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SOLID LIPID NANO PARTICLES - A REVIEW

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ABSTRACT:

Solid lipid nanoparticles (SLN) are rapidly developing field of nanotechnology with several Potential applications in drug delivery and research. SLNs introduced in 1991 represent an alternative and better carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. The ability to incorporate drugs into Nano carriers offers a new prototype in drug delivery that could use for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery. This review presents a broad treatment of solid lipid nanoparticles discussing their aims, production procedures, advantages, limitations and their possible remedies. SLN stability and the influence of various excipients (used in SLN production) on stability with other secondary steps involved in their stabilization like freeze drying, spray drying etc. Analytical methods involved in SLN evaluations are discussed in detail and the major applications of SLNs mainly targeted drug delivery are discussed. Different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are described. Appropriate analytical techniques for characterization of solid lipid nanoparticles like photon correlation spectroscopy, Atomic force microscopy, NMR, Differential scanning calorimetry are highlighted.

Key Words: Nanoparticles, Nanotechnology, Liposomes, Drug targeting, Specific drug delivery

INTRODUCTION

Nanoparticles are subnanosized Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. The solid lipid nanoparticles are sub-micron colloidal carriers (50-100 nm) which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLNs as colloidal drug carrier combines the advantage of polymeric nanoparticles fat emulsions and liposomes. In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by solid lipid which eventually transformed into solid lipid nanoparticles. Solid lipid nanoparticles possess a solid lipid core

matrix that cansolubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers) [1].

The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), triglycerides (e.g. glycerol bahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetylpalmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.

SLNs are attracting major attention as novel colloidal drug carrier for intravenous applications. The SLNs are sub-micron colloidal carrier which is composed of

physiological lipid, dispersed in water or in an aqueous surfactant solution. They are made up of solid hydrophobic core having a monolayer of phospholipids coating. Solid core contains the drug dispersed or dissolved in lipid matrix. They have potential to carry lipophilic or hydrophilic drugs [2].

The successful implementation of nanoparticle for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the wide spread application of nanoparticle to clinical medicine.

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide [2]. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposome's and polymeric nanoparticle). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, nutraceutical and other materials.

SLNs are attracting major attention as novel colloidal drug carrier for intravenous applications. The SLNs are sub-micron colloidal carrier which is composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. The Pub med search till the date indicates the trends in SLN research, given in fig. 1. So if systematically investigated, SLNs may open new vista in research and therapy.

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carrier such as - emulsions, liposome's and polymeric micro - and nanoparticles. 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. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals [3].

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles (fig.1).

The reasons for the increasing interest in lipid based system are many – fold and include.

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale up. The important goals for research of nanotechnologies in drug delivery include:
 - a) Decrease in toxicity while maintaining therapeutic effects,
 - b) Specific drug targeting and delivery,
 - c) Biocompatible and greater safety, and
 - d) Development of safe medicine.

Fig. 1: Structure of solid lipid nanoparticle (SLN)

Advantages: [4, 5, 6, 7]

1. SLNs have better stability and ease of upgradability to production scale as compared to liposome.
2. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity
3. Very high long-term stability.
4. It is easy to manufacture than biopolymeric nanoparticles.
5. Better control over release kinetics of encapsulated compound.
6. SLNs can be enhancing the bioavailability of entrapped bioactive.
7. Chemical protection of labile incorporated compound.
8. Raw material which are to be required are same as that of emulsion.

Fig. 2: A diagrammatic representation on SLN over emulsions and liposomes

9. Large scale production is possible.
10. High concentration of functional compound can be achieved.
11. Lyophilisation possible.
12. Small size and relatively narrow size distribution which provide biological opportunities for site-specific drug delivery by SLNs.
13. Controlled release of active drug over a long period can be achieved.
14. Protection of incorporated drug against chemical degradation. Possible sterilization by autoclaving or gamma irradiation.
15. SLNs can be lyophilized as well as spray dried.
16. No toxic metabolites are produced.
17. Avoidance of organic solvents.
18. Relatively cheaper and stable.
19. Ease of industrial scale production by hot dispersion technique.
20. Incorporation of drug can reduce distinct side effects of drug, e.g. Thrombophlebitis that is associated with i.v. injection of diazepam
21. Surface modification can easily be accomplished and hence can be used for site-specific drug delivery system.

Disadvantages: [8, 9]

1. Poor drug loading capacity.
2. Drug expulsion after polymeric transition during storage.
3. Relatively high water content of the dispersions (70-99.9%).

4. The low capacity to load hydrophilic drugs due to partitioning effects during then production process.

Aims of solid lipid nanoparticles [10, 11]

- Possibility of controlled drug release
- Increased drug stability.
- High drug pay load.
- No bio-toxicity of the carrier.

Preparation techniques for solid lipid nanoparticles [12, 13, 14]

1. High pressure homogenization

- Hot homogenization
- Cold homogenization

2. Ultrasonication/high speed homogenization

- Probe ultrasonication
- Bath ultrasonication

3. Solvent evaporation method

4. Solvent emulsification-diffusion method

5. Supercritical fluid method

6. Micro emulsion based method

7. Spray drying method

8. Double emulsion method

9. Precipitation technique

10. Film-ultrasound dispersion

High pressure homogenization (HPH) technique

This technique is well established at large since fifties and still being used by the pharmaceutical industries. It has emerged as the most extensively used technique for the preparation of SLNs. It makes use of high pressure homogenizer which is accessible from several manufacturers.

High pressure homogenizers push a liquid with high pressure (100-2000 bar) thorough a narrow gap of size of few microns.

Previously this technique was used for manufacturing of nano-emulsions used for parenteral nutrition. In contrast to emulsions for parenteral nutrition which are normally stabilized by lecithin, the SLNs can be stabilized by other surfactants or polymers and their mixtures.

The two basic production methods for SLNs are as follows-

- Hot homogenization technique.
- Cold homogenization technique.

For both techniques the drug is dispersed or solubilise in the lipids above their melting points. In hot homogenization technique lipid components are first melted by heating above their melting points. Therefore it can be regarded as the homogenization of an emulsion. Drug is either dispersed or dissolved in the molten lipids. Following this aqueous surfactant is added at the same temperature. This pre-emulsion of the drug loaded lipid melt and aqueous surfactant phase, is obtained with the help of high shearing device such as Ultra-Turrax.

High-pressure homogenization of the pre-emulsion is taken at the temperature higher than the melting point of the lipid. The raised temperature results in lower viscosity of the inner phase.

However, considerations regarding degradation of the drug and carrier have to be kept in mind while increase in temperature during the process.

A. 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. HPH 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 process is continued till desired particle size. In most cases, 3-5 homogenization cycles are sufficient for the requisite particle size. However unnecessary increase of cycles results in increase in particle size due to particle coalescence. After the homogenization

process, then no-emulsion is formed due to liquid nature of the lipid which on cooling gives rise to solid lipid nanoparticles.

This technique has the advantage, as it is suitable for scale up. However possible concerns regarding hot homogenization is the stability of the drug molecule to the elevated temperatures of the lipid melt. So to avoid heat-accelerated drug degradation, the length of time for drug exposure should be shortened. Muller et al. 2005 prepared SLNs by hot homogenization method in which acetyl palmitate was used as matrix lipid 10.0% w/w. The polymer concentration (poloxamer, poloxamine) was kept constant at 1.2% w/w. The melted lipid at approximately 5°C above its melting point was dispersed by an Ultra-TurraxT-25 in a hot surfactant mixture heated at the same temperature. The pre-emulsion was obtained and was then homogenized at the same temperature using a Micron LAB-40 by applying three homogenization cycles at 500 bars. A hot Nano-emulsion resulted; cooling led to crystallization of the lipid and formation of the SLNs.

Cold homogenization has been developed to overcome the following problems of the hot homogenization technique: (a) drug distribution into the aqueous phase during homogenization, (b) temperature induced drug degradation, (c) complexity of the crystallization step of the Nano emulsion leading to several modifications and/or super cooled melts.

Fig. 3: Solid lipid nanoparticles preparation by hot homogenization process

Cold homogenization technique:

In cold homogenization technique the drug containing lipid melt is cooled by means of liquid nitrogen or dry ice to obtain drug loaded lipid. Rapid cooling leads to formation of solid solution (homogeneous distribution) of drug in lipid matrix and then the solid lipid is ground to lipid Microparticles (approximately 50-100 mm) 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, to obtain the required particle size. Since high shear homogenization process involved here is assumed that it does not elevate the temperature of the dispersion, this method provides protection to heat sensitive drug entities (Fig 6).

This method has the potential of minimizing the partitioning of less hydrophobic drug out of lipid to the aqueous phase during homogenization. The schematic representation for the production of solid lipid nanoparticles (SLNs) through hot as well as cold homogenization.

Fig.4: Solid lipid nanoparticles preparation by cold homogenization process

Advantages

- Low capital cost.
- Demonstrated at lab scale.

Disadvantages

- Energy intensive process.
- Demonstrated at lab scale Bio molecule damage.
- Polydisperse distributions.
- Unproven scalability.

Ultra sonication or high speed homogenization

SLN were also developed by high speed stirring or sonication. A most advantages are that, equipments that are used here are very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer range. This lead physical instability likes particle growth upon storage. Potential metal contamination due to Ultra sonication is also a big problem in this method. So for making a stable formulation, studies have been performed by various research groups that high speed stirring and Ultra sonication are used combined and performed at high temperature.

Advantages

- Reduced shear stress.

Disadvantages

- Potential metal contamination.
- Physical instability like particle growth upon storage.

SLN prepared by solvent emulsification/evaporation

For the production of nanoparticle dispersions by precipitation in o/w emulsions the lipophilic material is dissolved in water-immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as model drug and lecithin/sodiumglycocholate blend as emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen, who produced the cholesterol acetate nanoparticles of mean size 29.

Advantages

- Scalable.
- Mature technology.
- Continuous process
- Commercially demonstrated.

Disadvantages

- Extremely energy intensive process
- . Polydisperse distributions.
- Biomolecule damage

Solvent emulsification-diffusion method

The particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique.

Fig.5: Systematic representation for emulsification-diffusion method

Micro emulsion based method

Gasco and co-workers developed NLC preparation techniques which are based on the dilution of micro emulsions. They are made by stirring an optically transparent mixture at 65-70 °C which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, phosphatidylcholine, and sodium taurodeoxycholate), co emulsifiers (sodium monoctylphosphate) and water (fig 8).

The hot micro emulsion is dispersed in cold water (2-3 °C) under stirring. Typical volume ratios of the hot micro emulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the micro emulsion. According to the literature, the droplet structure is already contained in the micro emulsion and therefore, no energy is required to achieve submicron particle sizes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co solvents of the micro emulsion might play a similar role in the formation of lipid nanoparticles as the acetone for the formation of polymer nanoparticles

Advantages

- ❖ Low mechanical energy input.
- ❖ Theoretical stability.

Disadvantages

- ❖ Extremely sensitive to change.
- ❖ Labor intensive formulation work.
- ❖ Low nanoparticle concentrations.

Supercritical fluid

This is a relatively new technique for NLC production and has the advantage of solvent-less processing. There are several variations in this platform technology for powder and nanoparticle preparation. NLC can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

Advantages

- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method

Spray drying method

It's an alternative procedure to Lyophilization in order to transform an aqueous NLC dispersion into a drug product. It's a cheaper method than Lyophilization. But this method can cause particle aggregation due to high temperature, shear forces and partial melting of the particle.

Double emulsion method

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary was stabilized by stabilizer. Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier. Thereafter, the double emulsion was stirred and was isolated by filtration.

Fig. 6: Micro emulsion method

Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of a lipid-PEG derivative. A major drawback of this is the formation of high percentage of micro particles.

Precipitation method

The glycerides are 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.

High-speed homogenization followed by Ultrasonication method

The formulations of different ingredients are the same as the NLC, prepared by melt emulsification and the low-temperature solidification method. Drug and Phospholipids are dissolved in methanol and mixed with an acetone solution containing a blend of fatty acids. The mixture is then added drop wise to Pluronic solution at 70°C. A pre-emulsion is obtained by homogenization using an Ultra-Turrax T25 at 15000 rpm for 10 minutes at 70°C. This pre-emulsion is ultrasonicated (20w) for 15 minutes to prevent the crystallization of lipids. The emulsion obtained is subsequently cooled down to room temperature with continuous stirring, and the lipid is recrystallized to form NLC. The obtained NLC dispersions are lyophilized and used for further studies.

Solvent injection technique:

Solvent injection technique is a new approach to prepare SLN. It has following advantages 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 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. Solvent injection lyophilization method was used to prepare cinnarizine SLNs, a lipophilic drug. This was found to be an efficient method for preparing stable drug-loaded SLNs. SLNs bearing oxybenzone were prepared by ethanol injection method to improve its effectiveness as sunscreen and were characterized for particle size, polydispersity index.

Fig.7: Schematic representation of solvent injection method

Drug incorporation models are as follows

Models for incorporation of active compounds into SLN

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

- I. Homogeneous matrix model
- II. Drug-enriched shell model
- III. Drug-enriched core model

Solid solution model:

1. Drug is molecularly dispersed in lipid matrix when SLN is prepared by cold homogenization.
2. Drug-enriched shell model.
3. A solid lipid core forms upon recrystallization temperature of the lipid is reached.
4. Drug-enriched core model.
5. Cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt leads to recrystallization of the lipid.

Table No. 1: Materials used in SLN

Solid lipid	Hard fat types	Co emulsifier	Triglycerides
Glyceryl mono state	Witepol	Egg lecithin	Tricaprin
Soya lecithin	Steric acid	Soyabean lecithin	Trilaurin
Phosphatidyl choline	Palmitic acid	Polysorbate 20,60,80	Trimyristin
	Dehenic acid	Butanol	Tri palmitin
	Behenic acid	Butaric acid	Tri sterine

Fig. 8: Different models for incorporation of drug

The structure obtained is a function of the formulation composition (lipid, drug, and surfactant) and of the production conditions (hot versus cold homogenization). A homogeneous matrix with molecularly dispersed drug or drug being present in amorphous clusters is thought to be mainly obtained when applying the cold homogenization method and when incorporating very lipophilic drugs in SLN with the hot homogenization method. In the cold homogenization method, the bulk lipid contains the dissolved molecularly dispersed form, mechanical breaking by high pressure homogenization leads to nanoparticles having the homogeneous matrix structure. The same will happen when the oil droplet produced by the hot homogenization method is being cooled, crystallizes and no phase separation between lipid and drug occurs during this cooling process. Drug enriched shell can be obtained when phase separation occurs during the cooling process from the liquid oil droplet to the formation of a solid lipid nanoparticle. The lipid precipitates first forming a practically drug-free lipid core. At the same time, the concentration of drug in the remaining liquid lipid increases continuously during the formation of the lipid core and the drug enriched shell is crystallised. This drug enriched shell model leads to a very fast release. This fast release is highly desired when application of SLN to the skin, which is required to increase the drug

penetration, especially when using the occlusive effect of SLN at the same time. Drug enriched core can be formed when the opposite occurs, which means the drug starts precipitating first and the shell will have distinctly less drug (Fig.6 c). This leads to a membrane controlled release governed by the Fick's law of diffusion. Each of these three models represents the ideal type. Of course, there can also be mixed types which can be considered as a fourth model. From this, the structure of SLN formed, depends on the chemical nature of active compound and excipients and the interaction thereof. In addition, the structure can be influenced or determined by the production conditions.

Types of solid nanoparticles [15]

The types of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore 3 incorporation models have been proposed for study.

SLN, Type I or homogenous matrix model

The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenation method. A lipid blend can be produced containing the active in a molecularly dispersed form.

After solidification of this blend, it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

SLN, Type II or drug enriched shell model

It is achieved when SLN are produced by the hot technique and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w nanoemulsion the lipid will precipitate first, leading to as readily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model is the incorporation of coenzyme Q 10.

SLN, Type III or drug enriched core model

Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.

SLN versus Other colloidal carriers

SLN have been proven to be a better alternative carrier system than conventional O/w emulsion in the following aspects.

- ✓ If protection of drug against chemical degradation is required.
- ✓ Incorporation of drug in the solid lipid matrix surely offer a better protection than can be achieved in the oily internal phase of emulsion and liposome's.
- ✓ Prolonged release of drug from emulsion is not feasible which can be achieved to a certain extent from SLN
- ✓ SLNs is found to be a better carrier than polymeric nanoparticles in the following aspects
- ✓ Lower cytotoxicity due to the absence of solvents
- ✓ Low cost of excipients
- ✓ Large scale production is possible by the simple process of high-pressure homogenization

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- ✓ Low cost of excipients
- ✓ Large scale production is possible by the simple process of high-pressure homogenization

SLNs versus liposomes

In comparison with liposomes SLNs offer better protection to drug against chemical degradation there is no or little access of water to the inner core of lipid particles. Depending upon the nature of the drug higher payload might be achieved.

Principles of drug release [16]

The general drug principles of drug release from lipid nanoparticles are as follows:

- ❖ There is an inverse relationship between drug release and the partition co-efficient of the drug.
- ❖ Higher surface area due to smaller particle size in the nanometer size range gives higher drug release.
- ❖ Slow drug release can be achieved when drug is homogeneously dispersed in the lipid matrix.
- ❖ It depends on the type and the drug entrapment model of SLN.
- ❖ Crystallinity behavior of the lipid and high mobility of the drug lead to fast drug release.
- ❖ There is an inverse relationship between crystallization degree and mobility of drug.

Factors contributing to a fast release are the large surface area, a high diffusion co-efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug. The increase in the velocity with decreasing particle size was reported.

Storage stability of SLN [17, 18]

The physical properties of SLN's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be

Table No. 2: Comparative properties of solid lipid nanoparticles, polymeric nanoparticles, liposomes and lipid emulsion

Property	SLN	Polymer nano particles	liosomes	Lipid emulsion
Systemic toxicity	Low	>toSLN	Low	Low
Large scale production	Yes	No	Yes	Yes
Cytotoxicity	Low	>to SLN	Low	Low
Residues from organic solvents	No	Yes	May or may not	No
Sterilized autoclaving	No	No	No	Yes
Sustained release	Yes	No	<to SLN	No
Avoidance RES	No	No	Yes	Yes

of primary importance for long – term stability. The zeta potential should be in general, remain higher than -60mV for a dispersion to remain physically stable.

- 4⁰C - Most favourable storage temperature.
- 20⁰C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.
- 50⁰C - A rapid growth of particle size was observed.

***In vitro* and *ex vivo* methods for the assessment of drug release from SLN [19, 20]**

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN.

Various methods used to study the *in vitro* release of the drug are:

- Side by side diffusion cells with artificial or biological membrane.
- Dialysis bag diffusion technique.
- Reverse dialysis bag technique.
- Agitation followed by ultracentrifugation or centrifugal ultra-filtration.

***In vitro* drug release**

Dialysis tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre-washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

***Ex vivo* model for determining permeability across the gut**

Ahlin et al. demonstrated the passage of enalaprilat SLN's across rat jejunum. In short the rat jejunum (20–30 cm distal from the pyloric sphincter) was excised from the rats after sacrificing the animal used for the study. Qing Zhi Lu et al. excised 10 cm long segments of duodenum (1 cm distal to pyloric sphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal to cecum) were immediately cannulated and ligated on both sides used for their permeability studies.

Characterization of SLNs

Adequate and proper characterization of the SLNs is necessary for its quality control. However, characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters evaluated for the SLNs include particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution processes, drug content, in-vitro drug release and surface morphology.

Particle size [21]

Alteration of the size significantly affects the physical stability, biofate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated

systems (liposome's, Nano spheres and nanoparticles) should display a narrow particle size distribution in the submicron size range (as having size below 1 μ m), according to the definition of colloidal particles

Zeta potential [22]

Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement (Luo *et al.*, 2006). Higher value of zeta potential may lead to deaggregation of particles in the absence of other complicating factors such as stearic stabilizers or hydrophilic surface appendages. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions

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 (Meyer and Heinzlmann, 1992).

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (non contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool (Mukherjee *et al.*, 2009).

Dynamic light scattering (DLS)

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function. The advantages of the method are the speed of analysis, lack of required calibration and sensitivity to sub micrometer particles.

Static light scattering (SLS)/Fraunhofer diffraction

This method studies the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. It is fast and rugged method, but

requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.

Differential scanning Calorimetry (DSC)

DSC and powder X-ray diffractometry (PXRD) is performed for the determination of the degree of crystallinity of the particle dispersion. 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 (Siekman and Westesen, 1994).

Acoustic methods

Another ensemble approach, acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.

Nuclear magnetic resonance (NMR) [23]

NMR can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Table No. 3: Characterization of SLN and NLC

Parameter	Method
Particle size and zeta potential	Photon electron microscopy Atomic force microscopy
Surface charge	Acoustic method
Diffusion physical characterization	Franz diffusion cell Scanning electron microscope Transmission electron microscope
Parenteral delivery	Administered through

Sterilization of SLNs [24, 25]

- ❖ For intravenous and ocular administration SLN must be sterile. The high temperature reach during sterilization by autoclaving presumably causes a hot o/w micro emulsion to form in the autoclave, and probably modifies the size of the hot nanodroplets.
- ❖ On subsequent slow cooling, the SLN reformed, but some Nano droplets may coalesce, producing larger SLN than the initial ones.

- ❖ Since SLN are washed before sterilization, amounts of surfactant and co surfactant present in the hot system are smaller, so that the Nano droplets may be not sufficiently stabilized.
- ❖ For parenteral administration, SLN dispersions must be sterile. The mean particle diameter of SLNs is often more than 200 nm, so sterile filtration is not possible in these cases.
- ❖ Autoclaving the finished dispersion is not practical as the lipids melt at temperatures used to terminally heat-sterilize pharmaceutical products, and the molten lipid droplets coalesce as there is no applied shear to prevent this.
- ❖ Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma or e-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO).

Bacterial endotoxins in raw materials need to be monitored, especially when raw materials are of natural origin. It may be possible to lyophilize the SLN dispersion, and this lyophile can be irradiated or exposed to EO.

Measurement of crystallinity and lipid modifications

Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates decrease in the following order: Super cooled melt < α -modification < β 9-modification < β -modification. Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning Calorimetry (DSC) and X- ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids²⁷. Their potential to characterize SLN dispersions has yet to be explored.

Co – existence of additional structures

The magnetic resonance techniques, nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are powerful tools to investigate dynamic phenomena and the nano-compartments in the colloidal lipid dispersions. Dilution of the original SLN dispersion with water might cause the removal of the surfactant molecules from the particle surface and induce further changes such as crystallization changes of the lipid modification.

Applications [26]

There are several potential applications of SLNs some of which are given below:

SLNs as gene vector carrier

SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

SLNs for topical use

SLNs and NLCs have been used for topical application for various drugs such as tropolide, imidazole antifungal, anticancer, vitamin A, isotretinoin, ketoconazole , DNA, Flurbiprofen and glucocorticoids. The penetration of podophyllotoxin-SLN into stratum corneum along with skin surface lead to the epidermal targeting. By using glyceryl behenate, vitamine A-loaded nanoparticles can be prepared.

The methods are useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipidnanoparticles was formulated for topical delivery of drug. The soyabean lecithin and Tween80 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin.

Production of the flurbiprofen loaded SLN gel for topical application offer a potential advantages of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Polyacrylamide, glycerol and water were used for the preparation of this type of SLN gel.

SLNs as Cosmeceuticals

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream. SLN and NLCs have proved to be controlled release innovative occlusive topicals. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.

Table No. 4: Shows Comparison of different formulation methods [27]

Formulation procedure	Advantages	Disadvantages
High pressure homogenization	Low capital cost. Demonstrated at lab scale	Energy intensive process. Biomolecule damage. Polydisperse distributions. Unproven scalability.
Ultrasonication/ High speed homogenisation	Reduced shear stress	Potential metal contamination
Solvent Evaporation Method	Scalable. Continuous process. Commercially demonstrated	Extremely energy intensive process. Polydisperse distributions. Biomolecule damage.
Solvent Emulsification Diffusion Method	Avoidance of heat during the production procedure	
Super critical fluid method	Avoid the use of solvents. Particles are obtained as a dry powder, instead of suspensions. Mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent	Very expensive method
Micro emulsion based method	Low mechanical energy input. Theoretical stability.	Extremely sensitive to change.
Membrane contractor method	Allow large scale production Stability demonstrated	Labor intensive formulation work Low nanoparticle conc.

Table No. 5: Shows list of excipients used in SLN preparation [27]

Lipids	Surfactants
Triglycerides Tricaprin Trilaurin Trimyristin (Dynasan 114) Tripalmitin (Dynasan 116) Tristearin (Dynasan 118) Hydrogenated coco-glycerides (Softisan 142) Hard fat types Witopsol W 35 Witopsol H 35 Witopsol H 45 Witopsol E 85 Acyl glycerols Glyceryl monostearate (Imwitor 900) Glyceryl distearate (Precirol) Glyceryl monooleate (Peceol) Glyceryl behenate (Compritol 888 ATO) Glyceryl palmitostearate (Precirol ATO 5) Waxes Cetyl palmitate Fatty Acids Stearic acid Palmitic acid Decanoic acid Behenic acid Acidan N12 Cyclic complexes Cyclodextrin <i>para</i> -acyl-calix-arenes	Phospholipids Soy lecithin (Lipoid S 75, Lipoid S 100) Egg lecithin (Lipoid E 80) Phosphatidylcholine (Epikuron 170, Epikuron 200) Ethylene oxide/propylene oxide copolymers Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamine 908 Sorbitan ethylene oxide/propylene oxide copolymers Polysorbate 20 Polysorbate 60 Polysorbate 80 Alkylaryl polyether alcohol polymers Tyloxapol Bile salts Sodium cholate Sodium glycocholate Sodium taurocholate Sodium taurodeoxycholate Alcohols Ethanol Butanol Butyric acid Dioctyl sodium sulfosuccinate Monooctylphosphoric acid sodium

Table No, 6: Shows list of drugs incorporated in SLNs [27]

Pharmacological category	Drugs
Anticancer Drugs	Camptothecin
	Etoposide
	Paclitaxel, Docetaxel
	Vinorelbine, Vinpocetine
	Doxorubicin, Idarubicin, Adriamycin, Mitoxantrone
	Methotrexate, 5-Fluorouracil
	Oxaliplatin, Tamoxifen, Ubidecarenone, Cholesteryl
	Butyrate, Chlorambucil, Temozolomide, β -elements,
	Podophyllotoxin, All trans retinoic acid.
	Verapamil, Nifedipine, Nitrendipine.
Cardiovascular Drugs	Hydrocortisone, Cortisone, Prednisolone,
Hormonal Drugs	Deoxycorticosterone, Progesterone, Estradiol,
	Mifepristone, Betamethasone, Sildenafil Citrate, Insulin.
Vitamins	Vitamin-A, Vitamin-E, Vitamin-K, Ascorbyl Palmitate,
	Retinol.
NSAIDS	Ibuprofen, Flurbiprofen, Diclofenac, Nimesulide,
	Naproxen, Ketorolac.
Antifungal Drugs	Ketoconazole, Miconazole, Itraconazole, Econazole,
	Terbinafine, Amphotericin.
Antibacterial Drugs	Ciprofloxacin, Tobramycin, Clotrimazole
Antitubercular Drugs	Rifampicin, Isoniazid, Pyrazinamide.
Antiviral Drugs	Aciclovir, Saquinavir, Penciclovir, Adefovir, Dipivoxil,
	Thymopentin, 3-Azida-3-deoxyuridine, Oxymetrine,
Drugs acting on Nervous System	Quinine, Chloroquine.
	Diazepam, Oxazepam, Carbamazepine
	Clozapin, Olanzapin
	Piribedil
	Cyclosporin, Tacrolimus
	Timolol, Pilocarpine, Tetracaine.
	Lovastatin, Simvastatin
	Etomidate
	Actarit
	Reserpine
Anxiety and Epilepsy	Domperidone
Antipsychotic Drugs	Praziquantel
Parkinson's disease Drugs	Sodium Cromoglycate
Immunosuppressant Drugs	Clobetasol Propionate
Miscellaneous Drugs	Repaglinide
Glaucoma Drugs	Diminazine, Gamma Oryzanol, Calixarene, Resveratrol,
Hypolipidaemic Drugs	Taspine, Apolipoprotein P, Tashione.
Anaesthetic drugs	
Antiarthritic Drugs	
Adrenergic Drugs	
Antiemetic Drugs	
Anthelmintic Drugs	
Antiasthmatic Drugs	
Steroidal Drugs	
Antidiabetic Drugs	
Other Drugs	

SLNs for potential agriculture application

Essential oil extracted from *Artemisia arborescens* L when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticides. The SLN were prepared hereby using Compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as surfactant.

SLNs as a targeted carrier for anticancer drug to solid tumors:

SLNs have been reported to be useful as drug carriers to treat neoplasms. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.

SLNs in breast cancer and lymph node metastases

Mitoxantron-loaded SLN local injections were formulated to reduce the toxicity and the safety and bioavailability of drug. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.

Oral SLNs in antitubercular chemotherapy

Antitubercular drugs such as rifampicin, isoniazide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance. By using the emulsion solvent diffusion technique this antitubercular drug loaded solid lipid nanoparticles are prepared. The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

Methods to prolong brain retention of SLNs

The body distribution of SLNs is strongly dependent on their surface characteristics viz a size, surface hydrophobicity, surface mobility etc. The SLNs have been proposed as suitable system to deliver hydrophilic drugs like diminazine and also for other BCS class IV drugs like paclitaxel, vinblastine, camptothecin, etoposide, cyclosporine etc 44, 47, 48.

These carriers can gain access to the blood compartment easily (because of their small size and lipophilic nature) but the detection of these particles by the cells of the reticuloendothelial system (RES) i.e. the mononuclear phagocytic system; MPS cells of the liver (Kupffer) and that of spleen macrophages is a major limitation for their use. Uptake of nanoparticles

by RES could result in therapeutic failure due to insufficient pharmacological drug concentration build up in the plasma and hence at the BBB. To overcome these limitations various researchers have tried to increase the plasma half-life of SLNs by the following methods.

Surface coating with hydrophilic polymers/surfactants

The high rates of RES mediated detection and clearance of colloidal carriers by liver, significantly reduce the half-life of the drug. The interaction of the colloidal carriers with blood plasma proteins (opsonins) and thus with the membranes of macrophages (opsonization) is believed to be the major criteria for clearance of these systems from the blood stream. Hence to prevent this clearance and to increase their availability at the target site the RES removal of these particulate systems should be prevented. This RES recognition can be prevented by coating the particles with a hydrophilic or a flexible polymer and/or a surfactant.

Stability

The shelf-life stability of SLNs can be very good. Lipids can be chosen that do not hydrolyze in aqueous suspension (another advantage over nanoparticles made from polymers, such as PLGA, which hydrolyzes with a rate that is dependent on polymer structure, and therefore must be lyophilized for practical use). The very small particle size and density close to unity of SLNs means gravity has little effect on the particles in dispersion, and Brownian motion insufficient to maintain colloidal dispersion without creaming or sedimentation. Any such separation can usually be completely reversed by gentle agitation, even if it is observed. The particle size distribution and zeta potential remains stable over time as neither Ostwald ripening nor particle dissolution occur in these systems, and the surface charge determining moieties are immobile. For SLNs made with natural lipids, and not made by an aseptic process, they can be prepared with long-term stability against biological growth using standards preservatives when tolerable.

CONCLUSION

Lipid nanoparticle drug delivery technology presents considerable opportunities for improving medical therapeutics, but the technology's potential remains unrealized. The review has focused on the variety of aspects of SLNs and their applicability in the encapsulation of various drugs. In recent years, number of research works has been successfully carried out in this area. It would result in a simultaneous improvement in the quality, efficacy, and safety profile of drugs.

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