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A Review on Solid Lipid Nanoparticle

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Abstract: Solid lipid nanoparticles (SLN) have attracted attention during recent times. Solid lipid nanoparticles were developed in early 1990s as a volition to other traditional colloidal carriers like liposomes, polymeric nanoparticles and mixes as they've advantages like controlled drug release and targeted drug delivery with increased stability. The present review focuses on the mileage of SLN in terms of their advantages & disadvantages, product methodology and characterization. The network of the SLNs improves drug stability and releasing the drug in a controlled way, which also offer a many advantage over ordinary details, including great physical stability, globular morphology, invariant size, positive zeta capabilities, typical high cell penetration effectiveness, core – shell pattern and excipients of GRAS status make the SLNs delivery system all the more promising. lately, adding attention has been concentrated on these SLN as colloidal drug carriers for incorporating hydrophilic or lipophilic drug.

Key words: Solid Lipid Nanoparticle, Colloidal drug carriers, Homogenization, Lipid, Biocompatibility.

Introduction:

Several systems, including micelles, liposomes, polymer nanoparticles, nano emulsions, solid dissipation and nano capsules have been developed. A promising strategy to overcome these problems involves the development of suitable drug carrier system like solid lipid nanoparticles. In the middle of the 1990s, the attention of different exploration groups concentrated on indispensable nanoparticles made from solid lipids, the so-called solid lipid nanoparticle (SLNs). Solid lipid nanoparticles are at the van of the fleetly developing field of nanotechnology with several implicit operations in drug delivery, clinical drug and exploration as well as in other fields. Due to their unique size-dependent parcels, lipid nanoparticles offer the possibility to develop new rectifiers. The capability to incorporate drug into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary situations of drug targeting. Hence, solid lipid nanoparticles hold great pledge for reaching the thing of controlled and point specific drug delivery and hence have attracted wide attention of researchers.

Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid grounded colloidal carriers, introduced in beforehand nineties. This is the one of the most popular approaches to ameliorate the oral bioavailability of the inadequately water answerable drug. SLNs are in the submicron size range of 50- 1000 nm and are composed of physiologically permitted lipid factors which are in solid state at room temperature. The schematic representation of different particulate medicine carriers similar as mixes and liposomes and their advantages are compared with SLNs in combine all the advantages of polymeric nanoparticles, fat mixes and liposomes.

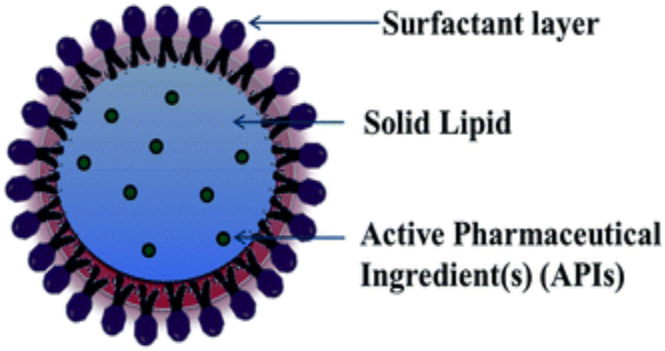


Fig 1: Structure of Solid Lipid Nanoparticle

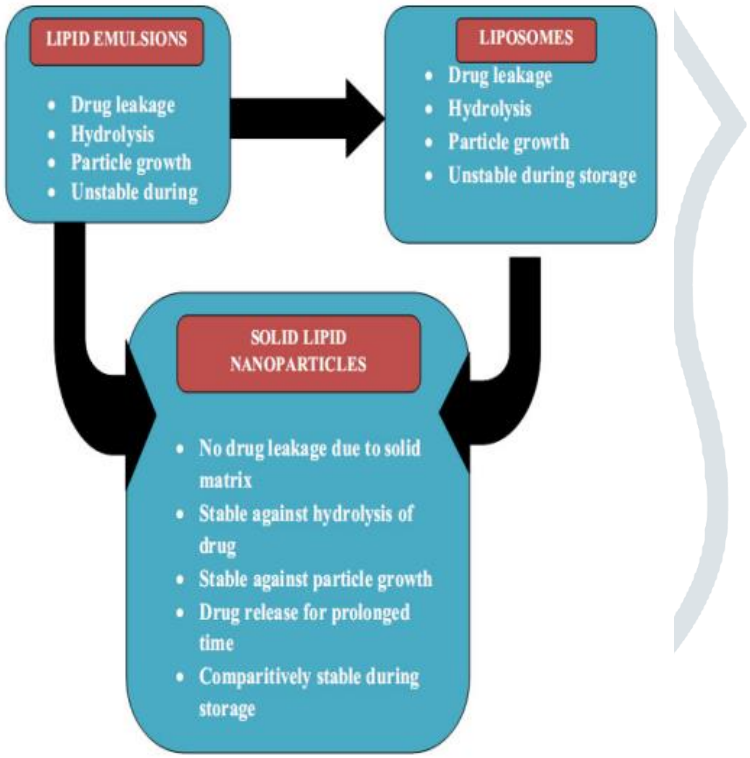


Fig 2: A diagrammatic representation on SLN over emulsions and liposomes

Aims of SLN:

• Possibility of controlled drug release and drug targeting

• further affordable(less precious than polymeric/ surfactant grounded carriers).

• incorporation of lipophilic and hydrophilic drug doable

• Avoidance of organic detergents.

• Problems with respect to large scale product and sterilization

• Increased drug stability.

• High drug cargo.

• No biotoxicity of the carrier because, utmost lipids are biodegradable

Table 1: Advantages and Disadvantages of Sln

Advantages	Disadvantages
Enhanced bioavailability	Having lesser capacity to load hydrophilic drugs
Controlled release	High water content in the formulation leads to stability problem
Easy scale up and sterility	Formulation with poor drug loading capacity
Formulation with particle size 120-200 nm will pass easily through res system thereby bypasses first pass metabolism	Particle growth during storage
Lesser usage of organic solvents	Instability during storage due to polymer transition

Types of solid Lipid Nanoparticle

TYPE 1 Homogenous matrix model

The homogenous matrix model can be attained using the cold homogenization system and by incorporating lipophilic active molecules into the SLNs with the hot homogenization system.

TYPE 2 drug- amended shell model

In this system, a solid lipid core forms once the recrystallization temperature of the lipid is achieved, and the drug concentrates in the still-liquid external shell of the SLN due to dissipation temperature reduction.

TYPE 3 Drug- amended core model

In this system, the active emulsion starts pouring first and the shell will have distinctly less drug. This leads to a membrane-controlled release governed by the Fick law of diffusion.

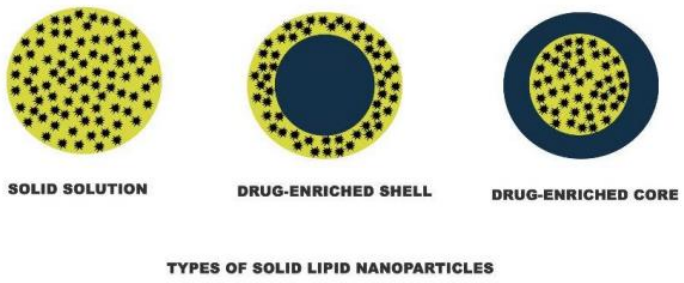


Fig 3: Types of Solid lipid Nanoparticles

Components of Solid lipid nanoparticles

General ingredients include solid lipids, emulsifiers, and water. The term lipid is used here in a broader sense and includes triglycerides (e.g., tristearin), partial glycerides (e.g., Imwitor), fatty acids (e.g., stearic acid), steroids (e.g., cholesterol) and waxes (e.g., cetyl palmitate). All classes of emulsifiers (concerning charge and molecular weight) have been used to stabilize lipid dispersion.

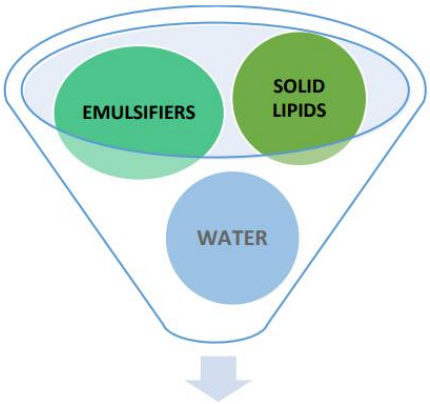
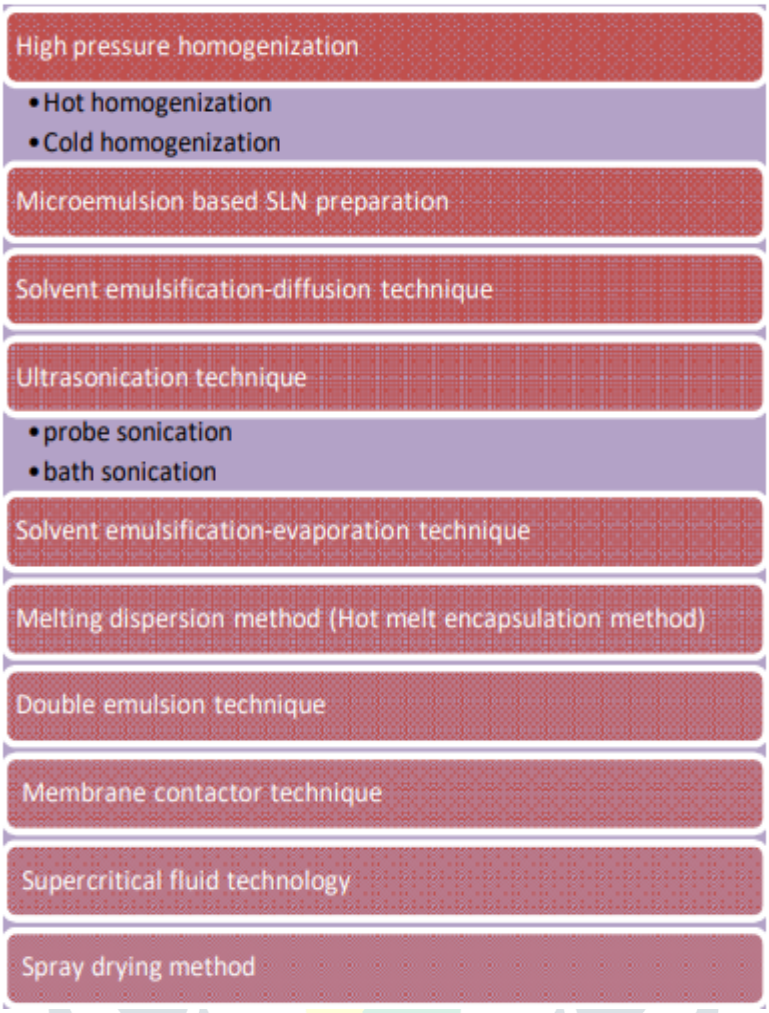


Fig 4: General ingredients of Solid lipid Nanoparticle

The general norms of drug discharge from lipid nanoparticles are as per the following Advanced surface territory because of little patch measure in nanometer extent gives advanced drug discharge. Slow drug discharge can be fulfilled when the drug is homogenously scattered in the lipid frame. It depends on kind and drug trap model of SLN. Crystallization conduct of the lipid carrier and high portability of the drug lead to quick drug discharge. Fast original medicine release in the first 5 min in the medicine – fortified shell model as a result of the external subcaste of flyspeck due to larger face area of medicine deposit on the particle face the burst release is reduced with adding particle size and dragged release could be attained when the patches were sufficiently large, i.e., lipid macromolecules. The type of surfactant and its concentration, which will interact with the external shell and affect its structure, should be noted as the external factor which is important, because a low surfactant concentration leads to a minimum burst and prolonged medicine release. The particle size affect medicine release rate directly depends on various parameters similar as composition of SLN expression (similar as surfactant, structural concentration of lipid, drug) production system and conditions (similar as production time, outfit, sterilization and lyophilization

PREPARATION TECHNIQUES FOR SLNs

There are different methods of SLNs preparation like



1. High pressure homogenization (HPH)

High pressure homogenization is a powerful method used for the production of SLNs with high pressure (100- 200 bars) through a narrow gap. The fluid accelerates on a veritably short distance to veritably high velocity (over 1000 Km/ h). veritably high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally, 5- 10 lipid content is used but over to 40 lipid content has also been delved. Two general approaches of HPH are hot homogenization and cold homogenization, work on the same conception of mixing the medicine in bulk of lipid melt.

Hot homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and can thus be regarded as the homogenization of an emulsion. A pre-emulsion of the medicine loaded lipid melt and the aqueous emulsifier phase (same temperature) is attained 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 dropped viscosity of the inner phase. still, high temperatures increase the degradation rate of the medicine and the carrier. adding the homogenization pressure or the number of cycles frequently results in an increase of the particle size due to high kinetic energy of the particle.

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.

In this technique the drug containing lipid melt is cooled, the solid lipid is ground to lipid micro particles and these lipid micro particles are dispersed in a cold surfactant solution yielding a pre-suspension. When this pre suspension is homogenized at or below room temperature, the gravitational force is strong enough to break the lipid micro particles directly to solid lipid nanoparticles.

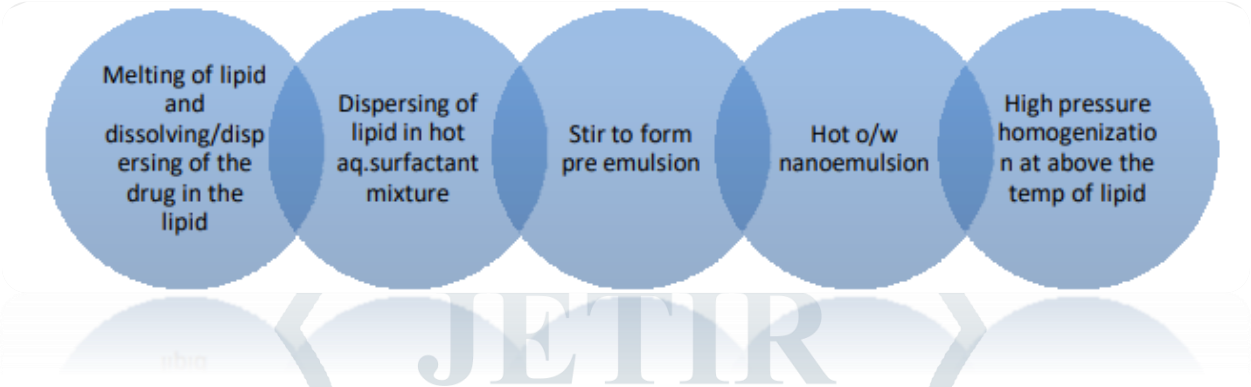


Fig 5: Schematic representation of hot homogenization technique

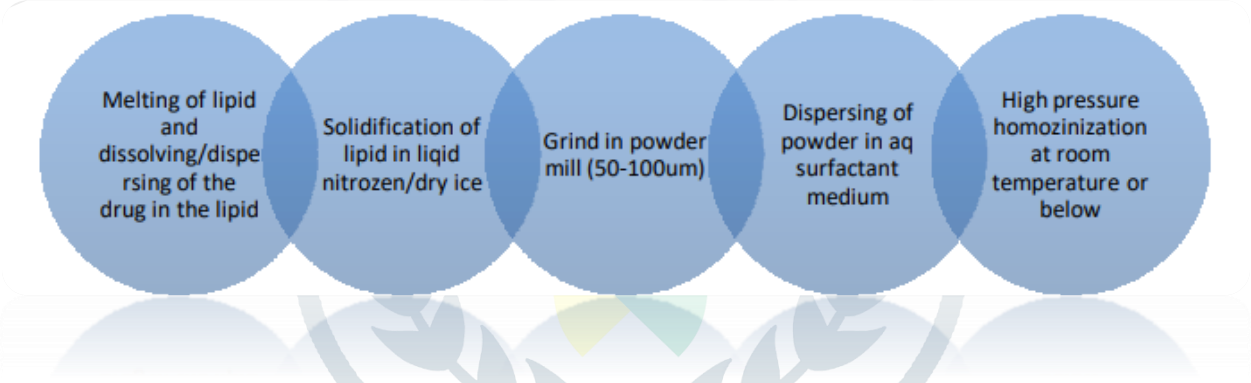


Fig 6: Schematic representation of cold homogenization technique

Advantages:

- Demonstrated at lab scale.
- Low capital cost.

Disadvantages

- Polydisperse distributions.
- Unproven scalability
- Energy intensive process.

2. Micro emulsion based SLN preparation

Gas co and other scientists have developed and optimized a suitable method for the preparation of SLN via micro emulsion. Micro emulsion was an optically transparent mixture at 65-70°c or a slightly bluish solution which is typically composed of

- low melting lipid,

- emulsifier(s),
- Co-emulsifier and water.

A typical volume ratio of the hot micro emulsion to cold water is usually in the range of 1:25 to 1:50. The excess water is removed by ultra-filtration in order to increase the particle concentration and remove excess of emulsifier(s) residue. Considering micro emulsions, the temperature gradient and pH value fix the product quality in addition to the composition of the micro emulsion. High temperature gradients facilitate rapid lipid crystallization and prevent aggregation.

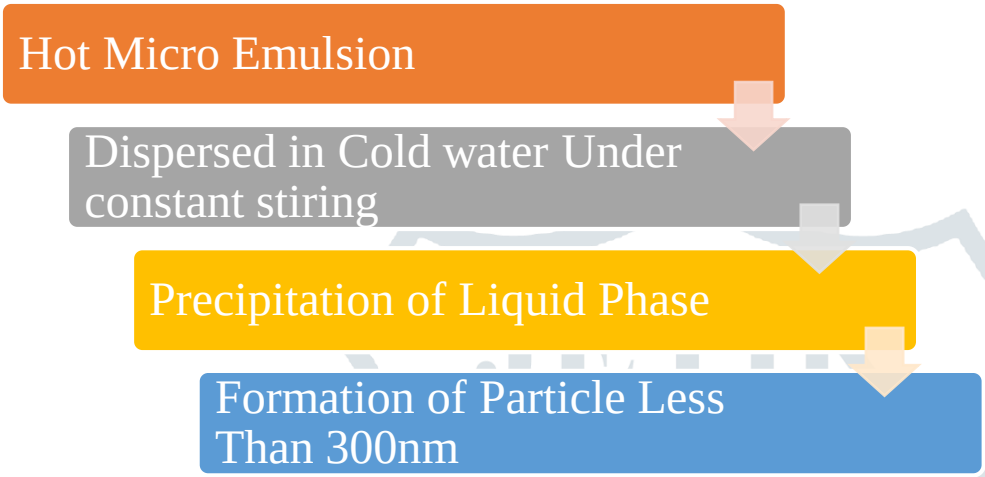


Fig 7: Schematic representation of microemulsion technique

Advantages

- Low mechanical energy input.
- Theoretical stability.

Disadvantages

- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticles due to dilution of lipid concentrations.

Ultrasonication/high speed homogenization

SLNs are also be prepared by ultrasonication or high-speed homogenization techniques. For smaller particle size combination of both ultrasonication and high-speed homogenization is required.

Advantages

- Reduced shear stress.

Disadvantages

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

3. Solvent evaporation

SLNs can also prepared by solvent evaporation method. The solution is emulsified in an aqueous phase by high pressure homogenization. The organic solvent is removed from the emulsion by evaporation under reduced pressure (39–60 mbar).

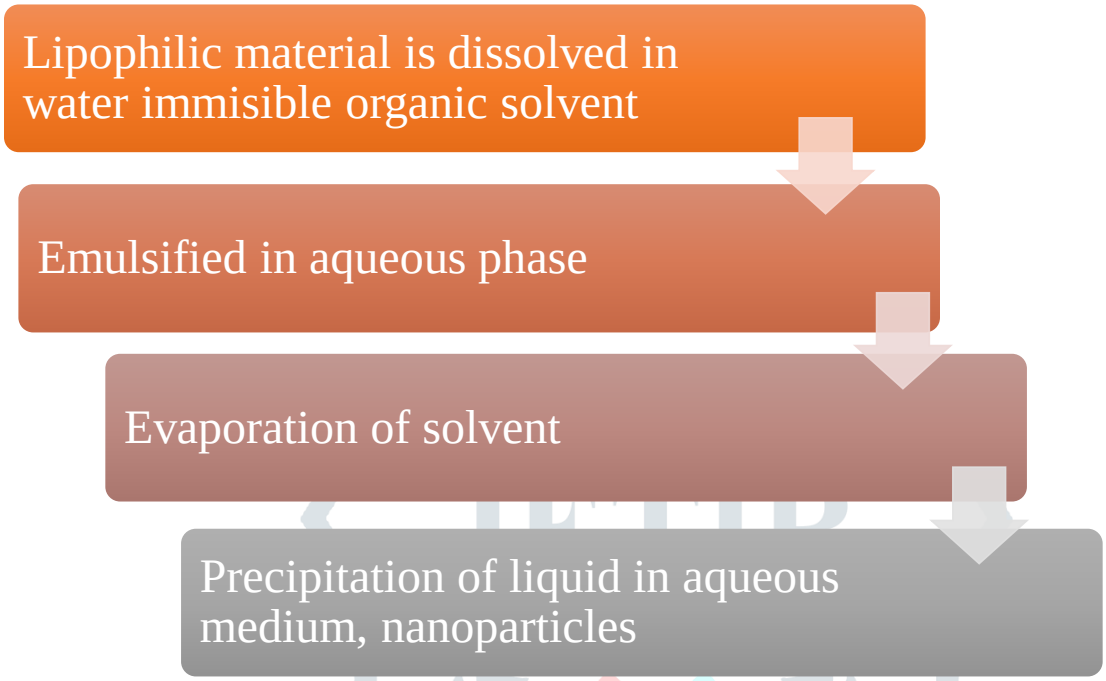


Fig 8: Schematic representation of solvent evaporation technique

Advantage

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

Disadvantages

- Extremely energy intensive process.
- Polydisperse distributions.

4. Solvent emulsification-diffusion method

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

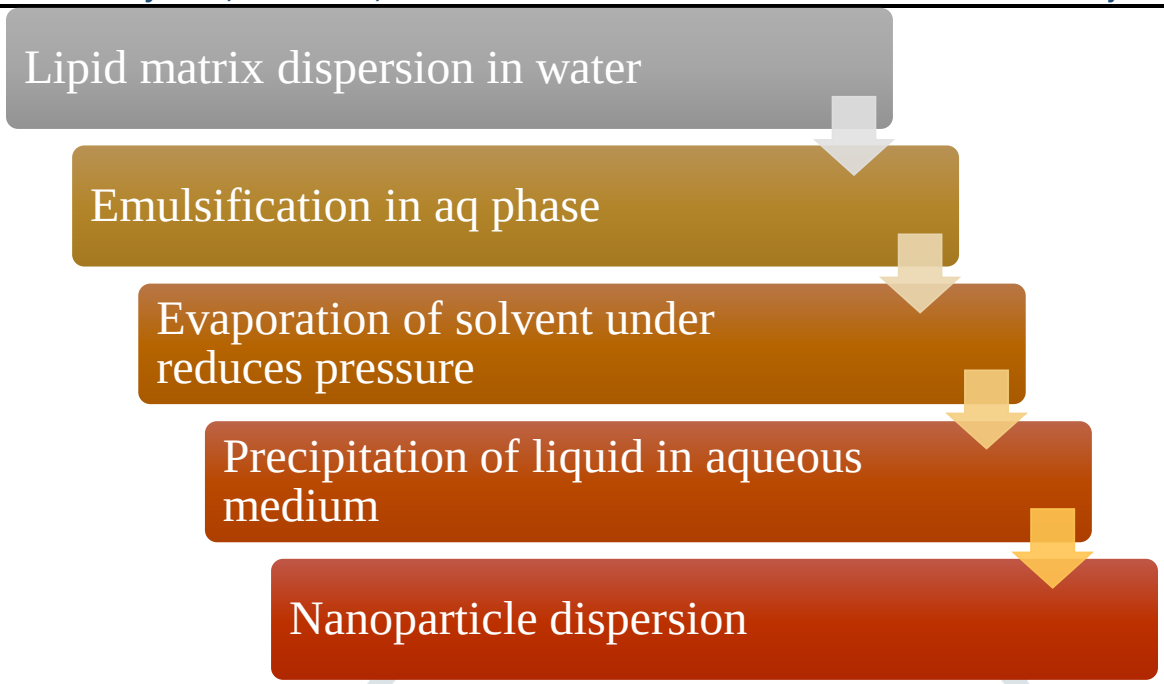


Fig 9: Schematic representation for emulsification diffusion method

5. Supercritical fluid method:

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

Advantages

- Solvent free method.
- 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.

6. Spray drying method

It's an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than lyophilization. This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle. Frites and Muller recommended the use of lipid with melting point more than 70° C by using this method. The best result was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

CHARACTERIZATION OF SLNs

Acceptable and proper characterization of the SLNs is necessary for its quality control. still, characterization of SLN is a serious challenge due to the colloidal size of the particle and the complexity and dynamic nature of the delivery system. The important parameters estimated for the SLNs include particle size, size distribution kinetics (zeta implicit), degree of crystallinity and lipid revision(polymorphism), concurrence of fresh colloidal structures (micelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution processes, drug content, in-vitro drug release and surface morphology.

1.Dimension of particles size and zeta potential

Photon correlation spectroscopy (PCS) and ray diffraction (LD) are the most important ways for routine measures of particles size. PCS (also known as dynamic light scattering) measures the change of the intensity of the scattered light which is caused by particles movement. This system covers a size range from a many nanometer to about 3 microns. PCS is a good tool to characterize nanoparticles, but it isn't suitable to descry larger micro particles. Electron Microscopy provides, in discrepancy to PCS and LD, direct information on the particles shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measures allow prognostications about the storehouse stability of colloidal dispersion.

2.Photon Correlation Spectroscopy (PCS)

It is an established method which is based on dynamic scattering of laser light due to Brownian motion of particles in solution/suspension. This method is suitable for the measurement of particles in the range of 3 nm to 3 mm. The PCS device consists of laser source, a sample cell (temperature controlled) and a detector. Photomultiplier is used as detector to detect the scattered light. The PCS diameter is based on the intensity of the light scattering from the particles.

3.Electron Microscopy

Electron Microscopy methods such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample.

4. Atomic Force Microscopy (AFM)

It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the probe, when the probe is kept in close proximity to the sample which results in a spatial resolution of up to 0.01 nm for imaging.

5. Determination of Incorporated Drug

Amount of drug incorporated in SLNs influences the release characteristics hence it is very important to measure the amount of incorporated drug. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation filtration or gel permeation chromatography. The drug can be assayed by standard analytical technique such as spectrophotometer, a spectroflurophotometry, HPLC or liquid scintillation counting.

6. In vitro drug release

a) Dialysis tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersions 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.

b) 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.

7. Rheology

Rheological measurements of formulations can perform by Brookfield Viscometer, using a suitable spindle number. The viscosity depends on the dispersed lipid content. As the lipid content increases, the flow becomes non-Newtonian from Newtonian.

Applications of Solid Lipid Nanoparticles

1. Controlled Release of Drug

SLNs offer an advantage to modulate release of loaded drug either by varying drug lading approach or by altering surface parcels or composition. In a recent study, SLN loaded with TNF- α siRNA was developed to achieve its prolonged release in treatment of rheumatoid arthritis. SLNs were prepared via a solvent relegation system using biocompatible lecithin and cholesterol, and a complex of siRNA with 1,2- dioleoyl-3-trimethylammonium-propane was reprised therein. In vitro release study of siRNA from SLNs demonstrates absence of burst release, and only 5 of siRNA was released in 30 days. This prolonged release property without burst release was attributed to the presence of cholesterol and complex of siRNA in expression.

2. SLNs for topical use

SLNs used for topical operation for colorful drug similar as anticancer, vitamin- A isotretinoin, flurbiprofen. Using glyceryl behenate, vitamin A loaded nanoparticles can be set. This system is useful for the enhancement of penetration with sustained release. The isotretinoin- loaded lipid nanoparticles were formulated for topical delivery of drug. production of the flurbiprofen- loaded SLN gel for topical operation offer an implicit advantage of delivering the drug directly to the point of action, which will produce advanced tissue attention.

3. SLN for Nasal Application

Nasal administration was a promising volition noninvasive route of drug administration due to fast immersion and rapid-fire onset of drug action, avoiding declination of labile drug (similar as peptides and proteins) in the GI tract and inadequate transport across epithelial cell layers in order to ameliorate drug immersion through the nasal mucosa, approaches similar as expression development and prodrug derivatization have been employed. SLN has been proposed as indispensable transmucosal delivery systems of macromolecular remedial agents and diagnostics by various exploration groups. In a recent report, sheeting polymeric nanoparticles with PEG gave promising results as vaccine carriers (The part of PEG coating of polylactic acid nanoparticles in perfecting the transmucosal transport of the encapsulated bioactive molecule reported to be successful. This conception can be useful for solid lipid nanoparticles.

4. SLN for Ocular Application

Ocular drug administration via SLN has been reported several times. Bio-compatibility and mucoadhesive parcels of SLN ameliorate their commerce with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. estimated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. As a result, SLN significantly enhanced the drug bioavailability in the water less humor. Also studied pilocarpine delivery via SLN, which is generally used in glaucoma treatment, before. They reported veritably analogous results in order to enhance the optical bioavailability of drug.

5. SLN in Cancer chemotherapy

From the last two decades several chemotherapeutic agents have been reprised in SLN and their in- vitro and in- vivo efficacity have been evaluated. Anticancer drug has been incorporated in SLN to protract the release of drug following administration in breast cancer. Tumor targeting has been achieved with SLN loaded with drugs like methotrexate and calprotectin. Metoxantrone SLN original injections were formulated to reduce the toxin and ameliorate the safety and bio efficacy of the drug in treating breast cancer and lymph node metastases.

6. SLN for Respiratory Application

The lungs offer a high surface area for drug immersion by avoiding first- pass effects. Rapid medicine immersion by aerosolization of drugs (in the 1- 3 μm size range) occurs since the walls of alveoli in the deep lung are extremely thin. Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to ameliorate their bioavailability

Table 2: Biopharmaceutical Classification System Class II drugs

Sr.No.	Category	Drugs
1	Antihypertensive	Felodipine, Nicardipine, Nifedipine, Nisoldipine
2	Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin,
3	Antiarrhythmic agents	Amiodarone hydrochloride
4	Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole
5	Antidiabetic and Antihyperlipidemic	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
6	NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
7	Cardiac drugs	Carvedilol, Digoxin, Talinolol
8	Anticoagulant	Warfarin
9	Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone.
10	Antipsychotic drugs	Chlorpromazine Hydrochloride Antiretrovirals Indinavir, Nelfinavir, Ritonavir, Saquinavir
11	Antianxiety drugs	Lorazepam
12	Antiepileptic drugs and Steroids	Phenytoin, Danazol, Dexamethazone

Table 3: Example of solid lipid Nanoparticles

Drug	Solid lipid nanoparticles	vehicles	Category
Raloxifene HCl	Chloroform, Methanol	Non-steroidal drug	Bioavailability
Ciprofloxacin	Methanol, Acetonitrile	Broad spectrum Fluoroquinolone antibiotic	Invitro release & Anti-bacterial
Irbesartan	Ethanol, Lipid-GMS	Anti-hypertensive	Characterization, Optimization & Pharmacokinetic studies
Rosuvastatin calcium	Lipid-GMS surfactant- Tween 80 & polaxomer188	HMG COA Reductase	Development studies
Celecoxib	Lipid-GMS Surfactant-sodium deoxycholate &Tween 80	NSAIDs	Characterization
Cloricromen	Lipid- palmitic acid Surfactant-Epicuren	-	Preparation & characterization
Docetaxel	Lipid - cholesterol	Breast cancer targeting	Development &characterization
Paracetamol	Lipid-GMS. Surfactant-Tween 80& soya lecithin.	NSAIDs	Preparation & Evaluation
Quercetin	Lipid-GMS Surfactant-Tween 80& soya lecithin.	Anti -oxidant & Anti-inflammatory	Prevents formation of skin scars
Meloxicam	Lipid Geleol, Compritol & precirol Surfactant-polaxomer188.	NSAIDs	Development & characterization
Tofacitinib	-	Immunosuppressive drug	Maturation & Alostomuoatory capacity
Berberine	Lipid-glyceryl Behenate Surfactant-sodium cremophorel	Isoquinoline derivatives	Anti-hepatocarcinoma
Pomegranate	Lipid- lecithin & Stearic acid	Antioxidant & Anticancer Activity	Design, Optimization & invitro cytotoxicity
Garlic oil	Lipid- GMS, stearic acid	Volatile oil	Evaluation & Characterization

Conclusion:

SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions and liposome; due to various advantages, including feasibility of incorporation of lipophilic and hydrophilic drugs, bettered physical stability, low cost, ease of scale- up, and manufacturing. SLNs are prepared by various advanced ways. The point specific and sustained release effect of drug can more achieved by using SLNs have been used considerably for operations in drug discovery, drug delivery, and diagnostics and for numerous others in medical field. They're fairly new drug delivery systems, having entered primary attention from the early 1990s and future holds great pledge for

its systematic disquisition and exploitation. We can anticipate numerous patented dosage forms in the form of SLNs in the future

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