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SOLID LIPID NANOPATICLES – AN OVERVIEW

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ABSTRACT

Objective: The aim of the study is discussing briefly about the review on preparation, characterization of solid lipid nanoparticles and its future application.

Discussion: Solid lipid nanoparticles are most developing formulations of nanotechnology with few applications in various fields like drug delivery, clinical medicine, cosmetics, and research even in other varied sciences. Nowadays researchers are focused on solid lipid carriers as colloidal drug carrier systems. Indeed, the solubility and bioavailability of poorly soluble drugs can be enhanced and utilizing diverse biodegradable and bio acceptable polymers helps to overcome the harmful impact of traditional drug carrier system.

Conclusion: This review focuses mainly on various approaches in industrial scale-up techniques of solid lipid nanoparticles with its merits and demerits, production methodology, and applications. The characterization of solid lipid nanoparticles is usually using different analytical techniques like photon correlation spectroscopy, scanning microscopy, differential scanning calorimetry, etc. Simultaneously, this review underlines on recent research trends concerning to this carrier system.

Keywords: Solid lipid nanoparticles, solid lipid, surfactants, biocompatibility, drug delivery

INTRODUCTION

Targeted delivery system is one of the most testing research zones in pharmaceutical sciences. By creating colloidal delivery systems like liposomes, micelles and nanoparticles,solid lipid nanoparticles, nanosuspension, nano emulsion, nanocrystals new test have opened for improving drug delivery **[1]**. The Colloidal particles ranging in size between 10 to 1000 nm (1.0µm), in which the standard (drug or biologically active material) are disintegrated, entrapped, or to which the active principle is adsorbed or connected are known as nanoparticles **[2]**. Nanoparticles with their unique attributes small particle size, enormous surface area and the ability of changing their surface properties have various advantages compared with other delivery systems **[3]**. Solid lipid nanoparticles are morphologically round with a smooth surface having mean width ranging between 50 to 1,000nm **[4, 5]**. In this article the main focus is on solid lipid nanoparticles (SLNs) **[6]**. SLN introduced in 1991 represent an alternative and better transporter system to traditional colloidal carrier system. SLN are colloidal carrier system made out of a high melting point lipid as a solid core coated by water surfactant and the drugs utilized are of BCS Class II and IV **[7]**. In SLN when contrasted with another colloidal carrier fluid lipid is replaced by solid lipid. The utilization of solid lipid as a matrix material for drug delivery is well known from lipid pellets for oral drug delivery (for example Mucosolvan retard capsules) **[8, 9]**. SLN arranged by any method are in dispersion form which on long term storage results in instability mainly because of hydrolysis response so to increase their stability they can be changed over into solid dry reconstituable powders through lyophilization. A modest and simple variant to lyophilization is spray drying method **[10]**. A comprehensive understanding of different production techniques is also considered.

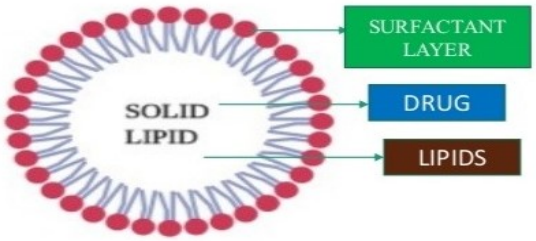

Figure 1: Diagram Solid Lipid Nanoparticles (SLN)

MERITS OF SOLID LIPID NANOPARTICLES:

1. Use of biodegradable physiological lipids which decreases the danger of

acute and chronic toxicity and avoidance of organic solvents in production methods **[11]**.

2. Improved bioavailability of poorly water-soluble molecules.
3. Possibility of scaling up. Possibility of controlled drug release and drug targeting. Lyophilization possible **[12, 13, 14]**.
4. SLN have better stability compared to liposomes
5. Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
6. Conventional emulsion manufacturing methods applicable.

DEMERITS OF SOLID LIPID NANOPARTICLES:

1. Particle growth.
2. Unpredictable gelation tendency.
3. Sometimes burst release.
4. Poor drug loading capacity.
5. Drug expulsion after polymeric transition during storage.
6. Relatively highwater content of the dispersions (70-99.9%) **[15]**.
7. Unforeseen motion of polymeric transition **[16]**.

PREPARATION OF SOLID LIPID NANOPARTICLES:

The solid lipid nanoparticles are prepared with lipid, emulsifier and water/solvent by using various methods and are discussed below.

METHODS OF PREPARATION:

I. High shear homogenization
   A. Hot homogenization
   B. Cold homogenization
II. Ultrasonication/high speed homogenization
III. Microemulsion based method
IV. Supercritical fluid method
V. Solvent emulsification/evaporation method
VI. Solvent emulsification-diffusion
VII. Double emulsion method
VIII. Spray drying method
IX. Solvent injection method
X. Precipitation technique
XI. Film-ultrasound dispersion

I. High pressure homogenization method:

This system is reliable and powerful. It includes high homogenization which pushes the fluid with high (100-2000 bar) through a restricted gap ranging a couple of microns. The liquid accelerates to a short distance at exceptionally high viscosity of more than 1000 km/h. High

shear pressure and cavitation powers disrupt the particles right down to submicron range. Two type of approaches in High pressure Homogenization such as hot homogenization and cold homogenization they work on the similar ideas of blending the drug in bulk of lipid melt.

A. Hot homogenization method:

Hot homogenization is completed at temperatures over the melting point of the lipid and may subsequently be viewed because of the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and therefore the aqueous emulsifier stage (same temperature) is obtained by high-shear blending device. The resultant item is hot o/w emulsion and therefore the cooling of this emulsion prompts crystallization of the lipid and the development of SLNs **[17, 18]**.

B. Cold homogenization method:

Cold homogenization has been developed to defeat different issues related with hothomogenization. Here, drug is joined into melted lipid and therefore the lipid melt is cooled quickly using dry ice or liquid nitrogen. The solid material is ground by a ball mill. The prepared lipid microparticles are then dispersed during a cold emulsifier arrangement. The temperature should be regulated effectively to make sure the solid state of the lipid during homogenization. When compared with hot homogenization, larger particle sizes and more extensive size distribution are typical of cold homogenization test **[19]**.

II. Ultrasonication method:

Ultrasonication or high speed homogenization is another technique for the creation of SLN. Drug and lipid should be dissolved in a suitable organic solvent. lipid and drug mixture are dispersed byusing high shear equipment. Once pre emulsion is formed, then it is placed in a ultrasonicator. After ultra-sonification, then the emulsion is subsequently cooled down to room temperature under stirring. Then the lipid is recrystallizing to solid lipid nanoparticles. The advantage of this method is that the equipment used is usually available at lab scale **[20]**.

III. Microemulsion based method:

Gasco and coworkers developed solid lipid nanoparticles based on the dilution of microemulsion. As micro-emulsions are two-phase systems composed of an inner and external phase (for example o/w microemulsions). The blending of lipid phase and aqueous phase to form transparent or translucent, which usually

composed of a low melting fatty acid, an emulsifier, co-emulsifiers and water. The hot microemulsion is dispersed in cold water (2-3°C) under mild stirring. Finally, the microemulsion should be precipitated forming nanoparticles **[21]**.

IV. Supercritical fluid technology

This is a completely unique technique recently applied for the creation of SLN. Drug is dissolved in a melted lipid. Agitation of lipid and drug mixture with continuous heating leads to the formation of pre emulsion. Homogenization of pre emulsion into a colloidal emulsion. Then the emulsion istransfer into a supercritical fluid (Co_2) column. Finally, precipitation of solid lipid nanoparticles **[22]**.

V. Solvent emulsification / evaporation method:

The production of nanoparticle dispersions by precipitation in oil in water emulsions, the lipophilic material is dissolved in water-immiscible organic solvent that's emulsified in an aqueous phase. Finally, evaporation of the solvent nanoparticle dispersion is made by precipitation **[23, 24]**.

VI. Solvent emulsification-diffusion method:

SLN can be produced by solvent emulsification-diffusion technique. Here, the lipid matrix is disintegrated in partially water-soluble organic solvent followed by emulsification in an aqueous phase. In this method the solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium **[25]**.

VII. Double emulsion method:

In this method the drug dissolved in an aqueous solution (buffer). Then the lipid is melted, blending of drug aqueous solution into the lipid (emulsification). Formation of primary emulsion and then followed by addition of aqueous solution of hydrophilic emulsifier. Finally, dispersion of above mixture needs to the formation of solid lipid nanoparticles **[26]**.

VIII. Spray drying method:

In this Spray drying method, the drug and lipid are dissolved in a suitable organic solvent. Then the lipid mixture is pumped into the spray dryer. Then spraying of the given mixture under drying leads to the evaporation of solvent. Once the solvent is completely evaporated, solid lipid nanoparticles should be formed **[27]**.

IX. Solvent injection method:

Here, the solid lipid is dissolved in water miscible solvent. The lipid solvent mixture is injected into stirred aqueous phase with or without surfactant. Finally, the

dispersion filtered to remove excess lipid. Emulsion within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion gets finished **[28, 29]**.

X. Precipitation method:

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The lipidis dissolved in an organic solvent. Dissolve drug in an aqueous phase separately. Then dispersion of aqueous phase into an organic phase (emulsification). The organic solvent should be evaporated and the lipid is precipitated. Finally, the solid lipid nanoparticles should be formed.

XI. Film-ultrasound dispersion technique

In this method the lipid and the drug were dissolved in a suitable organic solvent, then aqueous phase containing surfactant solution is added. The mixture is stirred continuously, leads to the evaporation of organic solvent. The lipid film is formed. Further continuous stirring using the ultrasound with the solicitor. Finally, the solid lipid nanoparticles should be formed **[30, 31]**.

Table 1: A List of API and Excipients Used For The Preparation of SLN Using Different Method [32-40]

S.NO	API	EXCIPIENTS	METHOD OF PREAPARTION
1	BROMOCRIPTINE	Poloxamer 188, Tristearin, stearic triglyceride (tristearin), Compritol 888 ATO	Homogenization or Ultrasonication method
2	CEFIXIME	Comprotrol ATO 888, tween 20, span 80	Solvent- evaporation method
3	CELECOXIB	Tristearin (TS softisan 100), (SOFTI, saturated glycerides, Sodium deoxycholate	Ultrasonic melt emulsification method
4	ENROFLOXACIN	Tripalmitin as lipid carrier, tween 80 and span 80 as surfactants and Polyvinyl alcohol (PVA) as a stabilizer	Hot homogenization, followed by Ultrasonication technique
5	EZETIMIBE	Glyceryl monostearate (GMS) and Poloxamer 188 were employed as lipid carrier and surfactant respectively.	High speed homogenization Method
6	IRBESARTAN	Poloxamer 407 Glyceryl mono stearate, methanol	Solvent emulsification method followed by probe sonication
7	ISONIAZID	Phospholipon R 80, Tristearin	Ethanol injection method
8	PIROXICAM	Phospholipon 80, stearic acid	High-speed homogenization followed by Ultrasonication method
9	RITONAVIR	Tristearin, HSPC (hydrogenated soybean phosphatidyl choline), poloxamer 188	Hot homogenization

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES:

Adequate and appropriate characterization of the SLNs is necessary for its quality control. The significant parameters evaluated for the SLN are given below;

I. Particle size:

The physical stability of SLNs depends on their molecule size. Photon correlation

spectroscopy and laser diffraction are the most powerful techniques for determination of particle size. PCS (otherwise called dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle development. The particle size determination by photon correlation spectroscopy identifies size range of 3nm to 3µm and by laser diffraction in size range of 100 nm to 180 µm. The Laser Diffraction method is based on the dependence of the diffraction angle on the particle size **[41, 42]**.

II. Zeta potential:

Zeta potential estimation can be carried out using zeta potential analyzer or zetameter. Before estimation. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions **[43]**.

III. Electron microscopy:

Scanning electron microscopy and transmission electron microscopy provide way to directly observe nanoparticles. Scanning electron microscopy is anyway better for morphological examination. Transmission electron microscopy has a small size limit of detection **[44]**.

IV. Static light scattering:

In this technique to analyze the pattern obtained from the light scattered from a solution of particles.From this light pattern we have to determine the size of the nanoparticles.

V. Differential scanning calorimetry:

Differential scanning calorimetry and powder X-ray diffractometry is performed for the determination of the level of crystallinity of the particle dispersion. The rate of crystallinity using Differential scanning calorimetry is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion **[45]**.

VI. Acoustic methods:

It may analyze the attenuation of sound waves scattered by the particles and utilize the sound waves to measuring the particle size.

VII. Nuclear magnetic resonance:

Nuclear magnetic resonance can be used to estimate both the size and the qualitative nature of nanoparticles. Nuclear magnetic resonance selectivity of the chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle **[46]**.

APPLICATION OF SOLID LIPID NANOPARTICLES:

The solid lipid nanoparticles have wide variety of applications in medical and health science **(Figure 2)**.

PATENT RELATED INFORMATION:

The search of documents was performed by use of the different database which includes Google patents, USPTO search engines. Considering the main criteria, only a few patents on solid lipid nanoparticles were considered for review and are listed in **Table 3**.

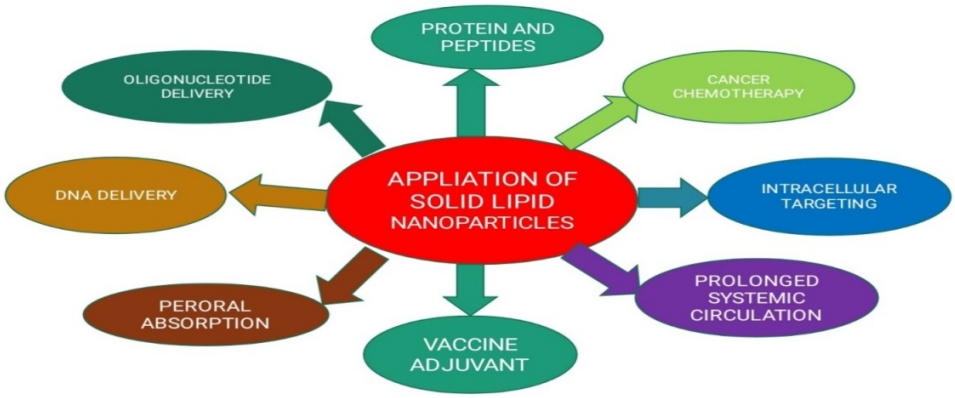

Figure 2: Application of Solid Lipid Nanoparticles

Table 2: Pupose Solid Lipid Nanoparticles Used in Different Delivery System [47-52]

APPLICATION	PURPOSE	MATERIALS
1. Cancer therapy	Drug targeting, reduced toxicity, enhanced uptake of anticancer drug, improved in vitro and in vivo stability.	Poly (alkyl cyanoacrylate) nanoparticles with anticancer agent, oligonucleotide.
2. Intracellular targeting	Target reticuloendothelial system for intracellular infection	Poly (alkyl cyanoacrylate) polyester nanoparticles with antiparasitic or antiviral agent.
3. Prolonged systemic circulation	Prolonged systemic drug effect, avoid uptake by reticuloendothelial system	Polyester with adsorbed polyethylene glycols or Pluronic's or derivatized polyesters.
4. Vaccine adjuvant	Enhance immune response, alternate acceptable adjuvant	Poly (methyl methacrylate) nanoparticles with vaccines(oral and intramuscular immunization)
5. Peroral absorption	Enhanced bioavailability, protection from GI enzymes	Poly (methyl methacrylate) nanoparticles with protein and therapeutic agent
6. DNA delivery	Enhanced delivery and significantly higher expression level	DNA gelatin nanoparticles, DNA chitosan nanoparticles, PDNA- (DL-Lactide- CO glycolide) nanoparticles
7. oligonucleotide	Enhanced delivery of oligonucleotide	Alginate poly (D, L), Lactic acid nanoparticles
8. Protein and peptides drug delivery	Enhanced the delivery of high molecular weight protein and peptide drugs.	Poly (D, L/lactide-co-glycolide) (PLGA), Poly lactic acid, polyacrylic acid (PAA).

Table 3: Patent Information on Solid Lipid Nanoparticles

PATENT ID	COUNTRY	TITLE
CN104706622B	China	Total toad poison lactone lyophilization of Solid lipid nanoparticles.
AU2014273118B2	Australia	Fluorescent solid lipid nanoparticles composition and preparation.
US20140348938A1	United states	Process for preparing solid lipid sustained release nanoparticles for delivery of vitamins.
ES2726603T3	Spain	Paramagnetic solid lipid nanoparticles (pSLN) containing metal amphiphilic complexes for MRI.
CN103655519A	China	Curcumin solid lipid nanoparticles with P-gp inhibiting effect and preparation method.

CONCLUSION AND FUTURE PERSPECTIVE:

For more than 20 years of research the current and future applications of SLN seem well shaped. Furthermore, it may provide controlled release of the drug and their system are used as drug carrier for lipophilic drugs to enhance the bioavailability of poorly water-soluble drugs through SLN. In this present review we discussed about the various methods available for preparation of SLN. But from my view the hot homogenization and ultra-sonification methods are the most compatible and reliable methods for the production of SLN. Due to its broad application in future, it is essential that of pharmaceutical industries specialized in the development of new drug delivery system should engage in novel formulation technology and promote their scale up to bring them into the pharmacist shelves. In future, this solid lipid nanoparticles may also have the ragnostics approach within a new direction.

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