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SOLID LIPID NANOPARTICLES: A REVIEW

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ABSTRACT

Solid Lipid Nanoparticles(SLNs) are fast developing field of nanotechnology with many uses in drug delivery because of their nano size and ability to incorporate various drugs. SLNs provides combine advantages of polymeric nanoparticle and lipid emulsion systems to overcome the invivo stability issues that troubles the polymeric nanoparticles and also the conventional drug delivery. SLNs can be used for drug targeting as they incorporate drug into nanocarriers providimg controlled and site specific drug delivery. This paper reviews present state of solid lipid nanoparticles discussing about its aims, production procedures, need, advantages, limitations and possible remedies available. Also a discussion of analytical techniques used for the characterization of SLN is given like differential scanning calorimetry(DSC), scanning electron microscopy(SEM), photon correlation spectroscopy (PCS), etc.

KEYWORDS: Solid lipid nanoparticles, Colloidal drug carrier, Nanotechnology, homogenization.

INTRODUCTION

The Solid lipid nanoparticles (SLNs) term introduced in 1991 was a growing field of lipid nano technology. SLNs are typically spherical with an average diameter between 10 and 1000 nanometers and possess a solid lipid core matrix that can solubilize lipophilic molecules. The use of surfactants-emulsifiers according to their charges and molecular weights can stabilize the lipid core. The lipids used here includes monoglycerides-glycerol monostearate, diglycerides-glycerol bahenate, triglycerides-tristearin, waxes-cetyl palmitate, fatty acids-stearic acid, steroids- cholestrol. Combination of emulsifiers are found to be effective in preventing particle agglomeration. There are many disadvantages related to liquid state of oil

droplets to overcome those disadvantages liquid lipid was replaced by a solid lipid forming SLNs which were useful for following reasons- Lipids enhanced oral bioavailability. Reduced plasma profile variability. For better characterization of lipoid excipients. To scale-up manufacture processes.

Aims of solid lipid nanoparticles[4]

- Drug release is in controlled manner.
- No carrier related bio-toxicity.
- High drug loading capacity.
- Drug stability is increased.
- Avoidance of organic solvents.
- Can incorporate hydrophilic and lipophilic drugs.

Advantages of SLN's[4]

- Highly enhanced drug content.
- Biocompatible.
- Sterilization is easy by commercial sterility procedures.
- Stability is for longer periods.
- Controlled and targeted site specific delivery.
- High and enhanced drug content.
- Easy to sterilize and can be subjected to commercial sterilization procedures.
- Long-term stability
- Targeted and controlled drug release.
- Requires no special solvent.
- Release kinetics of encapsulated compounds is in controlled manner.
- Bioavailability of entrapped bioactive compounds is enhanced.
- Improved stability of pharmaceutical formulations.
- Easy to manufacture.
- Chemical protection to incorporated drugs or compounds.

Disadvantages of SLN's[2]

- Unexpected dynamics of polymeric transitions.
- Gelation like tendency occuring is usually unpredictable.
- Particle growth occurs.
- Low capacity towards hydrophilic drugs because of partitioning effects during the

manufacturing.

- Water content of dispersion is very high.
- Incorporation rate is slow.

Principle of Drug Release from SLN[5]

The standards of drug discharge from lipid nanoparticles are as follows:

There is a relationship between drug discharge and its coefficient-high surface because of low moleculer measure gives high drug discharge while slow discharge is when the medication is homogenously placed onto the lipid framework dependimg on model of SLN.

A backwards relationship is there between medication portability and degree of crystallization. The medication model of SLN is important for medication discharge design. There occurs an initial drug release in first 5mins in drug model as outer layer of particle have large surface area for drug deposition on particle surface. The release get reduced when particle size increases and when particles is large release is prolonged. These steps depends on parameters like composition of SLN, its production and conditions. The most important is concentration of surfactant used as they reacts with outer shell and can affect the structure. Lower the surfactant concentration minimal is the burst and prolongs the release. The 3 drug incorporation model for drug release from SLN are as follow.

1. Solid solution model:-It is formed by Cold homogeniation technique in this drug is dispersed in lipid matrix and solubilizing surfactant is not used.
2. Core-shell model:-It is formed by Hot homogenization technique.Drug core is formed at recrystallization temperature of lipid.
3. Core-shell model(Drug enriched core):-It is formed by dispersion cooling technique leading to supersaturation of drug dissolved in lipid, Drug precipitates and on cooling causes lipid recrystallization.

Preparation of SLN's

General method-solid lipid, emulsifier and water/solvent

- LIPIDS

Glycerol, Glycerolmonostearate, Glycerolbehenate, Acylglycerol, glycerol palmitostearate, Trimiyristin, Tripalmitin, Triacylglycerol tricaprin.

- Waxes

Cyclodextrin, Cetyl palmitate, Para acyl calix arenes.

- Fatty acids

Decanoic acid, palmitic acid, Stearic acid, Behenic acid.

- Surfactants

Ethylene oxide, Propylene oxide, Egg lecithin, Phosphotidylcholine, Phospholipid, copolymers:- Poloxamer 908, Poloxamer 407, Poloxamer 188, Poloxamer 182.

- Bile Salts

Sodium traucholate, Sodium glycholate, Sodium cholate.

- Alcohols- Butanol, Ethanol.

Factors influencing SLN's[7,8]

- Influence of excipients

Particle size:-If particle size of SLNs is altered the physical stability, biofate of lipid particles and release rate of drug loaded gets affected. Therefore, particle size has to be controlled within reasonable range. According to colloidal particles defination, the size of well formulated system like liposomes, niosomesand nanoparticles should have narrow particle size distribution in the submicron size range i.e below 1μm.

- Influence of the ingredients on product quality.

Various parameters such as composition of the formulations, production methods and conditions can affect the particle size of lipid nanoparticles. if low processing temperature the particles size obtained is large while small particle size generally below 500nm is obtained during hot homogenization technique and a narrow particle size distribution during cold homogenization. When homogenization pressure is increased upto 1500 bar and 3-7 cycles then polydispersity index (PI) and mean particles size is reduced.

- Influence of the lipids

The average particle size of SLN dispersions increases with high melting lipids when Hot homogenization technique is used while other parameters like velocity of lipid crystallization, shape of lipid crystals, lipid hydophilicity, etc. is different for various lipid. If lipid content is increased over 5-10% then it will form broad and larger particles.

- Influence of the emulsifiers

The concentration the surfactant/surfactant mixtures can affect the particle size of

foprmulations. When surfactant/lipid ratio was high small particle sizes was observed and when low big particle sizes was observed during storage. Surface tension between the interface of the particles was decreased by surfactants and also surface area as increased.

Methods of preparation of SLN's[6]

1. High pressure homogenization (HPH)

It is a powerful technique used for the manufacturing of SLNs. High pressure homogenizer pushes liquid with high speed of 100-2000 bar through a narrow few micron size gap. The fluid comes from short distance to very high velocity over 1000 Km/h. Particles are disrupted to a submicron range by cavitation force acting on it and also the high shear stress. In this process only 5-10% lipid content is used. High pressure homogenization is of two type Cold homogenization and Hot homogenization. Both the processes work in similar manner.

Hot homogenization

Hot homogenization is generally carried out at temperatures above the melting point of the lipid. Preemulsion formed of drug loaded in lipid melt and aqueous emulsifier kept at similar temprature is prepared by high shear mixing. At inner phase the viscosity is decreased when temperature is high and particle size is lowered leading to increase in drug and carrier degradtion. The particle size increases when homogenization pressure is increased.

Cold homogenization

In Cold homogenization the drug containing lipid melt is cooled to form solid lipid then grounded to lipid microparticles later dispersed in a cold surfactant solution containing a pre suspension maintained at room temperature, the gravitational force acting on it breaks the lipid particles to form SLNs. Cold homogeninization has overcomed all issues related to Hot homogenization technique.

2. Ultrasonication/high speed homogenization

Ultrasonication/high speed homogenization technique is used to obtain SLNs with smaller particle sizes.

3. Solvent evaporation

In solvent evaporation method the lipophilic material is dissolved in a water-immiscible organic solvent like cyclohexane later emulsified in an aqueous phase. Then the solvent is evaporated and nano particles dispersion is formed as lipid precipitates in aqueous medium

through high pressure homogenization. The nano sized particles formed are of 25nm. The organic solvent is removed under reduced pressure of 40–60 mbar from emulsion.

4. Solvent emulsification-diffusion method

Solvent emulsification used to prepare SLNs having particle size of 30-100 nm average diameter. This technique avoids heat during prepartion.

5. Supercritical fluid method

This method involves preparing of SLNs by particles from gas saturated solutions (PGSS).

6. Microemulsion based method

Microemulsion method involves dilution of microemulsions which consists of inner and outer phase which is made by stirring an optically transparent mixture at 65-70°C, an emulsifier, water and a low melting fatty acid. While stirring the hot microemulsion is dispersed in cold water at 2- 3°C. SLN dispersion are used as granulation fluid for making of solid products like tablets and pellets. Lipid crystallization and aggregation is prevented using higher temperatures.

7. Spray drying method

Spray drying is an alternative technique to lyophilization process that involves use of lipid which have melting point more than 70°C. SLN having concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture provided best results for this techniques.

8. Double emulsion method

In double emulsion method stabilizer prevents partitioning of drug in external phase during solvent evaporation for encapsulated drug.

9. Precipitation method

In precipitation method organic solvent like chloroform is use to dissolve glyceride and then the solution is emulsified in aqueous phase. When the organic solvent evaporates, the lipid precipitates and form nanoparticles.

10. Film-ultrasound dispersion

In this method drug and lipid are introduced into suitable organic solution and then subjected to decompression, rotation and evaporation. when lipid film is formed, aqueous solution

containing emulsion is added. Sonicated to form SLN with little and uniform sized particles.

List of drugs incorporated in SLN's

I. Anticancer Drugs:- Doxorubicin, Methotrexate.
II. Cardiovascular Drugs:- Verapamil, Nifedipine.
III. Vitamins:- Vitamin-A,Retinol.
IV. NSAIDS:- Ibuprofen,Diclofenac.
V. Antifungal Drugs:- Ketoconazole,Itraconazole.
VI. Antibacterial Drugs:- Ciprofloxacin,Clotrimazole.
VII. Antitubercular drugs:- Rifampicin, Isoniazid.
VIII. Antiviral drugs:- Aciclovir, Saquinavir.
IX. Anxiety and Epilepsy:- Diazepam, Oxazepam, Carbamazepine
X. Immunosupressants drugs:- Cyclosporin.
XI. Miscellaneous glaucoma drugs:- Lovastatin,Simvastatin

Administration routes of SLN's[2]

Parenteral administration

It is not possible to deliver peptide and proteins drugs orally due to enzymatic degradation in GIT so, they are given parenterally to avoid the side effects of drug incorporated and also increases its bioavailability. Parentral route is suitable for drug targeting.

Oral administration

SLNs in cas of encapsulated drugs improve their intestinal degradation by increasing their uptake and transport through intestinal mucosa.

Rectal administration

Rectal route is preferred for rapid pharmacological effect. It can be used for pediatric patients due to its easy application.

Nasal administration

SLNs prevents the degradation of the fast and rapidly absorbed drugs in the GIT and improves their transport across epithelial cell layers.

Respiratory delivery

SLNs improve bioavailability of anti-asthmatic drugs, anti-tubercular drugs and anti- cancer drugs and reduce the dose frequency for better pulmonary action of these drugs.

Ocular administration

Ocular targeting is possible with SLNs because they are biocompatible and have muco-adhesive properties which improve their interaction with ocular mucosa and thereby prolongs drugs corneal residence time.

Topical administration

SLN used topically are well suited on skin and show desirable effects on it. They can also be used for damaged or inflammed skin as they are non toxic and non irritant.

Storage stability of SLN's[1]

SLNs physical properties during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity. Temperature and light appear to be primarily important for long - term stability. The zeta potential must be higher than -60mV for a dispersion to remain physically stable.

4°C - Most favorable storage temperature for SLNs. 20°C -SLN aggregation or loss of drug was not observed. 50°C - At this temperature particle size grow rapidly.

In vitro and ex vivo methods for the assessment of drug release from SLN's.[1]

Methods used to study the in vitro drug release are include:- Dialysis tubing.

Solid lipid nanoparticle dispersion is made and are placed in pre - washed dialysis tubing which hermetically sealed. The process of dialyses is carried using a suitable dissolution medium maintained at room temperature. The samples are then withdrawn from the dissolution medium at suitable intervals and the samples taken are centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

Number of small dialysis sacs containing 1 mL of SLN dispersion are displaced into the dissolution medium.

Ex vivo model for determining permeability across the gut

SLN's of enalaprilat is passed across rat jejunum which is 20 – 30 cm distal from the 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 excised from animals sacrifised for study.

Analytical characterization of SLN's[2]

Measurement of particle size and zeta potential

Laser diffraction (LD) and Photon correlation spectroscopy (PCS) are used for measuring of particle size. PCS is also known as dynamic light scattering which is used to measure fluctuation in intensity of scattered light caused by movement of particle and also focuses on size range from a few nanometers to about 3 microns. PCS is used for nanoparticle characterization, but it cannot detect large microparticles. Electron Microscopy gives information about particle shape.SLN dispersed have physical stability more than 12 months and its prediction is done by zeta potential.

Dynamic light scattering (DLS)

DLS measures variation in intensity of the scattered light on micro second time scale it is also called PCS.

Static light scattering (SLS)/fraunhofer diffraction

In a slution of particles SLS method is used to collect light scattered. Acoustic methods.

This method measures attenuation sound waves scattered determining its size by proper equations.

Nuclear magnetic resonance (NMR)

NMR is used to measure size and qualitative nature of nanoparticles. Electron microscopy.

Physical characterization of nanoparticles used for morphological examination can be determined by Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) direct. TEM can measure only smaller sizes.

Atomic force microscopy (AFM)

A topological map based on forces between tip and surface is produced by placing the probe tip with atomic scale across the sample.

Powder X - ray diffraction and differential scanning calorimetry (DSC)

X-ray diffratction is used in crystal planes to study their geometric scattering of radiation. DSC can be used to determine the crystallinity and nature of nanoparticles by measurement of glass transition temperature and melting points.

Sterilization of SLN's

SLNs sterility is maintained by using autoclave for intravenous and ocular formulations.

Autoclaving causes hot micro emulsion o/w type to form and even alter the size of the hot nanoparticles. When thry cools slows they reform SLNs. During this process few nanodroplets coalesce and produce bigger SLN than the original ones.SLN are washed properly before sterilization and the amount of surfactant and co-surfactant added is maintained as required so that the nano-droplets formed are well stabilized.

Measurement of crystallinity and lipid modifications in SLN's

Drug incorporation rates are in order as follows: Super cooled melt < α-modification < β9-modification < β-modification. Presence of emulsifiers and small size of the particles, lipid crystallization is highly affected.Differential scanning calorimetry (DSC) and X- ray scattering determines lipid content while for lipid properties Infrared and Raman spectroscopy are used.

Applications of SLN's

SLN in cancer chemotherapy[12]

Chemotherapeutic agents encapsulated in SLNs have improved in-vitro and in-vivo efficacy, reduce side effects, enhanced drug efficacy, improved pharmacokinetics and stability. This made chemotherapeutic agents less toxic and suitable for delivery. Example of this is Tamoxifen an anticancer drug used to treat breast cancer is incorporated in SLN has prolonged drug release after IV administration.

SLNs for targeted drug delivery in brain[12]

SLNs improves the ability of the drug to penetrate through the blood-brain barrier and is used as a targeted delivery to cure diseases related to central nervous system.

SLNs for parasitic diseases[7]

Malaria, leishmaniasis, tryanosomiasis are some of the parasitic diseases are one of the major problems. SLNs incorporated antimalerials used to treat these diseases have better stability profile, ease of commercialization and cost efficacy.

SLNs for malaria treatment[9]

For treatment and prophylaxis of malaria nano carriers have wide attention as they have improved side effects related to drugs and also enhanced their poor bioavailability.

SLNs for lung diseases[7]

Nanoparticles being smaller in size have ability to change surface properties which can be

used for targeted delivery hence enhance the profile of drugs incorporated in SLNs.

SLN for new adjuvant vaccines

Adjuvants are used in vaccination to enhance the immune response.

OBSERVATIONS AND REMARKS

Drugs and Diseases	Materials	Method used	Inference
1. Simvastatin- Hypercholesterolemia, dyslipidemia and coronary heart disease.	Glyceryl behenate, Glyceryl palmitostearate, Glyceryl monostearate, PEG, Glyceride, Dynasan 114, Dynasan 116, Pluronic F68, Polysorbate 80.	Hot melt emulsification method	Simvastatin is drug with poor oral bioavailability of 5%. Simvastatin. S LN prepared by hot emulsification method improved oral bioavailability up to 3. 7 folds. Optimization was based on drug loading and concentration of lipid and surfactant.
2. Ciprofloxacin hydrochloride- Ocular infections such as conjunctivitis, bacterial keratitis and keratoconjunctivitis	Monecol PC, Softemul 165, Dynasan, Imwitor 900, Distilled and deionized (DDI), Acetone.	Solvent diffusion method	SLN of ciprofloxacin HCl were prepared by solvent diffusion method have improved particle size and longterm physical stability by controlling stirring time and stirring speed.
3. ***Ketoconazole***- Fungal infections	Ketoconazole, Dynasan 118, Soy phosphatidylcholine 95%, Carbopol 934, xanthan gum	Hot homogenization method	SLNs of Ketoconazole were prepared for topical application by hot homogenization have improved therapeutic activity by controlling characteristics like shape, surface morphology, particle size, drug entrapment.
4. Nimesulide- NSAID	Nimesulide, Compritol 888, behenic acid, Miglyol 812, Soy phosphatidylcholine 95%, Taurocholic acid sodium salt.	Precipitation technique	SLNs to improve anti tumour activity of nimesulide was prepared by precipitation method.

CONCLUSION

Solid lipid nanoparticles as compared to other colloidal drug carriers are more convinient as they include better composition, effective production process, the use of organic solvents is avoided and the carriers are produced with higher encapsulation efficiency. Besides the advantages production processes like Homogenization, Hot melt extrusion, Solvent evaporation, etc used to modify characteristics like poor bioavailability, controls particle size, increases stability, improves drug loading capacity. Also topical application of drug like ketoconazole was improved by incorporation of drug as solid lipid nanoparticles with increase in its therapeutic activity.

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