



AN OVERVIEW ON SOLID LIPID NANOPARTICLES AS A NOVEL DRUG DELIVERY SYSTEM IN SKIN SUN PROTECTION

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ABSTRACT

Lipid based carriers have attracted increasing scientific and commercial attention during the last few years as an alternative material for novel drug delivery of various drug molecules such as peptides and proteins concerned with stability issues such delivery systems are discussed and exemplified regarding both more traditional lipid based delivery systems such as liposomes and lipid emulsions as well as more novel structures, e.g., lipid microtubules, microbubbles, and solid lipid particulate systems.^[1]

Several local or systemic therapeutic applications may be foreseen, such as immunization with protein antigens, infectious diseases treatment, chronic diseases and cancer therapy.^[2] In this study, we focused on SLN applications as sunscreen topical products and its efficacy (its skin protection strength against UV radiation).

KEYWORDS: Solid lipid nanoparticles, Proteins, Peptides, sunscreen, novel drug delivery, novel drug delivery.

1. INTRODUCTION

Protection against UV radiation has become an increasingly important issue in human life. Since sunscreens are intended to act on the surface of skin, they should penetrate as little as possible into the viable epidermis, the dermis and into the systemic circulation.^[3] Also, the presence of sunscreens on top of the horny layer prevents phototoxic and photo allergic reactions which have been observed for various molecular UV-blockers.^[3]

The degree of penetration depends strongly on the physicochemical properties of the active compound and of the nature of the vehicle in which the into sunscreen is applied, e.g. polarity of the solvent, particle size, type of vehicle.^[3] Therefore, the development of suitable products which prevent penetration of the sunscreen into the skin is a challenge for manufacturers of cosmetic products.

Solid lipid nanoparticles (SLN) have been introduced as carriers for active cosmetic ingredients and pharmaceutical drugs.^[4,5] It has been shown that they act as active carriers for sunscreens due to their particulate character,^[6,7] i.e. they represent physical sunscreens on their own. Incorporation of molecular sunscreens into SLN has a synergistic effect on the protective characteristics.

A promising strategy to overcome drug delivery problems involves the development of suitable drug carrier systems. The in vivo fate of the drug is no longer mainly determined by the properties of the drug, but by the carrier system, which should permit a controlled and localized release of the active drug according to the specific needs of the therapy. The optimized size of the carrier depends on the desired route of administration and ranges from few nanometers (colloidal carriers), to the micrometer (microparticles) and to several millimeters (implants). For parenteral administration, it is highly desirable to use biodegradable materials, which avoid surgery to remove the implant after complete drug release and which make the administration of micro- and nanoparticles feasible.^[8]

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro and nanoparticles^[9] and Since the same time, attention from various research groups has focused on an alternative to polymeric nanoparticles, the solid lipid nanoparticles (SLN).^[10-40]

Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLNs are sub-micron colloidal

carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals.^[41-43] In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many – fold and include:

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.^[44]

Solid lipid nanoparticles (SLN) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. Due to their unique size dependent properties, lipid nanoparticles offer possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could use for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers.^[44]

Solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid micro particles (LM) and lipospheres have been sought as alternative carriers to optimized drug delivery for therapeutic peptides, proteins and antigens. The research was developed in this area confirms that under optimized conditions they can be produced to incorporate hydrophobic or hydrophilic

proteins and seem to fulfill the requirements for an optimum particulate carrier system.^[6] Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary. Formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as sustained release of the incorporated molecules. Important peptides such as cyclosporine A, insulin, calcitonin and somatostatin have been incorporated into solid lipid particles and are currently under investigation.^[2] Aspects of SLN stability and possibilities of SLN stabilization by lyophilization and spray drying are discussed globally. Special attention is paid to the relation between drug incorporation and the complexity of SLN dispersions, which includes the presence of alternative colloidal structures (liposomes, micelles, drug nanosuspensions, mixed micelles, liquid crystals) and the physical state of the lipid (supercooled melts, different lipid modifications). Appropriate analytical methods are needed for the characterization of SLN. The use of several analytical techniques is a necessity.^[8]

Lipid carriers owing to the biological origin of the carrier material offer a number of advantages making it an ideal drug delivery vehicle (Table 1). Controlled release devices based on lipids as natural materials and which are derived from body tissue constituents exhibit a high biocompatibility after administration.^[45-47] Lipophilic matrices are not as susceptible to erosion phenomena as polymeric systems.^[48] Another advantage of these systems is their Simple manufacture by compressing or molding. As mentioned in the abstract, the aim of this study is to review SLN applications as sunscreen topical products (containing drug molecules) and its efficacy (its skin protection strength against UV radiation).

Table 1- Overview and Comparison of Different Lipid Carriers.^[1]

No	Carriers	Size range	Composition	Features	Common preparation techniques
1	Liposomes	25 nm-few microns	Natural or synthetic phospholipids	Bilayer vesicles containing an aqueous volume entirely enclosed by a membranous lipid bilayer	Passive loading • Mechanical dispersion • Solvent dispersion • Detergent removal • Active loading
2	Solid lipid nanoparticles	50-1000 nm	High melting point fats of natural or synthetic origin	Submicron colloidal carriers containing solid hydrophobic core having a monolayer of phospholipid coating	• High-pressure Homogenization • Microemulsion formation • Precipitation • As lipid nanopellets
3	Oily suspensions	Globule size 10 nm-few microns	Natural or synthetic oils	Dispersions of peptides and proteins in oils of high viscosity for sustained release of proteins	Dispersion technique

4	Submicron lipid emulsions	lipid globules 1-100nm	Lipids, hydrophilic liquid, surfactants	Multicomponent fluid made of water, a hydrophobic liquid, and one or several surfactants resulting in a stable system	Emulsification technique • o/w • w/o • w/o/w • w/o/o
5	Lipid implants	Variable size according to application site	Natural or synthetic lipids	Drug dispersions in lipid or fat compressed modules	Lipid compression
6	Lipid microtubules/microcylinders	< 1µm	Natural or synthetic lipids with suitable surfactant	Self-organizing system in which surfactants crystallize into tightly packed bilayers that spontaneously form cylinders	Self-emulsification
7	Lipid microbubbles	few microns	Lipids, polymers, proteins, phospholipids	Gas-filled microspheres stabilized by phospholipids, Polymers or proteins with low density and high elasticity of these bubbles	Sonication
8	Lipid microspheres (Lipospheres)	0.2-100 µm	High melting lipid, phospholipids	Water dispersible solid microparticles composed of a solid hydrophobic fat core stabilized by a monolayer of phospholipid molecules embedded in a microparticle surface	Passive loading • Melt method • Multiple microemulsion • Solvent method • Preincorporation into lipophilic carriers

Aims of solid lipid nanoparticles. It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers.^[16] Proposed advantages include:

- Possibility of controlled drug release and drug targeting.^[42] [43, 49-51]
- Increased drug stability^[52] and Chemical protection of labile incorporated compounds
- High drug payload^[42]
- Incorporation of lipophilic and hydrophilic drugs feasible
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization
- Application versatility.^[44]
- Can be subjected to commercial sterilization procedures.^[44] (Easy to scale up and sterilize)

- Conventional emulsion manufacturing methods applicable
- Much easier to manufacture than biopolymeric nanoparticles

2. COMPOSITION, STRUCTURE AND SPECIFICATIONS OF SLNS

The typical ingredients of SLN consist of solid lipid(s), surfactant(s) (plus co-surfactants if required), and incorporated active ingredients. To date, the lipids applied in the preparation of SLN include the following categories based on their structural diversity: fatty acids with different lengths of hydrocarbon chain; fatty esters; fatty alcohol; glycerides with different structures; and mixtures of glycerol esters. The cationic lipids are listed in Table 2^[4] and the frequently used anionic and non-ionic lipids and their structures in Table 3. Waxes such as Cutina CP (cetyl palmitate), solid paraffin,

Table2-Cationic Lipids Used for Preparation of Cationic SLN.

Stearylamine (SA)
N,N-di-(β-stearylethyl)-N,N-dimethylammonium chloride (EQ1)
Benzalkonium chloride (BA)
Cetrimide (CTAB)
Dimethyldioctadecylammonium bromide (DDAB)
N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTAP)
Chloroquine phosphate (CQ)
Cetylpyridinium chloride (CPC)
Dimethyldioctadecylammonium bromide (DDAB)

And beeswax are also sometimes used for SLN preparation. The surfactants used include amphoteric, ionic, and non-ionic ones (Table 4). Although ionic surfactants such as sodium dodecyl sulphate will allow the SLN to possess narrow size distribution and better

stability, some of them are associated with undesirable toxicity. In addition to the conventional lipid-based SLN, the synthesized para-acyl-calix^[44] arene-based SLN was also recently developed.^[53]

Table 3. Structures of Lipids Used in the Preparation of Solid Lipid Nanoparticles (SLN).

Chemical Structure	Name of Lipid
$\text{H}_3\text{C}-\left[\text{CH}_2\right]_n-\text{COOH}$	Dodecanoic acid (n=10) Myristic acid (n=12) Palmitic acid (n=14) Stearic acid (n=16)
$\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$	Caprylate triglycerides (n=6) Caprate triglycerides (n=8) Trilaurin (n=10) Tripalmitin (n=14) Tristearin (n=16) Tribehenin (n=20)
$\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{HC}-\text{OH}$ $\text{H}_2\text{C}-\text{OH}$	Glycerol monostearate (n=16)
$\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CHOH}-\left[\text{CH}_2\right]_m-\text{CH}_3$ $\text{HC}-\text{OH}$ $\text{H}_2\text{C}-\text{OH}$	Glycerol hydroxystearate (n=10, m=5)
$\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{HC}-\text{OH}$ $\text{H}_2\text{C}-\text{OH}$	Glycerol behenate (mono-, n=20)
$\text{H}_2\text{C}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{HC}-\text{O}-\text{OC}-\left[\text{CH}_2\right]_n-\text{CH}_3$ $\text{H}_2\text{C}-\text{OH}$	Glycerol behenate (di-, n=20)
$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{O}-\text{C}_{16}\text{H}_{33}$	Cetylpalmitate

In general, high drug loading in SLN can only be obtained when the drug has a high solubility in the lipid melt or a high partition coefficient between the molten lipid and aqueous phase. Based on the general principle of like-dissolve-like, scientists proposed a method to rationally screen the lipid carrier for SLN to obtain high drug loading capacity by a combination of the theoretical calculations and experimental partition coefficient measurements.^[55] The theoretical calculations include total solubility parameter, polarity, and mixing enthalpy. This method has already been used for the screening of 16 lipids from different categories, and it has shown good predictive power.

The occurrence of lipid polymorphism is a phenomenon fairly unique to SLN as compared to other lipid formulations. Lipid polymorphism is referred to the

multiple crystalline forms of solid lipids. One of these polymorphic forms, usually the one that forms perfect crystalline lattice, is more thermodynamically stable.

For example, triglyceride has three forms, i.e., α -form, β -form, and β' -form. Among them, only the β -form is stable.^[56] The relatively less stable or meta-stable forms would eventually transform to the stable polymorphic form, leading to a number of challenges in the development of SLN formulations. Drug molecules are primarily loaded into SLN in the defects of the lattices of solid lipids. When the lipid molecules are converted from the metastable forms into the stable form, they become more orderly packed, and some of the defects in the lattices disappear. As a result, drug expulsion from the lipid core to the particle surface may occur, contributing

to high initial burst release and drug leakage during storage.

Therefore, one additional criterion for choosing lipids for SLN formulation is the tendency of these lipids to form perfect crystals, or more precisely, their polymorphic transition rates. Once again, there is no strict rule to follow. However, in general, lipids with longer fatty acid chains have a slower transition rate than those with shorter chains.^[57] SLN made from waxes as lipid matrix exhibited significant drug expulsion phenomenon because of the more crystalline structure although wax-based SLN are usually more physically stable.^[58] In addition to the type of lipids, some other factors may also affect the lipid crystallinity, including the storage condition and SLN production methods.^[59-61] For example, rapid cooling process will be beneficial to maintain the lipid matrix in a meta-stable form.^[59] The choice of surfactant and co-surfactant plays a crucial role as well.^[62] The crystallization rate of Dynasan 114-based SLN was shown much faster when poloxamer was used as the surfactant than those stabilized by the sodium salt of cholic acid.^[63] An increased amount of the meta-stable form of stearic acid was also found when a high concentration of co-surfactant such as butanol was included in the SLN preparation.^[64] From the point of view of cytotoxicity, two tailed cationic lipids are usually preferable to the one tailed cationic lipids (i.e., CPC and CTAB) and cationic surfactants.^[4]

Surfactants Used in SLN

The main functions of surfactants in SLN are to disperse the melt lipid into aqueous phase in the SLN preparation process and then to stabilize the nanoparticles after cooling. A surfactant molecule has a hydrophilic head and lipophilic tail to reduce the surface tension between two phases. The hydrophile-lipophile balance (HLB) value of surfactants represents the relative proportion of the hydrophilic and lipophilic parts of the molecule.

As illustrated in Table 4, surfactants applied in SLN include four categories: anionic, e.g., sodium stearate and sodium dodecyl sulfate; cationic, e.g., dodecyltrimethyl ammonium bromide (DTAB); non-ionic, e.g., members of the Pluronics[®] or Tweens[®] family; and amphoteric, e.g., egg lecithin. In general, ionic surfactants employ the electrostatic approach, and non-ionic surfactants rely on steric repulsion to stabilize particles. Among them, most non-ionic surfactants consist of a hydrophobic moiety (i.e., hydrocarbon chain) and a hydrophilic part (i.e., ethylene oxide group). Amphoteric surfactants possess both positively and negatively charged groups and exhibit cationic surfactant's feature at low pH and anionic at high pH.

Several factors should be considered when choosing surfactants for SLN preparation, namely HLB value, route of administration, toxicity, and the effect on lipid modification and particle size. Surfactants with HLB values in the range of 8–18 are suitable for the

preparation of oil-in-water dispersion. Non-ionic surfactants are preferred for oral and parenteral preparations over ionic ones because of their lower toxicity and irritancy. In general, the order of the toxicity of surfactants is:

Cationic > anionic > non-ionic > amphoteric.

One important factor in the choice of a surfactant for SLN should be considered: different surfactants have variable influences on the *in vivo* biodegradation of the lipid matrix. For instance, non-ionic surfactants are more effective for inhibiting the degradation of lipid matrix *in vivo*.

Poly (ethylene oxide) (PEO) chains of non-ionic surfactants provided steric hindrance of the anchoring of lipase/co-lipase complex. Therefore, *in vivo* degradation rate of SLN may be tailored by adjusting the density of PEO chains on the particle surface. For SLN made of the same lipid but different non-ionic surfactants, the inhibitory activity against lipid degradation is in the order:

Cholic acid, sodium salt (NaCh) < lipid E80 < Tween[®] 80 < poloxamer 407 (64,65). Another study shows that Dynasan 114-based SLN have the fastest degradation rate when stabilized by lecithin and NaCh; intermediate rate using Tween[®] 80; and the slowest rate using poloxamer 407 (66). Mixing NaCh and poloxamer does not affect the degradation rate.^[4]

Finally, the choice of surfactants and co-surfactants also affects the particle size of SLN. SLN made of the same lipids may have different sizes because of the use of different surfactants.^[64] Zhang et al. prepared two types of long-circulating SLN using Brij[®] 78 or Pluronic[®] F68 as the surfactant, and they found that different surfactants led to the SLNs with totally different particle size.^[67] Bocca et al. showed that the average diameters of SLN systems produced by using glycocholate as the co-surfactant were larger than those using taurocholate.^[68] The authors attributed this phenomenon to the difference in pKa values of the co-surfactants, i.e., 4.4 for glycocholate and 1.4 for taurocholate.

Other Agents Used in SLN

In addition to lipids and surfactants (and sometimes co-surfactants), in some modified forms of SLN, other agents may also be used. For example, for the encapsulation of cationic, water-soluble compounds, a source of counterions is needed that includes organic anions and anionic polymers (see Table 4).

SLN can also be surface-modified. When a drug carrier was coated with hydrophilic polymers such as poloxamers, poloxamines, or poly (ethylene glycol) (PEG), this so-called stealth or long circulating carrier may reduce the capture by reticuloendothelial system (RES), and it stays longer in systemic circulation.^[69,70] For a detailed description of the stealth technique, refer to other chapters in the book that deal with long-

circulating nanoplaforms. This technique has been equally valuable to minimize clearance of SLN by phagocytosis.^[68] Because of the high surface hydrophobicity of SLN, the hydrophilic coating agents

are usually pre-conjugated to lipid moieties to form amphiphilic molecules (see Table 4) so their attachment on to the particle surface can be more secure.

Table 4- A List of Surfactants, Co-Surfactants, Counterions, and Surface-Modifying Agents Commonly Used in the Formulation of SLN-Based Systems (4).

Amphoteric surfactants	Non-ionic surfactants
Egg phosphatidylcholine (EggPC)	Brij78
Egg lecithin (Lipoid E80)	Poloxamer 188
Soy phosphatidylcholine (SP)	Poloxamer 407
(Epikuron 200, 95% SP)	Poloxamine 908
(Lipoid S100)	Polyglycerol methyl glucose distearate
(Lipoid S75, 68% SP)	(Tego care 450)
(Lipoid S75, 68% SP)	Solutol HS15
(Phospholipon 90G, 90%)	Span 85
Ionic surfactants	Trehalose
Sodium cholate	Tween 20
Sodium cocoamphoacetate	Tween 80
Sodium dodecyl sulfate (SDS)	Tyloxapol
Sodium glycocholate	Co-surfactants
Sodium oleate	Butanol
Sodium taurocholate	Butyric acid
Sodium taurodeoxycholate	
Counterions	
Organic salts	Ionic polymers
Monodecylphosphate	Dextran sulfate sodium salt
Monohexadecylphosphate	Hydrolyzed, polymerized epoxidized soy bean oil (HPESO)
Mono-octylphosphate	
Sodium hexadecylphosphate	
Surface-modifying Agents For long-circulating SLN	
Dipalmitoylphosphatidyl-ethanolamine conjugated with polyethylene glycol 2000 (DPPE-PEG 2000)	
Distearoyl-phosphatidylethanolamine-N-poly(ethylene glycol) 2000 (DSPE-PEG)	
stearic acid-PEG 2000	

Types, Proposed Structure, and Morphology of SLN

The structure and morphology of SLN are affected by several factors such as the physicochemical characteristics of the SLN ingredients and the production method adopted. To date, there has been no concrete data revealing the detailed structure of SLN. Most SLN researchers believe that SLN are probably spherical because a spherical subject has the smallest possible surface area-to-volume ratio. This may minimize the surface tension between the lipids and the aqueous phase, thereby leading to thermodynamic stability. Nevertheless, it should be noted that the platelet shape of SLN and NLC was also claimed by some groups, and they have provided evidence as well.^[71,72]

Classical SLN, Nanostructured Lipid Carrier (NLC), Polymer-Lipid Hybrid Nanoparticles (PLN), Polymer-Lipid Hybrid Nanoparticles (PLN) are the types of SLN, based on the composition of the lipid matrix and nature of drug to be loaded on SLN.

3. SLN MANUFACTURING METHODS

Currently, many techniques are available for SLN preparation. These include high pressure homogenization, microemulsion, and solvent diffusion.^[73-76] The more commonly used methods will be briefly described in this article. For detailed descriptions of SLN preparation, please refer to the up-to-date reviews.^[60,73-77] where the optimization of the processing variables is also discussed.

3.1. High shear homogenization and ultrasound

High shear homogenization and ultrasound are dispersing techniques which were initially used for the production of solid lipid nanodispersions.^[78] Both methods are widespread and easy to handle. However, dispersion quality is often compromised by the presence of microparticles. Furthermore, metal contamination has to be considered if ultrasound is used.

Ahlin et al. used a Lak Tek rotor-stator homogenizer (Omni International, Gainesville, USA) to produce SLN by melt-emulsification.^[81] They investigated the influence of different process parameters, including

emulsification time, stirring rate and cooling conditions on the particle size and the zeta potential. Lipids used in this study include trimyristin (Dynasan®114), tripalmitin (Dynasan®116), tristearin (Dynasan®118), a mixture of mono-, di- and triglycerides (Witepsol® W35, Witepsol®H35) and glycerol behenate (Compritol®888 ATO), poloxamer 188 was used as steric stabilizer (0.5 w%). For Witepsol® W35 dispersions the following parameters were found to produce the best SLN quality: stirring for 8 min at 20 000 rpm, the optimum cooling conditions: 10 min at 5000 rpm at room temperature. In contrast, the best conditions for Dynasan®116 dispersions were a 10-min emulsification at 25000 rpm and 5 min of cooling at 5000 rpm in cool water ($T=16^{\circ}\text{C}$). Higher stirring rates did not significantly change the particle size, but slightly improved the polydispersity index. No general rule can be derived from differences in the established optimum emulsification and cooling conditions. In most cases, average particle sizes in the range of 100–200 nm were obtained in this study.^[8]

3.2. High Pressure Homogenization

High pressure homogenization (HPH) has emerged as a reliable and powerful technique for the preparation of SLN. Homogenizers of different sizes are commercially available from several manufacturers at reasonable prices. In contrast to other techniques, scaling up represents no problem in most cases. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Typical lipid contents are in the range 5–10% and represent no problem to the homogenizer.^[8] Even higher lipid concentrations (up to 40 %) have been homogenized to lipid nanodispersions.^[80]

Two general approaches of the homogenization step, the hot and the cold homogenization techniques, can be used for the production of SLN.^[81-83] In both cases, a preparatory step involves the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt.^[8] The main advantages of these methods include narrow size distribution of nanoparticle produced and the possibility of scale-up production.

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-

shear mixing device (Ultra-Turrax). The quality of the pre-emulsion affects the quality of the final product to a large extent and it is desirable to obtain droplets in the size range of a few micrometers.^[8] In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase.^[84]

In cold homogenization, the first preparatory step is the same as in the hot homogenization procedure and includes the solubilization or dispersing of the drug in the melt of the bulk lipid.

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the solid state of the lipid due to the increase in temperature during homogenization.^[85]

However, the following steps are different. The drug containing melt is rapidly cooled (e.g. by means of dry ice or liquid nitrogen). The high cooling rate favors a homogenous distribution of the drug within the lipid matrix. The solid, drug containing lipid is milled to microparticles. Typical particle sizes obtained by means of ball or mortar milling are in the range 50–100 microns.^[8]

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

1. Temperature-induced drug degradation
2. Drug distribution into the aqueous phase during homogenization
3. Complexity of the crystallization step of the nanoemulsion leading

To several modifications and/or super-cooled melts^[8]

The cold approach minimizes the exposure of drug to heat (although brief period of heating is still required) and is more suitable for labile drugs sensitive to heating. Low temperatures increase the fragility of the lipid and favor, therefore, particle comminution. The solid lipid microparticles are dispersed in a chilled emulsifier solution. The pre-suspension is subjected to high pressure homogenization at or below room temperature. In general, compared to hot homogenization, larger particle sizes and a broader size distribution are observed in cold homogenized samples.^[86] The method of cold homogenization minimizes the thermal exposure of the sample, but it does not avoid it due to the melting of the lipid/drug-mixture in the initial step.

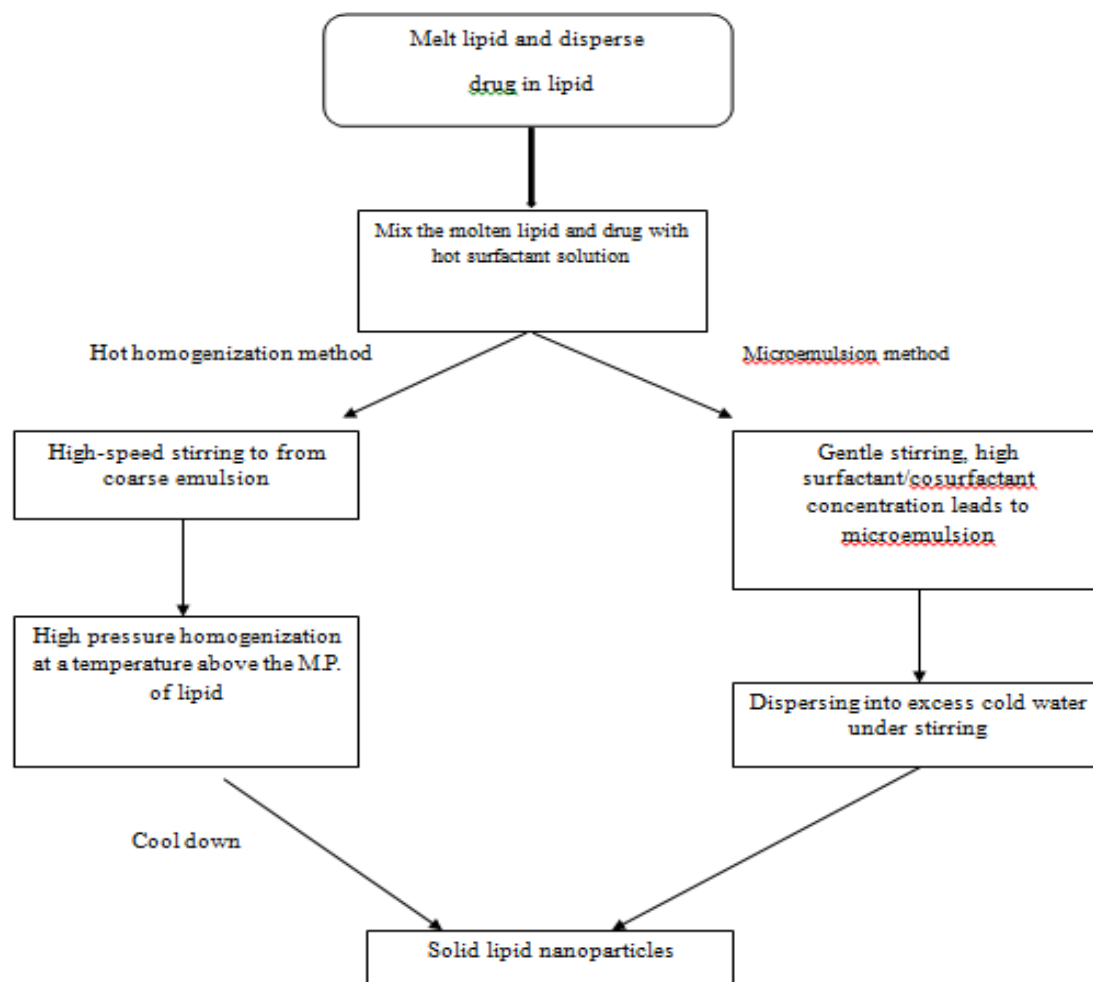


Fig. 3- Schematic procedures of hot homogenization and microemulsion for SLN production.

In the following years, it has been demonstrated that high pressure homogenization is a more effective method for the production of submicron sized dispersions of solid lipids compared to high shear mixing or ultrasound.^[81,87,88]

Most SLN dispersions produced by high pressure homogenization (HPH) are characterized by an average particle size below 500 nm and a low microparticle content. Other production procedures are based on the use of organic solvents (HPH/ solvent evaporation) or on dilution of microemulsions.^[89-91]

3.3. Microemulsion

A warm microemulsion is prepared under stirring before it is dispersed in a large volume of cold water at 2–48°C. The typical volume ratio of emulsion to cold water is in the range of 1–20. The procedure of microemulsion method for SLN preparation is illustrated in Figure 3.

Using this method, it is noted that the particle size, size distribution, and stability of SLN is correlated with the properties of microemulsion such as the lipids and surfactants applied, the concentration of surfactant, and the drug/lipid ratio.^[4] The procedure of microemulsion method for SLN preparation is illustrated in Figure 3.^[4] Cold homogenization method

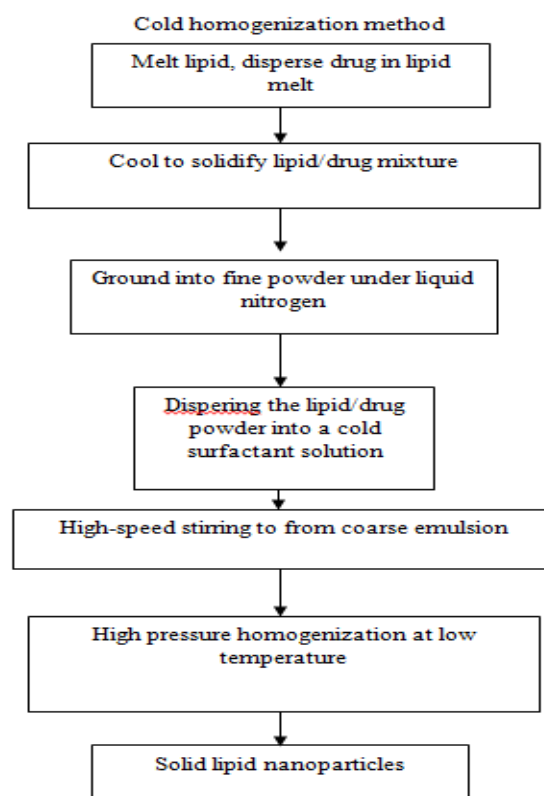


Fig. 4- Schematic procedure of cold homogenization for SLN production.

3.4. Solvent Evaporation

Sjöström and Bergenstål described a production method to prepare nanoparticle dispersions by precipitation in o/w emulsions.^[89] The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent a nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium.^[8] As

demonstrated in Figure 5, the lipid is dissolved in water-immiscible organic solvent first, and then the hydrophobic drug is added. Dispersing the drug-lipid-organic solvent mixture into an aqueous solution of emulsifiers produces an o/w emulsion. SLN are obtained by removing the organic solvent with evaporation under low pressure.^[4]

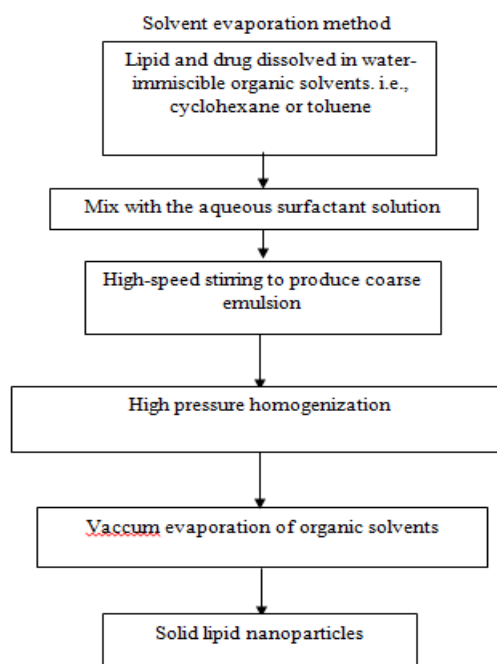


Fig. 5- Schematic procedure of solvent evaporation method for SLN production.

The mean particle size depends on the concentration of the lipid in the organic phase. Very small particles could only be obtained with low-fat loads (5 w %) related to the organic solvent. With increasing lipid content, the efficiency of the homogenization declines due to the higher viscosity of the dispersed phase. The advantage of this procedure over the cold homogenization process described before is the avoidance of any thermal stress. A clear disadvantage is the use of organic solvents^[8] Residues of organic solvent may raise the bio-safety concern.

3.5. W/O/W Double Emulsion Method

This method is designated for the delivery of hydrophilic drugs by using SLN.^[6] Highly concentrated drug solution is dispersed into a lipid phase under vigorous stirring and stabilized by a surfactant to form the primary w/o emulsion. The primary emulsion is subsequently dispersed into a large volume of aqueous solution containing another kind of surfactant to form w/o/w emulsion. The nanoparticles are obtained by ultrafiltration or solvent evaporation. The detailed procedure is illustration in Figure 6.^[4]

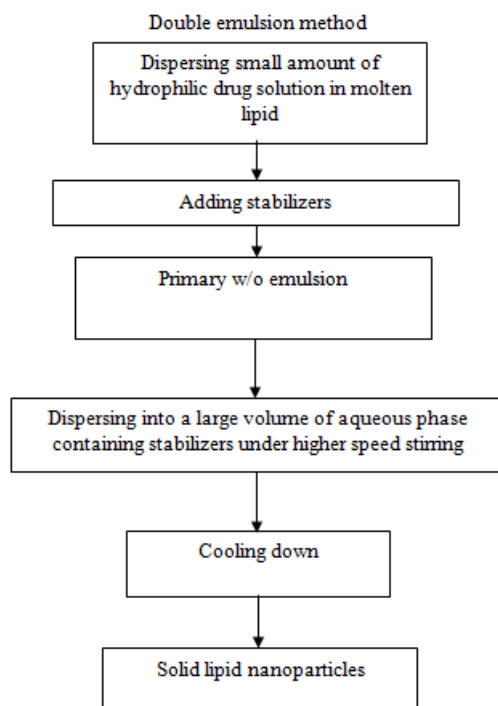


Fig. 6- Schematic procedure of w/o/w emulsion method for SLN production.

4. SLN BENEFITS^[3,8]

It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers (16). Proposed advantages include:

- UV attenuation by both absorption and scattering^[5]
- Possibility of controlled drug release and drug targeting
- Increased drug stability
- High drug payload
- Incorporation of lipophilic and hydrophilic drugs feasible
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization

5. DRUG INCORPORATION AND DRUG RELEASE

A large number of drugs with a great variety of lipophilicity and the general structure have been studied with regard to their incorporation into SLN, e.g. oxazepam, diazepam, cortisone, betamethasone valerate, retinol, prednisolone, retinol, menadione, ubidecarenone,

timolol, desoxycortisone, pilocarpine, progesterone, hydrocortisone, idarubicin, doxorubicin, thymopentin, (D-Trp-6)LHRH, gadolinium (III) complexes, 3'-azido-3'-deoxythymidine palmitate, azidothymidine palmitate, camptothecin, acyclovir, cyclosporine, vitamin E palmitate,^[93-111] etomidate, tetracaine.^[83]

As discussed before, drug loading might result in strong changes of the SLN characteristics (particle size distribution, zeta potential, lipid modification etc.). Drug incorporation implies the localization of the drug in the solid lipid matrix. However, several alternative incorporation sites (micelles, mixed micelles, liposomes, drug-nanosuspensions) exist in addition to the complex physicochemical status of the lipid (supercooled melt and several modifications). Unfortunately, these aspects have been neglected in the design and discussion of most SLN experiments.^[8]

The following precautionary remarks should be kept in mind during the interpretation of the published results: Particle size measurements alone are not sufficient for the characterization of SLN dispersions. The

modification of the lipid (and the drug) should be characterized by DSC, X-ray and NMR techniques. The selection of the control sample deserves special attention in order to prove that the observed result was due to the colloidal lipid carrier and not due to other colloidal structures which are present in the sample. For example, an appropriate control to a lecithin-stabilized SLN dispersion would be the liposome formulation produced under the same conditions. Glycocholate/lecithin stabilized SLN should be compared to mixed micelles.

A large number of drugs, including very hydrophilic molecules, has been postulated to be incorporated into SLN. However, few data exist on the localization site and the physical state of the drug molecule. Lukowski observed, by electron diffraction, that acyclovir is not molecularly dissolved in the lipid matrix.^[108] Most likely, the lipid and acyclovir nanoparticles are coexisting. Bunjes used NMR techniques to characterize the physicochemical state of diazepam, the lipid and the emulsifier. The published NMR spectra of diazepam indicate a high mobility of the drug.^[112] Ahlin and Kristl^[113] as well as our group^[114] used ESR techniques to monitor the physical state of model drugs. Independently, it was found that a high percentage of lipophilic nitroxides is localized in the polar environment and that distribution processes occur rapidly. It can be anticipated, that new NMR, ESR and synchrotron irradiation studies will shed more light on the incorporation and release processes of SLN. Especially solid state NMR techniques will be very powerful for the characterization of the molecular arrangement of the drug and the lipid.

In most cases, burst release is observed from SLN. For example, both hot and cold homogenization produced SLN released tetracaine and etomidate immediately.^[83] In contrast, it was possible to retard the release of prednisolone by the cold homogenization technique.^[82,83] An appropriate selection of the homogenization temperature permitted the modification of the release profile.

The release kinetics depend on the release conditions (sink or non-sink conditions, release medium etc.). Due to the colloidal size, release studies are not trivial experiments. Unfortunately, release experiments were conducted under several conditions (with sample separation by filtration or centrifugation or by dialysis) and therefore, it is not easy to compare the results. Every technique has its own advantages (simplicity, time) and drawbacks (possible artifacts due to separation; retardation of release by dialysis bag). Further experiments have to be done to elucidate the contribution of enzymes to drug release from SLN. It has been shown that matrix degradation by lipase depends on the lipid and the emulsifier. The balance between steric stabilizers and other surfactants can possibly be used to modify the release and particle degradation, because lipases need a lipid interface for activation of the enzyme (lid

opening).^[64] Therefore, PEG-coated SLN are not easily recognized by these enzymes.

6. SLNs ROUTE OF ADMINISTRATIONS AND THEIR APPLICATIONS IN SUNSCREENS

As mentioned in introduction section, SLNs can be in various routes of administration, such as parenteral routes, implants or by alternative routes such as oral, nasal and pulmonary.

Applications of SLNs in sunscreen products can be noted in these cases, briefly:

SLNs (as sunscreen carrier) act as physical sunscreens on their own, therefore the concentration of potentially hazardous molecular sunscreen can be decreased while maintaining the sun protection factor.^[3] A SLN has No biotoxicity as the carrier of sunscreen^[8] Researchers indicated that SLN-safranal formulations could be a promising carrier for topical delivery of safranal as an herbal UV blocking agent. SLNs enhanced ion due the skin hydration due to the free-SLNs.^[7] Nesseem developed carrier system for organic and inorganic sunscreen based on SLNs. UV-protection abilities of formulations were investigated by the in vitro sun protection factor test. SLNs showed pseudoplastic flow behavior. Significant increases in SPF values up to 50 were reported after encapsulation of organic and inorganic sunscreen in SLNs.^[115] In another study, Wissing and Muller used SLNs as carrier for in vivo skin protection. The aim of this study was the comparison two different formulations; SLNs and conventional o/w emulsion as carrier system for molecular sunscreen oxybenzone. In vivo penetration of oxybenzone into stratum corneum on the forearm was investigated by the tape stripping method. It was shown that oxybenzone accumulation into human skin was a greater extent from the SLNs.^[116] Jose and Netto reported that the disadvantages of conventional sunscreen can be overcome by SLNs. On comparing the SLNs traditional cosmetic products, the occlusion can be achieved without the use of paraffin and other greasy oils. The film formed by SLNs will be smooth as compared to the inflexible films formed by paraffin. They reported better photo protection that provided by SLNs^[118] lack of penetration across the epidermal layer(5) SLN are able to provide a sustained release carrier system (by their retention on the skin^[5]), therefore the sunscreen remains longer on the surface of the skin where it is intended to act.^[3]

7. CONCLUSION

SLNs are excellent carriers without any biotoxicity that can be used in various drug and cosmetic products. In this paper, we focused on SLNs properties and applications in sunscreens. We understood SLNs composition, manufacturing methods and also how to set SLNs particle size (depending our aim of using SLNs).

In brief, using SLNs as sunscreen carrier in sunscreens formulation -as a novel material (drug) delivery-causes more protective effect against hazardous UV

radiation, no problems with respect to large scale production, more stable sunscreen product on skin surface and so more convenience in use, high sunscreen material payload and incorporation of lipophilic and hydrophilic sunscreen material as desired by the sunscreen manufacturer.

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