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Solid Lipid Nanoparticles: An Over Review

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ABSTRACT

Beginning of 1990's, Solid lipid nanoparticles were introduced as an alternative to polymeric nanoparticles, liposomes, emulsions. This paper reveals the production methods for SLN, drug incorporation, loading capacity, drug release, various surfactants, lipids and various route of administration potentiality. SLN dosage form establishing the usage of solid lipid matrix materials as a lipid pellets for oral drug delivery systems. Rheological measurement revealed the increase in storage modulus and critical stress during storage at all temperatures. By using membrane contactor method the lipid phase is pressed, at a temperature above the melting point of the lipid through the membrane pores allowing the formation of small droplets. The structures of SLN based on glyceryl behenate and medium chain triglycerides were characterized by photon correlation spectroscopy (PCS) and laser diffraction (LD), field-flow fractionation (FFF) with multi-angle light scattering detection (MALS), and cryo transmission electron microscopy (cryo TEM).

Key words: Solid lipid nanoparticles, Controlled release, Particle size, Bio availability.

INTRODUCTION

In the recent years nano-drug carriers such as oil in water micro emulsions, liposome's microparticles widely applied in bio medicine.

How nanoparticles came into existence?

Development of new drugs alone is not sufficient to meet the demands of drug therapy, because positive data is obtained in *invitro* methods and negative results are obtained in vivo methods, because of the following reasons:-

- Insufficient drug concentration due to poor absorption, rapid metabolism and elimination.
- solubility of the drug
- After oral administration of the dosage form, high fluctuations of plasma levels observed due to unpredictable bioavailability

To overcome these problems, it involves suitable drug carrier systems, because in vivo fate of the drug depends on the carrier, which should permits controlled and localized release of the active drug according to the specific needs of the therapy. Localized drug release is the development of biodegradable implants for the treatment of the gliomas, which ensures very high drug concentration in brain compared to other parts of the body. Implants and micro particles are too large for drug targeting and i.v. administration, so colloidal carriers are used in recent days for target drug delivery systems (Sipos *et al.*, 1997).

As the investigations revealed, nanoparticles, nanoemulsions, liposomes, nanosuspensions etc came into existence. Considering the above systems, we can include that Drug loading capacity, Possibility of drug targeting ,In vivo fate of the carrier ,Acute and chronic toxicity, Scaling of production . In this way nano particles came into existence.

DEFINITION

Nanoparticles used for the purpose of drug delivery, these are defined as submicron (< 1µm) colloidal particles which includes monolithic nanoparticles in which the drug is adsorbed, dissolved, or dispersed throughout the matrix.

OR

Nano particles are defined as the microscopic particle whose size is measured in nanometers.

Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids. In the body, the drug loaded in nanoparticles is usually released from the

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matrix by diffusion, swelling, erosion, or degradation

ADVANTAGES

The following are among the important technological advantages of nanoparticles as drug carriers:

1. High stability (i.e., long shelf life)
2. High carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix)
3. Feasibility of incorporation of both hydrophilic and hydrophobic substances;
4. Feasibility of variable routes of administration, including oral administration and inhalation and also be designed to enable controlled (sustained) drug release from the matrix.
5. No biotoxicity of the carrier

Advantages of SLN also include the composition, the rapid and effective production, and the avoidance of organic solvents and possibility of high concentrated lipids suspensions.

A certain advantage of polymer systems is the wealth of possible chemical modification, including the synthesis of block and comb polymers. A problem associated with the usage of polymer is cytotoxicity, because nanoparticles were made from derivatives of organic solvent residues.

Drug release, in vivo stability and biodistribution are determined by size, surface charge, and surface hydrophobicity, membrane fluidity. Nanosuspensions are the colloidal particles which are composed of the drug and the emulsifier only. Possible production procedures include ball milling or high pressure homogenization. SLN dosage form establishing the usage of solid lipid matrix materials as a lipid pellets for oral drug delivery systems.

Nano emulsions were introduced during the 50s for the purpose of the parenteral nutrition, but now a days it is used as drug carriers for lipophilic drugs and several formulations e.g. diazepam as (diazepam-lipuro). The haemolytic activity of sodium oleate is decreased in lipid emulsions because the lytic agent is restricted at the interface and in the lipophilic core. The possibility of controlled drug release from nano emulsion is limited to small size and liquid state of the carrier. It has been estimated, that retarded drug release requires very lipophilic drugs, the octanal/water partition coefficient should be larger than 1000000:1.

Higher concentrations of the emulsifier result in the reduction of the particle size and also increases risk of toxic side effects. Most of the solid lipid nanoparticles dispersions are produced by high pressure homogenizations, characterized by an avg. particle size below 500nm and low micro particle content. SLN dosage form establishing the usage of solid lipid matrix materials as a lipid pellets for oral drug delivery systems (Mehnert *et al.*, 2001).

(Muller *et al.*, 1996; Al Khouri-Fallouh *et al.*, 1986).

DISADVANTAGES

1. Low drug loading capacities.
2. The presence of alternative colloidal structures.
3. Complexicity of the physical state of the lipid, results in stability and storage problems.

General Key Ingredients: Physiological lipids are decreases the acute and chronic toxicity such as triglycerides (eg.tristearin), partial glycerides (eg. Imwitor), fatty acids (eg. Stearic acid), steroids (eg. Cholesterol), waxes (eg. Cetyl palmitate), emulsifiers.

Solid lipid nanoparticles production

General ingredients include solid lipid, emulsifier and water. Lipid includes triglycerides (tri stearin), partial glycerides (imwitor), fatty acids (cholesterol) and waxes. All classes of emulsifiers used to stabilize the lipid dispersion. It has been found that combination of emulsifiers might prevent particle agglomeration more efficiently.

A clear advantage of SLN is the fact, that the lipid matrix is made from decreases the danger of acute and chronic toxicity. The choice of the emulsifier depends on the administration route and is more limited for parental administrations.

SLN PREPARATIONS METHODS

1) High Shear Homogenization and Ultrasound

High shear homogenization and ultrasound are dispersing techniques used for the production of SLN. Both methods are wide spread and easy to handle, but metal contamination occurs in ultra sound. In most cases avg. particle size range of 100-200nm were obtained in this method.

2) High Pressure Homogenization

High pressure homogenization has enlarged as a reliable technique for production of SLN. It is used for years in the production of nano emulsions for Nutrition. In HSH it pushes the liquid with high pressure (100-2000) through a narrow gap (microns). This fluid accelerates on a very short distance to a very high velocity (1000km/hr).

There are two methods involved in homogenization they are hot and cold homogenization.

Melting of the lipid and dissolving of the drug in the lipid.

Hot homogenization technique	**Cold homogenization technique**
1) Dispersing of the drug loaded lipid in a hot aqueous surfactant mixture 2) Pre mix using a stirrer to form a Coarse pre-emulsion 3) High pressure homogenization At a temperature above the Lipids melting point 4) Hot o\w nano emulsion	1) Solidification of the drug loaded lipid in liquid nitrogen or dry ice 2) Grinding in a powder mill (50-100µm) 3) Dispersing the powder in a aqueous surfactant dispersion medium. 4) High pressure homogenization at room temperature or below

Cold homogenization has been developed to overcome the following three problems of hot homogenization techniques:

1. Temperature induced drug degradation
2. Drug distribution into the aqueous phase during homogenization
3. Complexity of the crystallization step of the nano emulsion leading to several modifications.

3) SLN Prepared by Solvent Emulsification/Evaporation

Sjostrom and Berengenstahl described a production method to prepare nanoparticle dispersions by precipitation in o\w emulsions. The lipophilic material is dissolved in a water immiscible organic solvent (e.g.cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25nm with cholesterol acetate as model drug and by using a lecithin\sodium glycocholate blend as a emulsifier and these are conformed by Wesetesen. Wesetesen prepared nanoparticles of tripalmtin by dissolving the triglyceride in chloroform and the mean particle size obtained ranges from 30 to 100nm depending upon lecithin/co-surfactant blend. Particles with average diameters as small as 30nm were obtained by using bile salts as surfactants.

4) Micro Emulsion Based SLN Preparations

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of micro emulsions. They are made by stirring an optically transparent mixture at 65-70 ^{0} which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate) and water. The hot micro emulsion is dispersed in cold water (2-3 ^{0}c) under stirring. Typical volume ratios of the hot micro emulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the micro emulsion. Nano particles were produced only with the solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents.

5) SLN Preparation By Using Supercritical Fluid

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 the good choice as a solvent for this method.

6) SPRAY DRYING METHOD

Spray drying might be an alternative procedure to lyophyilization in order to transform an aqueous SLN dispersion into a dry product, but this method is scarcely used in SLN formulations although spray drying is cheaper than that of lyophylization. Spray drying might potentially cause aggregation due to high temperatures, shear forces and partial melting of the particles. Over all best result are obtained by using 1%solutions of 30% trehalose in water or 20%trehalose in ethanol-water mixtures (Mehnert *et al*., 2001).

Characterization of SLN Quality and Structure

An adequate characterization of the SLN is necessity for the control of the quality of the product, and it is a serious challenge due to the colloidal size of the particles and complexity of the system. Laggner stated about "lipids and fats, as soft condensed material in general, are very complex systems, which not only in their static structure but also with respect to their kinetics of super molecular formation."

Characterization of different parameters such as particle size, zeta potential, degree of crystallinity, lipid modification and additional colloidal structures.

Measurement of Particle Size and Zeta Potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the powerful techniques for routine measurements of particle size. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. The development of PIDS technology (Polarization Intensity Differential Scattering) greatly enhanced the sensitivity of LD to smaller particles.

The coulter counter method is rarely used to measure SLN particle size because of difficulties in the assessment in the assessment of small nanoparticles and the need of electrolytes which may destabilize colloidal dispersions.

In contrast to these Electron Microscopy provides direct information on the particle shape, but the investigator should be very careful to possible artifacts which may be caused by sample preparation.

The structures of SLN based on glyceryl behenate and medium chain triglycerides were characterized by photon correlation spectroscopy (PCS) and laser diffraction (LD), field-flow fractionation (FFF) with multi-angle light scattering detection (MALS), and cryo transmission electron microscopy (cryo TEM).

Drug Incorporation and Drug Release

A large number of drugs with a great variety of lipophilicity and general structures have been studied with regard to their incorporation into SLN. E.g. Oxazepam, cortisone, valerate, etc

Drug incorporation results in strong changes of the SLN characteristics. (Particle size, zeta potential, lipid modification etc), it also implies localization of the drug in the matrix. The following should be kept in mind that particle size alone is not sufficient for the characterization of SLN, but the modification of the lipid characterized by the DSC, X-ray and NMR techniques are required. The selection of the sample deserves special attention in order to prove that observed result was not due to the other colloidal structures present in the sample (Mehnert *et al*., 2001).

In most cases of SLN, drug release is observed by burst release. An appropriate selection of the homogenization temperature permitted the modification of release profile. For e.g., both hot and cold homogenization produced SLN released tetracaine and etomidate immediately, in contrast to this, it was possible to retard release of predinisolone by the cold homogenization technique. Therefore, it was conformed that, an appropriate selection of the homogenization temperature permits the release profile.

The release kinetics depends on the release conditions. Every release technique has its own pros and cons due to separation, because it is not easy to compare the results. Experiments have to be done to elucidate the contribution of enzymes to drug release from SLN, because different polymers are not easily recognized by the enzymes present in the body.

Storage stability:

SLN and nano emulsions have remarkable aspects with respect to their composition and production methods, but storage stability SLN and nano emulsions are due to the presence of additional colloidal structures. Beside these additional features of SLN include super cooled melts, different modifications which contribute in determining the stability of the colloidal lipid suspension.

Gelation phenomena, increase in particle sizes and drug expulsion from the lipid carrier are the major problems storage stability. A super cooled melt, which is first product formed after hot homogenization represents a nano emulsion.

The transformation of the lipid melt to lipid crystals results in an increase of particle surface, a decrease of loading capacity of the lipid and therefore, it leads to increased stability.

Stability of the lipid dispersions decreases as stability of the lipid modification increases.

Toxicity Aspects

Toxicity aspects of the SLN include the toxicity of the emulsifiers due to their potency of toxicity on other carriers also. The absence of pyrogens must be checked before i.v. administration because pyrogens cause gelation of SLN. The most important key factor is particle size for i.v. injection because they block the capillary resulting in fate. So, diameter of SLN particles should be less than 9microns.Both the reasons which are stated above are serious hurdles for the development of SLN dispersions suitable for i.v. injection in clinical practice.

A luminal based chemiluminescence's is used to compare SLN with polymer particles to assess the influence of the SLN composition on the phagocytosis rate and it was found that phagocytosis rate of poloxamer stabilized compritol and cetylpalmitate SLN was lower in comparison to polystyrene nanoparticles. The result of toxicity studies indicated that SLN are less toxic than that of polymeric nanoparticles.

Administration Routes and *in vivo* Studies

In vivo fate of the SLN particles depend mainly on the following points:

- administration route
- Interactions of the SLN with the biological surroundings including: distribution process and enzymatic process.

SLN are composed of physiologically related lipids or waxes, so transportation and metabolism are present in the body may contribute to the in vivo fate of the carrier. The important enzyme in SLN degradation is lipases, which results in splitting of ester linkage and form partial glycerides and free fatty acids. Degradation depends on the length of the fatty acids i.e. longer the length of the fatty acids slower is the degradation (Mehnert *et al*., 2001; Venkateswarlu and Manjunath, 2004; Muller *et al*., 2000).

The effect of the surfactant on the degradation can accelerate it (cholic acid sodium salt) or to hinder it (poloxamer 407, 188) due to stearic stabilization. Other than this Tween 80 has been used and the results showed that the hindering effect on the degradation process was less pronounced than that of poloxamer 407. This result seems to be correlated to the no. of ethylene glycol chain in the molecule which suppresses the anchoring of the lipase enzyme. SLN preparations can be given through per oral administration, parenteral administration and trans-dermal applications (Davis, 1974).

CONCLUSION

SLN are giving the clear advantages include the composition and possibility of large scale production, avoiding organic solvents. Controlled release is achieved by SLN with various route of administration. Nowadays, several researchers succeed in the explaining in the SLN interaction with their biological fluids and cells. Understanding about the structure and dynamics of sln on a molecular level *invitro* and *invivo* correlation is the obstacle challenge in front of the pharmaceutical scientists.

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