Nanostructured lipid carriers (NLCs): A Novel based nano carrier for drug delivery and drug targeting

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Abstract:
Aim: Nanostructured lipid carriers (NLCs) contains solid and liquid lipids as the significant principles in the drug delivery system. This review is focused on various aspects involved in the preparation, structure, advantages, limitations, types, physiochemical characterization and wide pharmaceutical applications of SLN has been explored.
Method: It is revealed that NLCs proved to be a promising drug delivery system over conventional carriers, including increase drug solubility, enhanced storage stability, developed permeability and bioavailability, decreased side effects, prolonged halflife and targeted delivery.
Result: Solid lipid nanoparticles are emerging field of nanotechnology with more importance in drug delivery, clinical medicine and research. They are very significant to reach the goal of controlled and site specific drug delivery and therefore it has attracted many research people in this field.
Conclusion: If this delivery system is properly designed and investigated it may open new vistas in therapeutics.

Key words: Nanostructured lipid carrier (NLCs), Solid lipid nanoparticles (SLN), drug targeting, conventional carriers, therapeutics

INTRODUCTION
In the field of nanotechnology, solid lipid nanoparticles gain more attention as novel colloidal drug carrier. They are sub micron sized lipid emulsions where the liquid lipid or oil has been substituted by a solid lipid. It is possible of designing the drug in controlled / sustained release profiles because of entrapment of drug in the carriers of solid lipid core matrix.

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Also the protection of drug in the GIT environment is achieved. Also Lipophilic drug solubility, small Sri Ramachandra University, Porur, Chennai size, larger surface area, drug loading efficiency, enhanced drug stability and targeting of drugs at cellular levels are the advantages of this method. SLNs is the best alternate carrier system to present colloidal carriers ( emulsions, lipsomes, and polymeric nanoparticles. ) in terms of good compatability, reduced side effects, modulating drug release profile, good production scalability and targeted approach. This review will highlight almost all the aspects related to the technique.

Advantages of SLNs:
1. Improved solubility of lipophilic drugs.
2. Protects from GIT environment.
3. Easy Modification at the surface level
4. Controlled release of drug through the lipid matrix
5. Biocompatabile with excipients
6. Easy manufacturing technique
7. High drug loading efficiency
8. Enhanced stability
9. Cost effective method
10. Lipophilic and hydrophilic drugs are incorporated
11. Avoid the use of organic solvents
12. Good production scalability.

Disadvantages of SLNs:

1. Growth of the particle and crystallization of drugs
2. Unpredictable gelatin tendency
3. Poor drug loading capacity in some cases
4. Expulsion of drug from lipids
5. Drug degradation due to high pressure
6. High water content in dispersion

MATERIALS USED TO PREPARE SLNs:6,7,8

The GRAS (Generally recommended as safe) status lipids, surfactants and emulsifiers are used to prepare SLNs.

LIPIDS:

Lipids used in the preparation of SLNs remain solid at room and body temperature. They are

(i) Saturated monoacid triglycerides: tristearin, tripalmitin, trilaurin, trimyristin
(ii) Partial glycerides: glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate
(iii) Fatty acids: stearic acid, behenic acid, palmitic acid, decanoic acid
(iv) Steroids: cholesterol
(v) Waxes: cetyl palmitate

SURFACTANTS/EMULSIFIERS

All class Emulsifiers is used to stabilize the lipid dispersions. Most widely used category is non ionic surfactants like poloxamer 188, poloxamer 407, tweens and spans.

METHODS OF PREPARATION OF SOLID LIPID NANO PARTICLES:7,9,10

High Pressure Homogenization (HPH) technique

This technique is very effective. Principle involved is High pressure homogenization where the liquid is pushed under high pressure (100 - 2000 bar) in the range of a few microns through a narrow gap. This technique evolved from its use in the preparation of o/w emulsion for Parenteral nutrition.

Hot homogenization technique (HHT)

In this technique the drug is added to the lipid at 5-10°C above lipid melting point, stirring is done with addition of aqueous surfactant solution along with dispersion at the same temperature. Emulsion formed is then homogenized, and resulting hot o/w microemulsion is cooled to room temperature or lower temperature to produce SLN. It is applied for lipophilic and insoluble drugs. Hence the exposure time is short with higher temperature most of the heat sensitive drugs are processed safely. This technique does not suit incorporating the hydrophilic drugs since, when homogenization is done low entrapment efficiency may be resulted in higher proportion of drug present in water. In this technique some drawbacks are induced by the temperature they are drug degradation and drug distribution into the aqueous phase.

Cold homogenization technique (CHT)

In order to overcome the problems of hot homogenization method such as: (i) drug degradation due to high temperature (ii) Partitioning of Hydrophilic compounds into aqueous phase at elevated temperature (iii) Particle growth and crystallization cold homogenization technique has been fabricated. The principle involved is dispersion of drug in molten lipid. Cool the melt, and solid lipid is
ground to lipid microparticles. The lipid microparticles are then dispersed in a cold surfactant solution. Homogenization is conducted at room temperature or below, producing SLNs. When compared to hot homogenization, there is increase in size of the particle and polydispersity index is seen in cold homogenization. The cold homogenization only reduces the thermal exposure of drug, but it does not avoid completely it due to melting of the lipid/drug mixture in the first step of preparation. This method is more suitable for heat sensitive products. It minimizes thermal exposure but does not avoid it. It is energy intensive process and results in formation of large particle size & broader size distribution.

Ultrasonication/High Speed Homogenization

The principle involved in SLNs preparation is ultrasonication or high speed homogenization. Both ultrasonication and high speed homogenization is necessary for smaller particles. In this method drug is added to hot lipid melt followed by the addition of hot aqueous phase is added to the above mixture. Then emulsification is done by probe sonicator or by using high speed stirrer. Emulsion formed is sonicated by using probe sonicator, o/w nanoemulsion is formed which is filtered to obtain SLNs. Advantage in this method is no temperature induced degradation, minimal shear stress and equipments are easy to operate. Disadvantage in this method is possibility of metal contamination, particle growth upon storage, broader particle size distribution.

Solvent emulsification - diffusion method

Technique of Solvent emulsification - diffusion method is dispersion of lipid matrix in water. Under reduced pressure emulsification is done in an aqueous phase and in the aqueous medium lipid gets precipitated so the nanoparticle dispersion is formed. The range of average particle diameter is found to be in the range of 30-100 nm. Merits of this method is devoid of thermal stress. It is an extremely energy intensive process and involves use of organic solvents.

Solvent evaporation/emulsification technique

Principle involved in this method is that in a water immiscible organic solvents like (cyclohexane, dichloromethane, toluene, chloroform) drugs and lipid are dissolved. By applying high speed homogenizer emulsification is done in an aqueous phase and at reduced pressure (40-60 mbar) the formed emulsion is evaporated to remove organic solvent by stirring at room temperature. Lipid gets precipitated to form SLNs.

Microemulsion based technique

Microemulsions consist of two-phase systems comprising of oil and aqueous phases. Principle of this method is about microemulsion dilution. These are formed by stirring an optical transparent mixture of emulsifier, co-emulsifier, lipid and water at 65-70ºC and in cold water (2-3ºC) the hot microemulsion is dispersed under stirring. The Volume ratios of the hot microemulsion to cold water were found to be in the range of 1:25 to 1:50. As the result, suspension of lipid particles are produced. It is filtered and then washed with dispersion medium and SLNs are obtained. Advantage of this method is low mechanical energy is required and is theoretically stable. Disadvantage of this is Low nanoparticle concentrations.

Spray drying method

Principle of this method is that an aqueous SLN dispersion is changed into a solid product by spray drying. The best results were found to be with 1% SLN concentration of trehalose in water solution or 20% trehalose in ethanol-water mixtures (10/90 v/v). Merits of this method is cheaper method in comparison to lyophilization. Some of the demerits are: lipid having more than 70ºC of melting point are used, particle aggregation.
Supercritical fluid (SCF) method

The good choice of solvent for this method was found to be Carbon dioxide (99.99%). It is considered to be safer as oxidation of drug material is not possible. This technique generally uses miscible SCF-CO2 organic solvents (DMSO, DMFA). This technique produces nanoparticles by various methods which are: i) Rapid expansion of supercritical solution (RESS) ii) Particles from gas saturated solution (PGSS) iii) Gas/supercritical antisolvent (GAS/SAS) iv) Supercritical fluid extraction of emulsions (SFEE).

Double Emulsion Method

This method is suitable for mainly hydrophilic drugs and the principle is based on solvent emulsification-evaporation method. Double emulsification is carried out to form w/o/w double emulsion. Stabilizer is added to encapsulate the drug and to prevent drug from dividing into external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. In aqueous solution drug is dissolved and it is emulsified in melted lipid, stabilizer is added to stabilize it. Then this stabilized emulsion is dispersed in aqueous phase containing hydrophilic emulsifier. Hence results in production of double emulsion which is then stirred and isolated by filtration. Advantage in this method is higher percentage of microparticles are formed.

Precipitation method

Technique involved in this method is; Glycerides are dissolved (e.g. chloroform) in an organic solvent and in an aqueous phase the solution undergoes emulsification. Later the organic solvent gets evaporated the nanoparticles are formed due to the precipitation of lipid.

TYPES OF SOLID LIPID NANOPARTICLES

SLN, Type I or homogenous matrix model

The SLN Type I: It is obtained from a solid lipid solution and active ingredient. When SLN are developed by the cold homogenization technique a solid solution is produced. A lipid mixture is formed which contains the active ingredient in the of dispersed molecule. After solidifying, it is grounded in its solid state to reduce the active molecule enrichment.

SLN, Type II or drug enriched shell model

It is developed when SLN are made by hot homogenization technique, and the concentration of active ingredient in the melted lipid is less. On cooling the hot o/w nano emulsion, the lipid gets precipitated, initially it leads to steady increase in active molecule concentration in the rest of the melt; an external shell gets solidified resulting in both constituent active and lipid. The outer area enrichment contains drug and lipid matrix of the particles leading to burst release.

SLN, Type III or drug enriched core model

This type of Core model takes place only if there is higher concentration of active ingredient in the lipid melt and closer to its saturation solubility. The active constituent which is solubilized in the melt is minimized by cooling the hot oil droplet. When the saturation solubility exceeds, precipitation of active molecule takes place which leads to form a drug enriched core.
Physiochemical Characterization of SLN’s

1. Particle Size and Shape

SLNs are submicron sized, particle size and shape is characterized by:

a) Photon Correlation Spectroscopy (PCS)

This method is based on dynamic scattering of laser light by the effect of Brownian motion of particles in solution/suspension. This method is suitable for the dimension of particles in the range of 3 nm to 3 mm. It contains laser source, a sample cell (temperature controlled) and a detector. The diameter is based on the intensity of the light scattering from the particles.

b) Electron Microscopy

The physical characterization like shape and morphology of lipid nanoparticle can be visualized by Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM). The size of the particle and distribution can be determined by this method. In SEM electrons are transmitted from the surface of the sample while in TEM electrons are transmitted through the sample. Small size limit of detection can be done by TEM.

c) Atomic Force Microscopy (AFM)

It is an advanced microscopic technique. In this the original shape and surface properties of the particles are calculated. AFM measures the force acting between surface of the sample and the tip of the probe.

2. Measurement of zeta potential

To compute the charge on the particles zeta potential is used and it also predicts the storage stability of colloidal dispersion because of repulsion between particles. Malvern Zeta sizer is most widely used device for detecting Zeta potential and also for full electrostatic stabilization the Zeta potential below -25 mV and above +25mV are needed.

3. Determination of Incorporated Drug or Encapsulation efficiency

Release characteristics from SLNs nanoparticles has influence on the quantity of the drug entrapped. And it also determines the quantity of drug which is encapsulated per unit weigh of nanoparticles after separating the aqueous medium into free drug and solid lipids by ultracentrifugation, filtration or gel permeation chromatography. The drug can be assayed by spectroscopy and HPLC methods.

4. Acoustic methods

Acoustic spectroscopy detects the attenuation of sound waves which is used to find the particle size. In addition, it provides information regarding the surface charge through the oscillating electric field produced by the charged particle motion under the guidance of acoustic energy.

5. Nuclear magnetic resonance (NMR)

This is used to find out the size and the qualitative nature of SLNs. Functional groups modification can be detected by NMR spectroscopy.

6. Surface element analysis

It can be analyzed by Electrophoresis and Laser Doppler anemometry methods.

7. In vitro drug release studies for SLNs

To study the in vitro drug release from SLN various methods are used:

Dialysis tubing:

It is one of the release mechanism which could be performed by In vitro dialysis tubing. In pre-
washed dialysis tubing the nanoparticle dispersion is placed that can be hermetically sealed. The dialysis sac is then analyzed against a suitable dissolution medium and the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method like spectroscopy or HPLC.

**Reverse dialysis:**

In SLN dispersion many small dialysis sacs which consists of 1ml of dissolution medium are positioned. The SLNs are then displaced into the medium and samples are analyzed.

**Franz Diffusion Cell:**

In this method the release of drug from the formulation can be found out by the use of Franz diffusion cell fitted with a cellophane membrane. The dispersion of SLNs is located in the donar chamber. It is then detected against a suitable dissolution medium and at regular intervals the samples are taken from the dissolution medium, analyzed for drug content using suitable methods like spectroscopy and HPLC methods.

**Storage stability of SLN**

During prolonged storage the stability of the SLNs dispersion are monitored for their physical properties prolonged such as zeta potential, size of the particle, content of the drug and viscosity as the function of time. As far as the long term stability is concerned temperature and light are found to be the significant factor to be considered. For a dispersion to be stable the zeta potential should be in between -100 to + 100 mV. Most favourable storage temperature is 4ºC, at 20ºC aggregation or loss of drug and at 50ºC. A rapid growth on size of the particle is observed.

**Routes of Administration and Applications of SLN’s in drug delivery:**

Research has been carried out to access feasibility of various routes of administration for SLN

**Cosmetics:**

SLNs containing sunscreen topical preparations are proven to be successful UV blockers.

**Parasitic diseases:**

Treatment for parasitic infections is antiparasitic therapy. Immune response cannot be produced by these infections, so effective vaccination may not be possible. These nanoparticles due to their small particle size and characteristic structure, show better potential in the effective treatment of parasitic infections like malaria, leishmaniasis etc.

**Targeted carrier for anticancer drug to solid tumor:**

To treat neoplasms these drug carriers are found to be useful. Tumour targeting has been developed with SLNs loaded with drugs such as methotrexate and camptothecin. To prolong the drug release, an anticancer drug Tamoxifen was incorporated after i.v. administration.

**Used in treatment of Breast cancer and lymph node metastases:**

In order to reduce the toxicity and to improve bioavailability of the drug Mitoxantrone SLN local injections were formulated.

**Gene vector carrier:**

They have wide application in gene vector formulation. Several research reported the use of SLNs carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids were explored.

**Topical Use:**

In various drug like anticancer drugs, Vitamin-A Isotretinoin, Flurbiprofen SLNs are used topical
formulation. To improve the penetration and to obtain sustained release effects this method is useful and also provides an advantage of delivering the drug directly to the site of action, which will give higher tissue concentration.

CONCLUSION

They are a class of lipid nanoparticles and are proven to be potential drug carriers prepared from physiologically safe lipids and emulsifiers. They are more advantageous when compared to liposomes, emulsions and polymeric nanoparticles in terms of safety, drug loading capacity, effective with modulated release profiles and stability of encapsulated drugs. They can be manufactured with easily scalable advanced techniques. There are different types of preparation methods and the Best formulation of this class can be prepared by optimizing type and concentration of lipids/emulsifiers. Demerits of this nanostructured lipid carrier is expulsion of drug from lipid matrix and loading of hydrophilic drugs. But it can be overcomed by using combination of solid lipid and liquid lipid to prepare lipid matrix. Hence nano structured lipid carrier are novel formulations which can open new vistas in drug delivery systems.

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