization of SLN's[9,15,13,25]

Particle size analysis and Zeta potential

Many techniques are available for particle size analysis and zeta potential like scanning electron microscopy (SEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM) and photon correlation spectroscopy (PCS). Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement.

Zeta potential

Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Zeta potential gives information about the magnitude of the electrostatic repulsion or attraction between particles in the aqueous suspension of SLN. Zeta potential can serve as an important parameter in the predictions for long term stability of the formulations. High values of zeta potential (e.g., more than +30mV or less than-30mV) can stabilize the colloidal suspension by electric repulsion, Electric repulsion generally results in less contact between the particles and less aggregation. For example colloidal systems that contain steric stabilizers can express good long term stability even in cases when zeta potential is as low as around 0mV.

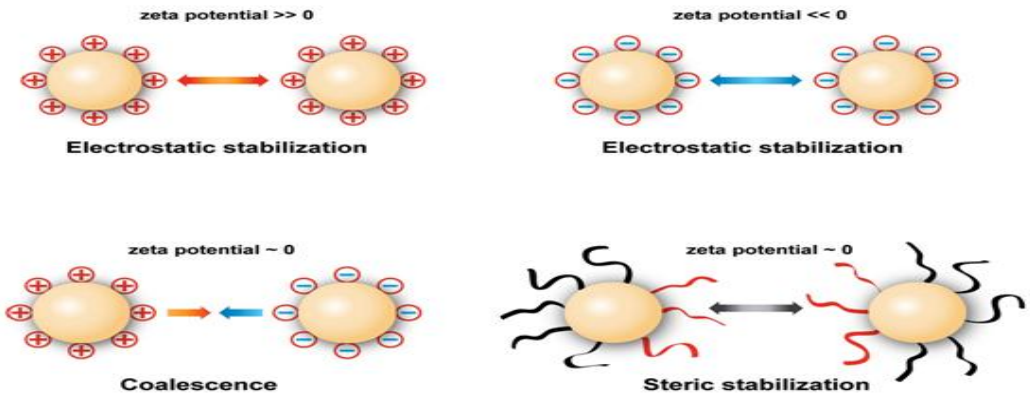

Figure. 10: Influence of zeta potential on the repulsion/coalescence of particles.

Electron Microscopy: Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide way to directly observe nanoparticles. SEM is however better for morphological examination. TEM has a small size limit of detection. Transition electron microscopy and light microscopy both are based on same principle but one difference is that in light microscopy light is used instead of electron.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is a widely used technique that measures differences in the amount of heat required to increase the temperature of a sample compared to a reference. Differences in heat flow may be positive or negative and are presented as function of the temperature. At phase transition there are differences in the sample compared to the reference. The rate of crystallinity using DSC is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion.

X-ray diffraction

A useful technique to exclude aggregate of more than 1μm and substantial polymorphic β1 transition form to stable; thus help in characterizing the crystalline nature of the compound and determine the polymorphic shifts present.[48] X-ray diffraction (XRD) play a prominent role because they are able to provide structural information on the dispersed particles.

Entrapment efficiency

The entrapment efficiency of the drug is determined by measuring the concentration of free drug in the dispersion medium. Ultracentrifugation was carried out using Centrisart, which consist of filter membrane (molecular weight cutoff 20,000Da) 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 amount of the drug present in the aqueous phase is determined by HPLC or UV spectrophotometer.

Stability and storage[6,25]

- 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 product. However, meeting the potency and purity profiles established in the pharmaceutical 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 parameters such as temperature and light appear to be of primary importance for long-term stability.
- The most favorable conditions for long term stability

- 4°C- Most favorable storage temperature
- 20°C-Long term storage did not result in drug loaded SLN aggregation or loss
- 50°C-A rapid growth of particle size was observed

Routes of Administration of slns and their biodistribution[26,27]

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 tobiological surroundings) and enzymatic processes. Various administration routes are

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

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

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

4. Nasal administration Nasal route is preferred due to its fast absorption and rapid onset of drug action also avoidingdegradation of labile drugs in the GIT and insufficient transport across epithelial cell layers.

5. Respiratory delivery Nebulisation 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 frequencyfor better management of pulmonary action.

6. Ocular administration Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocularmucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting.

7. Topical administration SLN are very attractive colloidal carrier systems for skin applications due to their various desirableeffects on skin besides the characteristics of a colloidal carrier system. They are well suited for use ondamaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Application of Slns[8,24]

- **For ocular drug delivery**: SLNs can improve the corneal absorption of drugs and progress the ocular bioavailability of both hydrophilic and lipophilic drugs .
- **As gene vector carrier**: Cationic solid lipid nanoparticles can well bind de- oxy ribo nucleic acid (DNA) directly via ionic interaction and intervene gene transfection and can be used in the gene vector formulation .
- **A targeted carrier for solid tumors**: SLNs have been reported to be useful as drug carriers to treat neoplasms.
- **Anti tubercular chemotherapy**: SLNs-based drug delivery is pulmonary delivery of antimicrobials to treat tuberculosis, a serious lung infection caused by Mycobacterium tuberculosis is another prominent example.
- **For topical use**: Topical SLN products show enormous prospective for treating dermatological conditions by targeting corticosteroids to dermal disease sites while decreasing systemic drug absorption.
- **For Parenteral Application**: SLN are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization.

CONCLUSION

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. The present review has focused on increasing awareness about nano technological field in drug delivery with the emergence of several promising approaches like solid lipid nanoparticles, nano structured lipid carriers, lipid drug conjugates etc. for improving medical therapeutics.. SLNs have already been proven as good formulations in cosmeceuticals and other allied fields, they must occupy a considerable place in the pharmaceutical market.

To exploit the broad applications of lipid based nanoparticulate formulations, it is essential that the pharmaceutical industries specialized in the development of new drug delivery

systems should engage in novel formulation technology to promote their scale up and bring them onto the pharmacist's shelves. SLN offer an economical and patient-friendly device for administration of drugs by various routes to maximize effectiveness while avoiding adverse effects on non-target tissues.

For more than 20 years of research the current and future applications of SLN seem well shaped. In parentral formulations they will offer more possibilities for many drugs with poor aqueous solubility, short half-life and low chemical stability. Moreover SLN are likely to find more applications as targeted drug delivery systems which will "direct" the drug molecules to specific organs of interest and to reduce the systemic toxicity. Thus they can provide solutions for APIs that failed clinical tests due inappropriate tissue localization.

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