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Solid Lipid Nanoparticles: An Effective Drug Delivery System- A Review

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ABSTRACT

SLN's are colloidal carriers developed in the 1990s as an alternative system to the existing traditional carriers (emulsions, liposomes, and polymeric nanoparticles)[1]. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for various applications as they have been proposed as an alternative particulate carrier system. The SLN_S are submicron colloidal carriers (50-1000 nm) which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution[2].SLNs are particles consisting of a matrix made from solid lipids. In aqueous dispersion they are stabilised by surfactants or polymers. They consist of a solid matrix protecting incorporated active substances against chemical degradation and providing high flexibility to modify release profiles. The SLN combine the advantages (e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability, and scalability to large-scale preparations, excellent biocompatibility) of other traditional colloidal systems[3].

Keywords: Solid lipid nanoparticles (SLNs), Stability, Administration routes, Controlled release, Colloidal drug carrier.

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INTRODUCTION:

Nanosized drug delivery systems have been developed to overcome one or several of the following problems;

I. Low or highly variables drug concentrations after per oral administration due to poor absorption, rapid metabolism and elimination.
II. Poor drug solubility which includes i.v injections of an aqueous drug solutions.
III. Drug distribution to other tissue combined with high toxicity (eg: cancer drugs).

Several systems, including micelles, liposomes, polymer nanoparticles, nanoemulsions, solid dispersion and nanocapsules 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 research groups focused on alternative nanoparticles made from solid lipids, the so called solid lipid nanoparticle.

Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research as well as in other fields. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers [7].

Aims of SLN's [6, 8]

- Possibility of controlled drug release and drug targeting.
- Increased drug stability.
- High drug payload.
- Incorporation of lipophilic and hydrophilic drugs feasible.
- No biotoxicity of the carrier because, most lipids are biodegradable.
- Avoidance of organic solvents.
- No problems with respect to large scale production and sterilization.
- More affordable (less expensive than polymeric/surfactant based carriers).

Advantages of SLN [2, 4, 9]

- Small size and relatively narrow size distribution which provide biological opportunities for site-specific drug delivery by SLNs.
- Controlled release of active drug over a long period can be achieved.

- Protection of incorporated drug against chemical degradation.
- Possible sterilization by autoclaving or gamma irradiation.
- SLNs can be lyophilised as well as spray dried.
- No toxic metabolites are produced.
- Avoidance of organic solvents.
- Relatively cheaper and stable.
- Ease of industrial scale production by the dispersion technique.
- Incorporation of drug can reduce distinct side effects of drug, e.g. Thrombophlebitis that is associated with i.v. injection of diazepam or etomidate.
- Surface modification can easily be accomplished and hence can be used for site-specific drug delivery system.
- Reduce the number of doses required.

SLN preparation

Ingredients:

SLNs are made up of solid lipid, emulsifier and water/solvent.

Lipids used may be – Triglycerides (e.g. tri-stearin), Glycerol monostearate (Imwitor), Fatty acids (e.g. stearic acid, palmitic acid), Steroids (e.g. cholesterol), Waxes (e.g. cetyl palmitate), Tripalmitin, Cacao butter, Monostearin, Lecithin, Tribehenate (Compritol 888 ATO), Trimyristin [Dynasan® 114]

Emulsifiers – Pluronics F 68, 127

The combination of emulsifiers might prevent particles agglomeration more efficiently.

Preparation techniques for SLNs

a. High pressure homogenization[10]

1. Hot homogenization
2. Cold homogenization

b. Microemulsion based SLN preparation[11,12]

c. Solvent emulsification-evaporation technique[13,14]

d. Solvent emulsification-diffusion technique[15]

e. Ultrasonication technique[16]

1. Probe ultrasonication
2. Bath ultrasonication

f. Melting dispersion method (Hot melt encapsulation method) [17]

g. Double emulsion technique[18]

h. Membrane contactor technique[19]

i. Supercritical fluid technology[7]

j. Spray drying method[20]

a. High pressure homogenization

HPH is suitable method for preparation of SLN, NLC, and LDC and can be performed at elevated temperature (hot HPH technique) or at or below room temperature (cold HPH technique). The particle size is decreased by cavitations and turbulences.

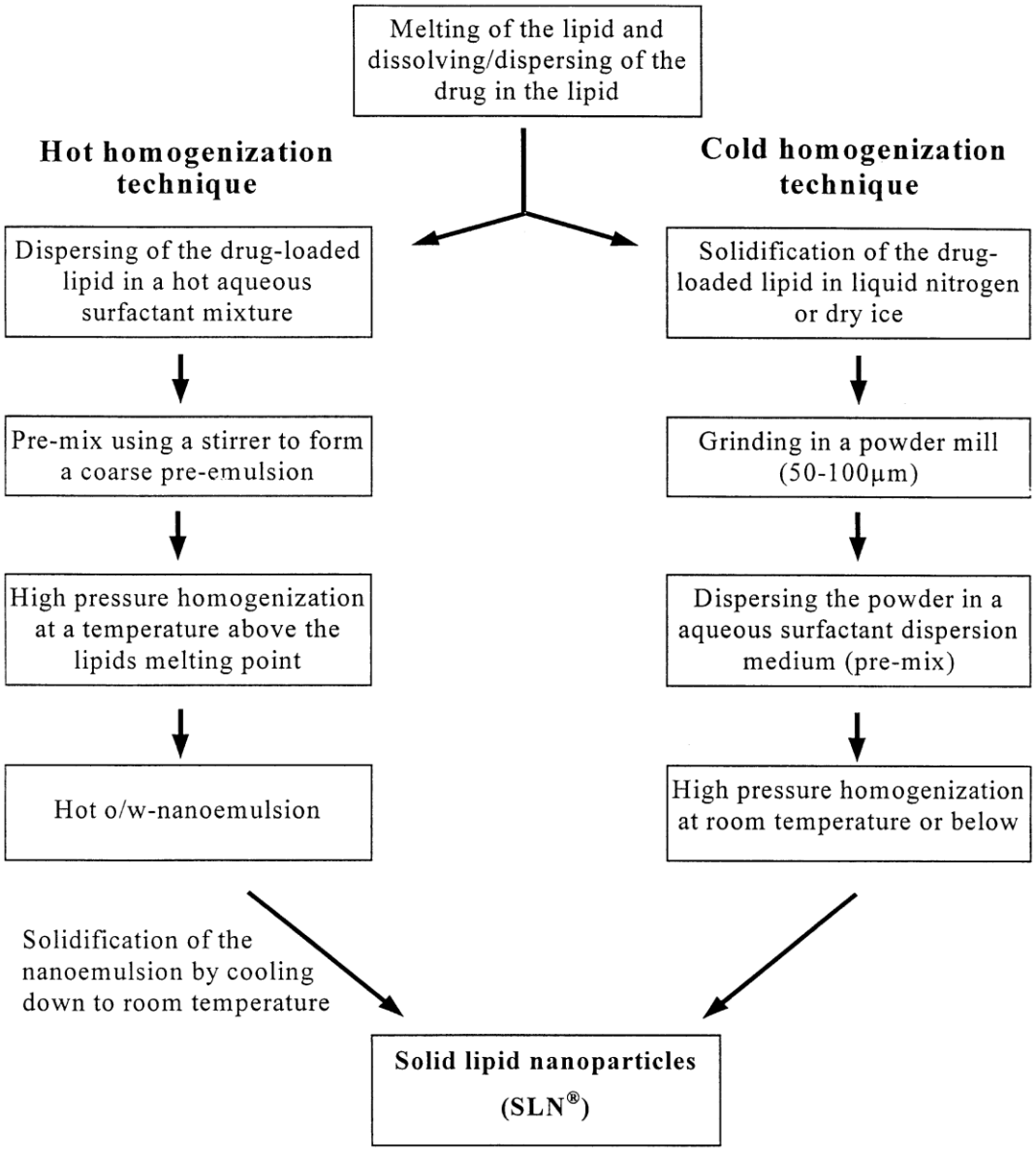

Figure. 1: Schematic procedure of hot and cold homogenization techniques for SLN production.

In high pressure homogenization technique lipids are pushed with high pressure (100-200 bars) through a narrow gap of few micron ranges. So shear stress and cavitation (due to sudden decrease in pressure) are the forces which cause the disruption of particle to submicron range. Normally the lipid contents are in the range of 5-10%. At this concentration it does not cause any problem to homogenizer. High pressure homogenization does not show any scaling up problem.

Basically, there are two approaches for SLN production by high pressure homogenization, hot and cold homogenization techniques. Figure 1 represents the schematic diagram for the preparation techniques for the hot and cold homogenization.

1. Hot homogenization

For the hot homogenization technique the drug loaded melted lipid is dispersed under stirring by high shear device (e.g. Ultra Turrax) in the aqueous surfactant solution of identical temperature. The pre-emulsion obtained is homogenized by using a piston gap homogenizer (e.g. Macron LAB 40 or Macron LAB 60 or APV-2000) and the produced hot o/w nanoemulsion is cooled down to room temperature. At room temperature the lipid recrystallizes and leads to formation of SLNs.

2. Cold homogenization

Cold homogenization is carried out with the solid lipid containing drug and therefore called as milling of a suspension. Cold homogenization has been developed to prevent: Temperature induced drug degradation, Partitioning of hydrophilic drug from lipid phase to aqueous phase. Complexity of the crystallization step of the nanoemulsion leading to several Modifications and/or super cooled melts. The first step of preparation is same as hot homogenization which includes dispersion or dissolving or solubilisation of the drug in the melted lipid. Then the drug lipid mixture is rapidly cooled either by means of liquid nitrogen or dry ice. The drug containing solid lipid is milled by means of mortar or ball mill to micron size (50-100 micron) and these microparticles are dispersed in chilled emulsifier solution yielding a pre-suspension. Then this pre-suspension is subjected to high pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLNs.

This process avoids or minimizes the melting of lipid and therefore minimizing loss of hydrophilic drug to aqueous phase. Another method to minimize the loss of hydrophilic drug to aqueous phase is to replace water with other media (e.g. oil or PEG 600) with low solubility for the drug. In comparison to hot homogenization, in cold homogenization particle size and polydispersity index (broader size distribution) are more. The cold homogenization only

minimizes the thermal exposure of drug, but it does not do so completely due to melting of the lipid/drug mixture in the first step of preparation.

b. Microemulsion based SLN preparation

Gasco and other scientists had developed and optimised a suitable method for the preparation of SLN via microemulsion. Microemulsion was an optically transparent mixture at 65-70 ^{o}c or a slightly bluish solution, which is typically composed of a low melting lipid, an emulsifier(s), co-emulsifier(s) and water. When the hot microemulsion is dispersed in cold water (2-3^{o}c) under constant stirring, precipitation of the lipid phase takes place, forming fine particles smaller than 300nm. A typical volume ratio of the hot microemulsion 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 microemulsions, the temperature gradient and pH value fix the product quality in addition to the composition of the microemulsion. High temperature gradients facilitate rapid lipid crystallisation and prevent aggregation.

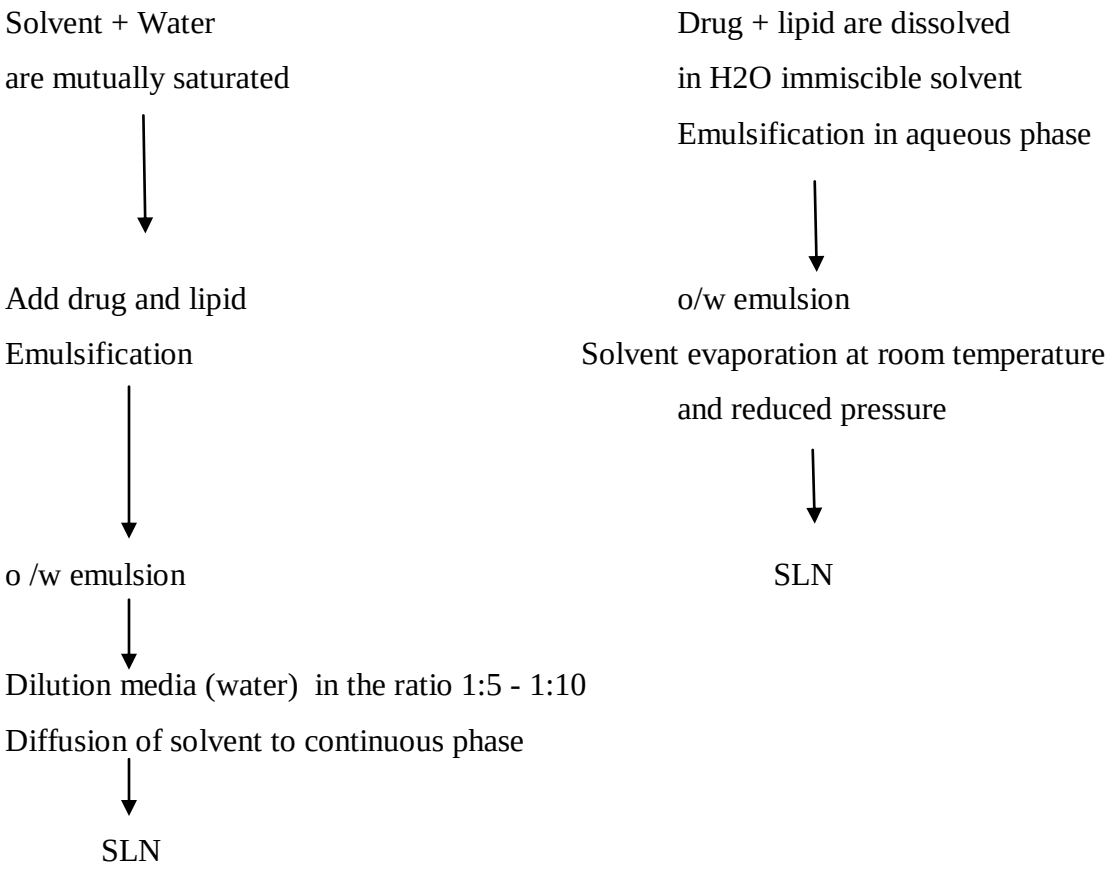

Figure 2: Schematic diagram of (a) Solvent emulsification-diffusion technique (b) Solvent emulsification-evaporation technique

c. Solvent emulsification-evaporation technique

In solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug was dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then that is emulsified in an aqueous phase using high speed homogenizer. To improve the efficiency of fine emulsification, coarse emulsion was passed through the microfluidizer. Thereafter, the organic solvents were evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates of SLNs as indicated in Figure 2. Here the mean particle size depends on the concentration of lipid in organic phase. Very small particle size could be obtained with low lipid load (5%) related to organic solvent. The great advantage of this technique is the avoidance of any thermal stress, which makes it suitable for the incorporation of highly thermolabile drugs. A clear disadvantage is the use of organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent.

d. Solvent emulsification-diffusion technique

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid. Then, the lipid is dissolved in the water-saturated solvent and subsequently emulsified with solvent-saturated aqueous surfactant solution at elevated temperatures. The SLN precipitate after addition of excess water (typical ratio 1:5 – 1:10) due to diffusion of the organic solvent from the emulsion droplets to the continuous phase.

e. Ultrasonication technique or High shear homogenization

SLN were developed by high speed stirring or sonication. The major advantages are that, equipment whatever used here is very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer size. This leads to physical instabilities likes particle growth upon aging. Potential metal contamination due to ultrasonication is also a big problem in this method. So, for making a stable formulation, studies have been performed by various research groups combining high speed stirring and ultrasonication at high temperature. This can be achieved by using less than 1% lipid concentration and high surfactant concentration.

f. Melting dispersion method (Hot melt encapsulation method)

The melting dispersion method is as follows, in first step, drug and solid lipid were melted in an organic solvent regarded as oil phase and simultaneously water phase also heated to same temperature as oil phase. Then in second step, the oil phase added into a small volume of water phase and the resulting emulsion was stirred at higher rpm for few hrs. At last it was cooled down to room temperature to give SLNs. The last step was same as solvent emulsification evaporation method except in melting dispersion method no organic solvent had to be evaporated. Reproducibility was less than that of solvent emulsification-evaporation method but more than ultrasonication method.

g. Double emulsion technique

For the preparation of hydrophilic loaded SLN, a novel method based on solvent emulsification-evaporation has been used. Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. This method is particularly used for achieving high incorporation of hydrophilic molecule.

h. Membrane contactor technique

It is a novel technique to prepare the SLN. In membrane contactor technique the liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores (kerasep ceramic membrane with an active ZrO_2 layer on an AlO_2-TiO_2 support) allowing the formation of small droplets as indicated in Figure 3. The aqueous phase was stirred continuously and circulated tangentially inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLNs were formed by the cooling of the preparation at the room temperature. Here both the phases were placed in the thermo stated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase.

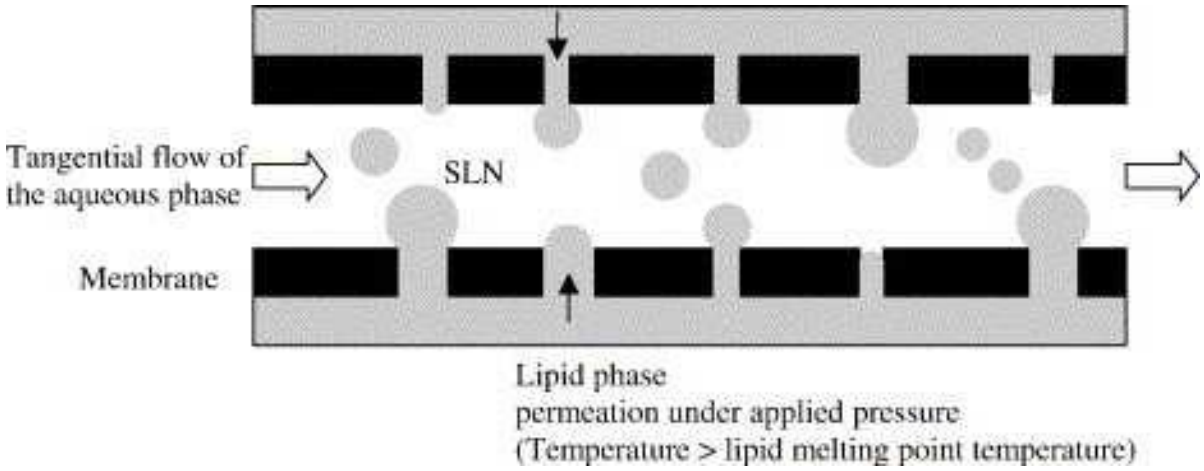

Figure 3: Schematic drawing of the membrane contactor for the SLN preparation

i. Supercritical fluid technology

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.

j. Spray drying method

It's an alternative procedure to Lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than Lyophilization. This method cause particle aggregation due to high temperature, shear forces and partial melting of the particle. Freitas and Mullera recommends the use of lipid with melting point >70 ^{o}C for spray drying. 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 SLN:

An adequate characterization of the solid lipid nanodispersion is a necessity for the control of the quality of the product. The characterization methods should be sensitive to the key parameters of SLN performance and should avoid artefacts. However, characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity of the system, which includes also dynamic phenomena.

Most important parameters which need to be studied for SLNs are-

1. Particle size.
2. Size distribution kinetics (Zeta potential).
3. Degree of crystallinity and lipid modification (polymorphism).
4. Coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles).
5. Drug content and drug release.
6. Stability

1. Particle size.

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size[21]. The Coulter Counter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticles and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known

dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. The development of polarization intensity differential scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. However, despite this progress, it is highly recommended to use PCS and LD simultaneously. It should be kept in mind that both methods do not 'measure' particle size. Rather, they detect light scattering effects which are used to calculate particle size. For example, uncertainties may result from non–spherical particle shapes. Platelet structures commonly occur during lipid crystallization and have also been suggested in the SLN[22]. Further, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of microparticles (microparticles of unit form or microparticles consisting of aggregates of smaller particles). Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artefacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape.

2. Size distribution kinetics (Zeta potential).

Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter[21].The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion[23]. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. However, this rule cannot strictly be applied for systems which contain steric stabilizers, because the adsorption of steric stabilizers will decrease the zeta potential due to the shift in the shear plane of the particle.

3. Degree of crystallinity and lipid modification (polymorphism).

Particle size analysis is a necessary, but not a sufficient step to characterize SLN quality. Special attention must be paid to the characterization of the degree of lipid crystallinity and the modification of the lipid, because these parameters are strongly correlated with drug incorporation and release rates. Due to the small size of the particle and the presence of emulsifiers, lipid crystallization and modification changes might be highly retarded. For example, it has been observed with Dynasan 112 SLN that if crystallization is not artificially induced, it may remain as a supercooled melt over several months and polymorphic transition occur very slowly. X-ray scattering and Differential scanning Calorimetry (DSC)[24] are widely used to investigate the status of the lipid. DSC uses the fact that different lipid modifications possess different melting points and melting enthalpies. By means of X-ray scattering it is possible to assess the length of the long and short spacing of the lipid lattice. It is highly recommended to measure the SLN dispersion themselves because solvent removal will lead to modification changes. Sensitivity and long measurement times of conventional X-ray sources might be overcome by synchrotron irradiation. However, this source has limited accessibility for most investigators. Infrared and Raman spectroscopy are useful tools to investigate structural properties of lipids. However, their potential to characterize SLN dispersions remains to be investigated.

4. **Coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles).**

The magnetic resonance techniques, ESR and NMR[25] are powerful tools to investigate dynamic phenomena and the characteristics of nanocompartments in colloidal lipid dispersions to detect presence of other colloidal species micelles, liposome, supercooled, melts, drug nanoparticles.

5. **Drug content and drug release**

A very important point to judge the suitability of a drug carrier system is its loading capacity. The loading capacity is generally expressed in percent related to the lipid phase (matrix lipid + drug). Drugs loading capacities vary from typically 1% to 5% [26] for hydrophilic drugs, for liphophilic drug loading capacity between 10%-30% was re[ported. For tetracaine and intimidate capacities of 10-20% for Ubidecarenone loading capacities of up to 50% was reported. For coenzyme Q_{10} it was 20% and 20% [27]-25% drug loading found for cyclosporine[28].

Factors determining the loading capacity of drug in the lipid are, for example:

- Solubility of drug in melted lipid.
- Miscibility of drug melt and lipid melt.
- Chemical and physical structure of solid lipid matrix.

- Polymorphic state of lipid material.

The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice (e.g. monoacid triglycerides) lead to drug expulsion, while more complex lipids being mixtures of mono-, di- and triglycerides and also containing fatty acids of different chain length from less perfect with many imperfections offering space to accommodate the drugs, However, the transition to highly ordered lipid particles is also the reason for drug expulsion[24].

6. Stability [24,29]

SLN and nanoemulsions have remarkable similarities with respect to their composition and production methods. However, SLN cannot simply be regarded as colloidal structures (micelles, mixed micelles, liposomes), it has additional features (super cooled melts, different modifications, and non-spherical shapes) which contribute to or determine the stability of the colloidal lipid suspension. Gelation phenomena, increase in particle sizes and drug expulsion from the lipid carrier are the major problems of storage stability. As described above, there is a close relation between the modifications of the lipid, gelation, particle aggregation and drug expulsion. A supercooled melt, which is the first product formed after hot homogenization, represents a nanoemulsions. It is characterised by spherical lipid droplets and a high incorporation rate for guest molecules (e.g. drugs). The transformation of the lipid melt to lipid crystals results in an increase of particle surfaces, a decrease of the loading capacity of the lipid and therefore, it leads to increased stability problems. Stability of the lipid dispersions decreases as stability of the lipid modification increases.

ADMIMISTRATION ROUTES OF SLNs & THEIR BIODISTRIBUTION[2,30-32]:

The In-vivo fate of the solid lipid nanoparticles will depend mainly on the administration route and distribution process (adsorption of biological material on the particle surface and desorption of SLN components into the biological surrounding).

- **Peroral administration:**

The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimise erratic absorption. Absorption of nanoparticles occur through mucosa of the intestine by several mechanisms, namely through Payer's patches, by intracellular uptake or by the paracellular pathway[30].Peroral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dosage forms, e.g. tablets, pellets or capsules. The microclimate of the stomach favours particle aggregation due to the acidity and high ionic strength[31]. Oral

administration of SLN is possible as aqueous dispersion or alternatively after transform into a traditional dosage form, i.e. tablets, pellets, capsules or powders in sachets. For the production of tablets the aqueous SLN dispersion can be used instead of a granulation liquid in the granulation process. Alternatively SLN can be transferred to a powder (e.g. by spray-drying) and added to the tabletting powder mixture. For the production of pellets the SLN dispersion can be used as wetting agent in the extrusion process[32].

- **Parenteral administration:**

Peptide and protein drugs are usually available for parenteral use in the market. Their conventional oral administration is not possible due to enzymatic degradation in GI tract. Repeated parenteral administration is necessary since their half-lives are too short (a few minutes). To solve the problems, improve patient compliances and provide an effective treatment, researchers have studies non-parenteral administration routes such as transdermal and nasal for years. As an alternative, the development of parenteral drug carriers, which will provide controlled drug release over a month or longer, has been attempted. SLN are promising colloidal drug carriers among many other carriers such as their polymeric counterparts and liposomes. Wissing et al (2004) intensively reviewed parenteral use of SLN. SLN are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilisation and/or sterilization.

SLN have been administered intravenously to animals. Pharmacokinetic studies of doxorubicin incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats. Concerning the body distribution, SLN were found to cause higher drug concentrations in lung, spleen and brain, while the solution led to a distribution more into liver and kidneys[33].

- **Rectal administration:**

When rapid pharmacological effect is required, in some circumstances, parenteral or rectal administration if preferred. Conventional rectal delivery of drugs is also very often used for paediatric patients all over the world due to easy application. In the meantime, plasma levels and therapeutic efficacy of rectally administered drugs were reported to bee higher compared with those given orally or intramuscularly in the same dose. Diazepam have been incorporated in SLN for rectal administration and applied on rabbits in order to provide rapid action[34]**.**

- **Nasal administration:**

Nasal administration was a promising alternative non-invasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as

peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers[35]. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. Additionally, hydrophilic coating of SLN will permit the interaction and transport of SLN through the nasal mucosa and therefore bring great benefits and compliance as nasal drug carriers especially for vaccines.

- **Respiratory delivery:**

The lungs offer a high surface area for drug absorption by avoiding first-pass effects. Rapid drug absorption by aerosolization of drugs (in the 1-3micrometer size range) occurs since the walls of alveoli in the deep lung are extremely thin[36]. The nebulisation of SLN is a new and upcoming area of research. Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN can be proposed as carriers of anticancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of SLN ranged from 1.1-2.1 micrometers and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. Nebulization of SLN carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis.

- **Ocular administration:**

Colloidal drug delivery systems are considered to enhance the ocular bioavailability of drugs[37]. Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Studies were carried out on rabbits eye by incorporating tobramycin in SLN, drug concentration in the aqueous humor was determined up to 6 hours and found to be significantly enhanced drug bioavailability in the aqueous humor.

- **Topical application:**

SLN and NLC are very attractive colloidal carrier system for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids. Researchers have reported intensively on the topical application of SLN. During the last few years, SLN have been studied with active compounds such as vitamin E. tocopherol

acetate, retinol, ascorbyl palmitate, clotrimazole, triptolide, phodophyllotoxin and nonsteroidal antiandrogen RU 58841 for topical application[30].

Applications of SLNs:

There are several potential applications of SLNs some of which are given below:

- **SLNs used topically:**

SLNs have been used for topical application for various drugs such as Tropolide, vitamin A, isotretinoin, ketoconazole, etc

- **SLNs as gene vector carrier[38]:**

SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA and other nucleic acids.

- **SLNs in cosmetics:**

Solid lipid nanoparticles (SLN) are novel delivery systems for pharmaceutical and cosmetic active ingredients.SLN possesses some features which make them promising carriers for cosmetic applications[39]:

- The protection of labile compounds against chemical degradation has been shown, e.g. for retinol and tocopherol.
- Depending on the produced SLN-type, controlled release of the active ingredients is possible. SLN with a drug-enriched shell show burst release characteristics whereas SLN with a drug-enriched core lead to sustained release.
- SLN act as occlusive, i.e. they can be used in order to increase the water content of the skin.
- SLN show a UV-blocking potential, i.e. they act as physical sunscreens on their own and can be combined with molecular sunscreens in order to achieve improved photoprotection.

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The in vivo study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream. SLN and NLCs have proved to be controlled release innovative occlusive topical.

- **SLNs can be used as a carrier for anticancer drug to solid tumours:**

SLNs have been reported to be useful as drug carriers to treat neoplasms[40]. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast

cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.

- **SLNs in breast cancer and lymph node metastases [2]:**

Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs[41]. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.

- **Oral SLNs in antitubercular chemotherapy:**

Antitubercular drugs such as rifampicin, isoniazid, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance[42]. By using the emulsion solvent diffusion technique this anti tubercular drug loaded solid lipid nanoparticles are prepared. The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

- **Stealth nanoparticles[43, 44]:**

These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. Theoretically, such nanoparticles can target specific cells e.g. antibody 19 labelled stealth lipobodies have shown increased delivery to the target tissue in accessible sites.

CONCLUSION:

The major advantage of SLNs includes preparation by using lipids which simulates physiological lipids, large scale production and avoidance of organic solvents. SLNs are relatively young delivery systems and holds great promise for its systemic investigation and exploitation.

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