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A Review Article on Solid Lipid Nanoparticles: Preparation Techniques and Applications

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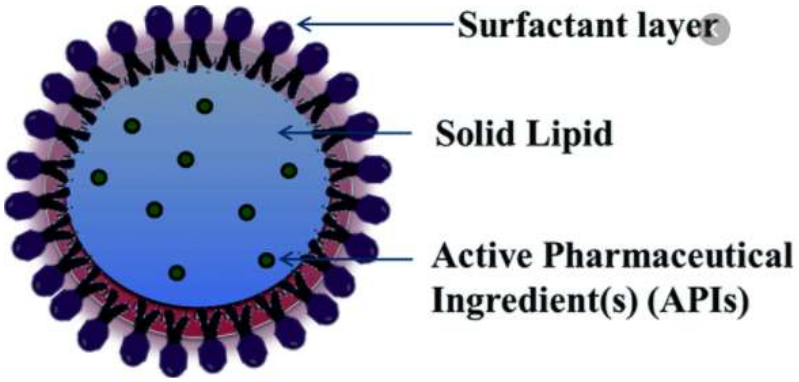
ABSTRACT
Solid lipid nanoparticle have emerged as a promising nanocolloidal system for drug delivery. In the field of nanotechnology, solid lipid nanoparticles are rapidly developed with potential applications. They are made up of lipids which are dispersed in aqueous surfactant solution. they act as nano carriers for drug delivery and site targeting. The present topic details about aims, advantages and drawbacksof SLPs, various preparation techniques like homogenization, ultrasonication, super fluid crystallization, solvent evaporation & emulsification etc. applications of solid lipid nanoparticles in various fields and treatment of various diseases like tuberculosis, cancer & parasitic diseases etc.
***Keywords:**solid lipid nanoparticles, super fluid crystallization, ultrasonication

I. INTRODUCTION

Solid lipid nanoparticles(SLPs) were introduced in the year 1991. Their ranges from size 50-1000 nm and they are made up of physiological lipid which is dispersed in aqueous surfactant solution or water. They have unique characteristics like large surface area, small particle size, high drug loading efficacy and ability to improve the performance of pharmaceuticals.[1]

Solid lipid nanoparticles are mostly spherical in shape and made up of lipids and selection of those lipids or lipid mixture is important in fabrication of solid lipid nanoparticles. The selected lipids are examined by Fourier transform infra-red spectroscopy, mass spectrometry. Lipids used in the preparation of solid lipid nanoparticles are triglycerides, acyl glycerol mixture and hard fat type.[12]

Surface tension between water and lipid in SLP is decreased by using surfactants. Rate of administration is an important factor in selection of surfactants. Mostly used surfactants for the preparation of solid lipid nanoparticles are poloxamer 188, poloxamer 182, polysorbate 20, polysorbate 60, polysorbate 80, sodium chlorate, sodium glycholate, soya bean lecithin.[2]
Most commonly used surfactants in parenteral and ocular route are poloxamer 188, lecithin.



Structure of solid lipid nanoparticles

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AIMS OF SOLID LIPID NANOPARTICILES [13]

- To incorporation of hydrophilic and lipophilic drugs.
- To improve biocompatibility and reduce toxic.
- To maximize drug bioavailability.
- To enhance the drug stability.
- To promote the controlled release kinetics.

Advantages Of Solid Lipid Nanoparticiles[1,16,3]

- Solid lipid nanoparticles having a size range of 50-200 nm can easily bypass liver and spleen filtration.
- Controlled release of drugs can be achieved by SLPs.
- High pressure homogenization method is very cost effective in production of SLPs.
- Drug targeting can be achieved by coating or attaching to ligands.
- Long term stability
- Biocompatible and low toxic.
- System is physically stable when lipophilic drugs are delivered by SLPs.
- They have promising sustained release & drug targeting for lipophilic and hydrophilic drugs.
- Incorporation of drugs is feasible.
- Chemically labile agents can be protected from acidic environment in the stomach and prevent from degradation in the gut.
- Release kinetics of encapsulated compounds can be controlled.
- Penetration can of drug through skin can be enhanced by dermal application.
- No special solvents are required & easy to scale up and sterilize.

DRAWBACKS OF SOLID LIPID NANOPARTICLES

- Due to the crystalline nature of the solid lipid nanoparticles the drug loading capacity is poor.[3]
- Polymeric transition can occur during the storage which may lead to drug expulsion.[4]
- Drug release profile cannot be adjusted.
- High water content in SLPs dispersions.
- Unpredictable gelation tendency & particle growth.

II. METHODS FOR PREPARATION OF SLPS

1. HIGH PRESSURE HOMOGENIZATON (HPH) METHOD

High pressure homogenization is the most commonly used method for preparation of SLPs and it is reliable. The high pressure homogenizer's forces the liquid to pass through the narrow gap at a pressure of 100-2000 bar. Particle size to submicron range can be achieved by fluid acceleration at high velocity, high shear stress and cavitation force. The approaches for HPH are hot homogenization & Cold homogenization. [4]

I) Hot homogenization

This method is carried above the temperature melting point of lipids, thus similar to homogenization of emulsion. High shear mixers are used to prepare pre emulsion of drug loaded lipid content and aqueous emulsifier phase. The product formed is hot o/w emulsion which is cooled to form crystals of lipid & form SLPs.the quality of the end product depends on the quality of pre emulsion. Smaller size particles are formed at higher temperatures because of low viscosity. But increased temperatures causes degradation of drug and carrier.

The temperature of the sample increases due to high pressure process.3-5 homogenization cycles (500-1500 bar) are sufficient.

Increases in the homogenization process and no of cycle's increases the size of the particles due to kinetic energy of the particles. [4]

II) Cold homogenization

This method is developed to reduce the degradation caused by increased temperatures. Lipid melt is prepared by incorporating drug into lipid and cooled to solidification. The solid particles are ground in a motor mill and the formed lipid microparticles are dispersed in colour surfactant at room temperature or relatively below room temperature .[5]

Regulation of temperature is essential during formation of solid state of lipid particles. But compared to hot homogenization the SLPs produced by this method have large size and broader size distribution.

2. ULTRASONICATION METHOD

In this method SLPs are produce by spray congealing of lipid nanoparticles using both ultrasonication and high speed homogenization. Smaller sized SLPs particles can be produced by this technique. Bath and probe sonication can be used. [5, 20]

Drawbacks:

Potential metal contamination.

Due to high speed broader size distribution ranges into µm range.

Another major drawback is particle growth upon storage and it can be reduced by increasing

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surfactant concentration but causes toxicological problems in parenteral administration.

3. SOLVENT EVOPARATION METHOD

In this method water immiscible organic solvents like chloroform, cyclohexane, dichloromethane and toluene are used. Lipophilic part is dissolved in water immiscible organic solvent and emulsified in aqueous phase. The solvent is removed by evaporation and the lipid content is precipitated to form nano dispersion in aqueous medium that produce nanoparticles of size 25nm.

High pressure homogenizers are employed to emulsify the solution in aqueous phase and organic solvent is removed by evaporating under reduced pressure. [5, 17]

4. Solvent Emulsification Diffusion Method

Lipids are dissolved in water immiscible organic solvent and emulsified with aqueous phase by HPH.solvent is removed by evaporation under reduced pressure and precipitated to form nanoparticle dispersion. [4'14]

Advantages:

SLPS in a size range of 30-100nm can be produced.
Thermal stress can be avoided.

Drawbacks:

Removal of additional organic solvent is impossible.

5. SUPERCRITICAL FLUID METHOD

It is an alternate approach to produce SLPs by particles from gas saturation solution. Super critical fluid is a substance above its pressure and critical temperature.it has special thermophysical properties which can be adjusted by minute modification of pressure.

Various techniques like rapid expansion of supercritical solution (RESS), precipitation with compressed anti solvent process (PCA) can be used for producing SLPs. [6]

Rapid expansion of supercritical solution (RESS):

This technique requires drug which has high solubility in ScCO2 solution. Solute is converted into nanoparticle by quick enlargement of ScCO2 fluid through nozzle. Factors that regulate the particles and particle size are short residence time and max.dilution of particles in expansion chamber. [6]

Precipitation with compressed anti solvent process:

Drugs with poor solubility in SC fluids are selected. The drug is dissolved in solvent. Solvent should be miscible with SC fluid. The SC fluid pulls out the organic solvent and the drug solution is atomized and introduced into chamber for super saturation & precipitate out as fine crystals in dry powder form. [6]

Advantages:

Solvent like carbon dioxide solution can be used instead of organic solvents.
Particles produced are available in dry form rather than in suspension.

6. SPRAY DRYING METHOD

It is a flip side method to lyophilization which modifies aqueous dispersion into drug. Particle gathering can be seen in elevated temperatures, so lipids with BP greater than 70°c are selected for spray drying.SLP dispersion of concentration 20% of trehalose in ethanol water mixture or 1% with a solution of trehalose in water is spray dried for best results. [8, 15]

7. DOUBLE EMULSION METHOD

It is a novel method to prepare hydrophilic loaded SLP by solvent emulsification evaporation method. Drug is dissolved in aqueous water solution and mixed with liquid melt.to the primary emulsion is stabilized by adding stabilizers and dispersed in aqueous phase containing hydrophilic emulsifier. The double emulsion is mixed and separated by sifting. For primary w/o emulsion emulsification poly (lactic-co-glycolic acid) (PLGA) is used.it shows no impact on particle size and also reduces zeta potential. As the concentration of PLGA increases drug loading capacity, stability & encapsulation efficiency also get enhanced.

This method is usefull in preparation of sodium chromoglycate SLPs. [7]

8. PRECIPITATION METHOD

A solution of glycerides dissolved in organic solvent is emulsified

With aqueous phase. The organic solvent in the lipid is removed by evaporation and precipitated to form SLPs. [7]

9. FILM ULTRA SOUND DISPERSION

In this method drug and lipid are mixed with organic solution. After decompression &

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rotation the organic solution is evaporated to form lipid film. Later aqueous solution which involves the emulsion is added to lipid film and subjected to ultrasonic with probe and diffuser to form uniformly sized particles.[7,18]

III. APPLICATIONS

❖ Solid lipid nanoparticles can be used for metal based complexes in cancer treatment due to reducing size and toxic effects of metal based complex.[17]

❖ **Oral delivery**

SLPs can be transformed into dosage form like tablets and powder sachets .SLP dispersion can be used as granulation liquid during granulation process. [8]

SLPs can be used for filling in hard gelatin capsules.

Pellets can be produced by using SLP dispersion as wetting agent.

❖ **Topical delivery**

SLPs can be formulated as creams, gels & sprays. They protect skin from UV rays. Mostly SLP dispersion is formulated as ointment or gel in order to achieve administration on skin.

Increase in the concentration of SLP dispersion content result in semi-solid gels which are acceptable for application on the skin.[8]

❖ **Parenteral delivery**

Due to their small size SLPs can be administered by Intravenous, Intramuscular & sub cutaneous route. [8]

❖ **Pulmonary delivery**

Drug delivery by pulmonary route can be achieved from good vascularization, large surface area drugs & large capacity for solute exchange.SLPs powder can be used in the form of dry powder inhalers.[20]

❖ **Solid lipid nano particles as a potential adjuvants for vaccines**

New safer vaccines are less effective in vaccination. So to enhance the Immunization effective adjuvants are required.SLPs being solid structure, the lipid content slowly degrade and provide longer Exposure to immune system.[9]

❖ **Solid lipid nano particles in cancer treatment**[18]

Solid lipid nano particles can be used as drug carriers.

Anticancer drugs are incorporated into SLPs to prolonged release after IV administration.

Tumor Targeting can be achieved by incorporating drugs like methotrexate and campothecin into solid lipid nanoparticles.

Mitroxantron SLP injection were formulated to reduce toxicity and improve bioavailability of the drug.

❖ **SLPs for delivery of peptides, proteins and antigens**

Proteins and antigens are incorporated or absorbed on to SLP and administered through IV or other routes like oral, nasal and pulmonary route. Peptides such as cyclosporine A, insulin, calcitonin & somatisation can be incorporated into SLPs.[10,19]

❖ **Targeted drug delivery to brain**

SLPs of size <50 nm can be effective for drug targeting. Smaller the size of a carrier less uptake of carrier by RE system.

Drug targeting can also be achieved by changing the surface of SLPs.the have ability to penetrate through BBB & achieve drug targeting for treatment of CNS disorders.[10]

❖ **SLP for treatment of parasitic disease**

SLPs can be effective in treatment of parasitic diseases due to their better stability profile, ease of scalability & low cost efficacy.[17,18]

Due to their nano structure and good particulate nature exhibit a potential in treatment of parasitic infections.

❖ **SLPs for ultrasonic drug & gene delivery**

Ultrasonic sound release the drug from the micelles by shear stress & shock waves.SLP are used in ultrasonic drug delivery into invivo and Invitro studies. Smaller packing of SLPs allows to extravasate drug into tumor tissue.[11]

❖ **SLPs for tuberculosis treatment**

Anti-tubercular drugs like Rifampicin, Isoniazid & Pyrazinamide SLPs reduce dosing frequency & improved patience compliance.[12,16]

❖ **SLPs for potential agricultural preparations**[22,10]

SLPs can be used as suitable carrier for pesticides in agriculture. Rapid evaporation of SLPs can be reduced by incorporation of essential oils like Artemisia arboreseens when compared to emulsions. [12]

IV. FUTURE TRENDS OF SLP[14,22]

❖ To enhance the oral bioavailability of encapsulated lipid soluble cyto toxic drug for cancer treatment

❖ Topical applications of bio active across for drug as well cosmetic are major areas for attention and research.

❖ Recently , controlled drug delivery of proteins, peptides & genetic material are surface

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modified for enhanced drug targeting to site specific and focused target.

❖ Nano structured lipid carriers are being paid more attention to develop more stable formulations based on lipid soluble drugs.

❖ Phyto constituents of plant extract or herbal organic like eugenol, quercetin etc are being explored for known therapeutic activity and load into SLP.

V. MARKETED PRODUCTS OF SLP

S.N0	BRAND NAME	DRUG	USES	MFG COMPANY
1	RESTASIS	cyclosporine	Increase tear from dry eyes	ALLERGEN
2	DIAZEMULUS	diazepam	Reduce Muscle spasm	RL FINE CHEM LTD.
3	AMIDATE	etomidate	Anaesthetic agent	BACHEM
4	LIPFEN	fenofibrate	Control cholesterol	SUN PHARMA
5	FLAGFOL	propofol	Anaesthetic agent	FLAGSHIP BIOTECH INTL.LTD
6	FLUOSOL-DA	fluosol	For coronary angioplasty treatment	GREEN CROSS OF JAPAN
7	VITALIPID	Retinol palmitate, Ergocalciferol,	Nutrient supplement	FRESENOUS KABI
8	LIMETHASONE	Dexamethasone-sulfate	Non steroidal anti-inflamattory agent	LI BIOPHARMA

VI.CONCLUSION

Solid lipid nanoparticles has advantages like effective in production process on a large scale equipment and has higher encapsulation efficiency.disadvantages also include like gelation tendency , stability problems during storage etc.This review is mainly focused on the various methods for production of SLPs,its applications,marketed dosage forms and future trends..SLPs have a potential to facilitate drug release in controlled manner at target site and its biocompatibility.in future there will be much development studies on SLPsfor their improvement of quality, efficacy and more detailed study on structure and dynamics of SLN at molecular level in-vitro and in-vivo studies.

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