Solid Lipid Nanoparticles: A Review

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Abstract
Solid lipid nanoparticle (SLN) dispersions have been proposed as a new type of colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. It is identical to an oil-in-water emulsion for parenteral nutrition (e.g., Intralipid, Lipofundin), but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e., yielding Solid Lipid Nanoparticles. SLN are particles made from solid lipid or lipid blends produced by high pressure homogenization. SLN introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. SLN combine advantages of the traditional systems but avoid some of their major disadvantages. This article reviews the present state of the art regarding production techniques for SLN, drug incorporation, loading capacity and drug release, especially focusing on drug release mechanisms. Relevant issues for the introduction of SLN to the pharmaceutical market, such as status of excipients, toxicity/tolerability aspects and sterilization and long-term stability including industrial large scale production are also discussed. The potential of SLN to be exploited for the different administration routes is highlighted.

Key Words
Spherical lipid particles, nanoparticulate system, polymeric particles.

Introduction
Solid lipid nanoparticle (SLN) dispersions have been proposed as a new type of colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. Generally, they are made of solid hydrophobic core having a monolayer of phospholipids coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics.

Various colloidal drug carrier systems, fat emulsions, nanoparticles for the controlled delivery of drugs by intravenous route are known.

Each of these particulate carriers possesses specific advantages and disadvantages. They are shown in following table. There are major difference between lipid emulsions and liposome. The basic sticture of lipid emulsion is neutral lipophilic oil core surrounded by a monolayer of amphiphilic lipid (phospholipids). In contrast, liposome contains an outer bilayer of amphipathic molecule such as phospholipids with an aqueous compartment inside. The amount of poorly water soluble drug that is possible to incorporate is, however, limited due to the relatively small volume (0.7ml/mmol of lipid) of the hydrophobic region of the lipid bilayer in comparison to the aqueous interior (2-3 ml/mmol of lipid). Emulsifier/ drug ratio is higher in case of liposomes. Moreover, incorporation of a lipophilic drug into bilayer membrane changes the properties of the particles and results in loss of control of delivery. A satisfactory long term physical and chemical stability for liposome is hard to achieve. They tend to fuse and are therefore relatively unstable on storage. They often display instability in the vascular system due to lipid exchange with lipoproteins. Liposomes have been sterilized by γ-radiations. However, this treatment causes the loss of integrity of bilayer component. The solid nanoparticulate supports, which are generally made...
with suitable biodegradable polymers, such as polyalkylcyanoacrylate, polymethylmethacrylate have been shown to prolong the release of the incorporated drugs. The major disadvantages of polymeric nanoparticles are their relatively slow biodegradability (up to 3-4 weeks), which might cause systemic toxicity by impairment of reticuloendothelial system as well as cytotoxicity towards macrophages, presence of residual toxic agents (organic solvents) employed during preparation and lack of reproducibility. Polymeric nanoparticles cannot be sterilized by autoclaving. They have been sterilized by γ radiation. However, this treatment causes the formation of unacceptable toxic reaction products. Solid lipid nanoparticles (SLNs) combine advantages of polymeric nanoparticles, fat emulsions and liposomes but simultaneously avoid some of their disadvantages. They are biodegradable and non-toxic; stable against coalescence, drug leakage, hydrolysis, particle growth oftenly observed in lipid emulsions and liposomes. Unlike lipid emulsions, which have a fluid core, they possess a solid matrix, which has the potential for allowing drug release over a prolonged period. Other advantages include low cost of ingredients, ease of preparation and scale up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drug, controlled particle size and extended release of entrapped drug after single injection from few hours to several days.

**Definition of SLN**

The SLN system can be easily explained. It is identical to an oil-in-water emulsion for parenteral nutrition (e.g., Intralipid, Lipofundin), but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e., yielding solid lipid nano particles. SLN are particles made from solid lipid or lipid blends produced by high pressure homogenization. The mean photon correlation spectroscopy (PCS) diameter is typically between approximately 80nm to 1000nm. Particles below 80nm are more difficult to produce because very often they do not recrystallized. The SLN are dispersed in an aqueous outer phase and stabilized by surfactants, e.g., Tween80, sodium dodecyl sulfate (SDS), lecithin. Alternatively, they can be produced surfactant free using steric stabilizers (e.g.poloxamer180) or an outer of increased viscosity (e.g. ethyl cellulose solution).SLN can also be produced in nonaqueous media, e.g., PEG-600 or oils like Miglyol 812. Production in PEG-600 gives a dispersion which can be directly filled into soft gelatin capsules. The aqueous SLN dispersion can be incorporated in traditional dosage forms like tablets and pellets. For producing pellets, the water for the extrusion mass is replaced by aqueous SLN dispersion. The pellets disintegrate and release the SLN completely nonaggregated. SLN can be transformed to a dry product by spray during or lyophilization.

**Status of Excipients in SLN Production**

Depending on route of administration, SLN must be differentiated in terms of status of excipients. The three major routes are:

1) External administration (e.g. topical).
2) Oral administration.
3) Parenteral administration.

For external administration the complete range of excipients used for cosmetics and pharmaceutical ointments / creams can be used. This provides a vast variety, especially with regard to the cosmetic excipients. There is no need to use any excipient which has not yet been accepted. For oral administration of SLN, all excipients can be employed that are frequently used in traditional oral dosage forms such as tablets, pellets, and capsules. Even surfactants with cell membrane-damaging potential, e.g. SDS, can be used. SDS is contained in many oral products and accepted as an excipient by the regulatory authorities. In general, all GRAS substances and materials of approved GRAS status can be employed. In addition, SLN can be made from food lipids and using surfactants contained in food (e.g. surfactants from ice cream, such as e.g. sugar esters.) of course it need to be considered that an excipient used in the food industry is not automatically accepted in pharmaceutical products; however the required documentation process is relatively unproblematic.

The situation is different for parenteral administration. The basic point is that SLN are a novel system; solid lipids have not yet been administered parenterally before-in contrast to liquid lipids (o/w emulsions for intravenous administration, prolonged release oil-based injectables for intramuscular administration). However, the glycerides used for SLN production are composed of compounds (glycerol, fatty acids) which are also present in emulsions for parenteral nutrition. This means that, apart from drug delivery,
the SLN are an additional nutritive. The only difference to emulsions for parenteral nutrition is that the composition of the glycerides is different. The oils contain glycerides of mixed composition of medium and long chain triglycerides (MCTs, LCTs). The glycerides used for SLN production need to be solid, i.e. are composed of longer chain fatty acids. In addition, many lipids are monoacid triglycerides, i.e. composed of just one fatty acid. Examples are Dynasan114 with myristic acid, Dynasan116 with palmitic acid, and Dynasan118 with stearic acid. In some cases the lipids used are mixtures of mono, di and triglycerides. Some of them are more or less just one glyceride type or contain preferentially one glyceride, e.g. triglyceride of behanic acid in the commercial lipid Compritol [with smaller fractions of mono (12-18%) and diglycerides].

Influence of Lipids and Surfactants Used In Solid Lipid Nano Particle Production

Influence of the lipid

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. These results are in agreement to the general theory of HPH and can be explained by the higher viscosity of the dispersed phase. However, other critical parameters for nanoparticle formation will be different for different lipids. Examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties) and the shape of the lipid crystals (and therefore the surface area). It is also noteworthy, that most of the lipids used represent a mixture of several chemical compounds. The composition might therefore vary from different suppliers and might even vary for different batches from the same supplier. However, small differences in the lipid composition (e.g. impurities) might have considerable impact on the quality of SLN dispersion (e.g. by changing the zeta potential, retarding crystallization processes etc.). For example, lipid nanodispersions made with cetyl palmitate from different suppliers had different particle sizes and storage stabilities. The influence of lipid composition on particle size was also confirmed on SLN produced via high-shear homogenization. The average particle size of Witexpol® W35 SLN was found to be significantly smaller (117.061.8 nm) than the size of Dynasan® 118 SLN (175.163.5 nm). Witexpol® W35 contains shorter fatty acid chains and considerable amounts of mono- and diglycerides which possess surface active properties. Increasing the lipid content over 5–10% in most cases results in larger particles (including micro particles) and broader particle size distributions. Both a decrease of the homogenization efficiency and an increase in particle agglomeration cause this phenomenon which has been observed for lipid nanoemulsions, too.

Influence of the emulsifier

The choice of the emulsifiers and their concentration is of great impact on the quality of the SLN dispersion. High concentrations of the emulsifier reduce the surface tension and facilitate the particle partition during homogenization. The decrease in particle size is connected with a tremendous increase in surface area. The increase of the surface area during HPH occurs very rapidly. Therefore, kinetic aspects have to be considered. The process of a primary coverage of the new surfaces competes with the agglomeration of uncovered lipid surfaces. The primary dispersion must contain excessive emulsifier molecules, which should rapidly cover the new surfaces. The excessive emulsifier molecules might be present in different forms e.g. molecular solubilized (emulsifier monomers), in form of micelles (SDS) or liposomes (lecithin). The time scale of the redistribution processes of emulsifier molecules between particle surfaces, water-solubilized monomers and micelles or liposomes is different. In general, SDS and other micelle-forming low molecular weight surfactants will rapidly achieve the new equilibrium. Redistribution processes will take a longer time for high molecular weight surfactants (poloxamer) and lecithin. However, it is not recommended to exclusively use rapidly distributing surfactants like SDS, because their ability to cover surfaces very rapidly is often combined with considerable water solubility and toxicity. Indeed, it has been reported that SLN stabilized with surfactant mixtures (Lipoid S 75/ poloxamer 188 or tyloxapol /lecithin) have lower particle sizes and higher storage stability compared to formulations with only one surfactant. The addition of sodium glycocholate to the aqueous phase as co-emulsifying agent decreases the particle size, too. Different emulsifier compositions might require different homogenization parameters. For example, the maximal degree of dispersing was
obtained with 500 bar and three cycles for poloxamer 188 stabilized systems. Homogenization with pressures of 1000 or 1500 bar did not result in further reduction of the particle size. In contrast, pressures of 1500 bar proved to be the best for lecithin (Lipoid S 75) stabilized systems. A possible explanation for this observation is the different velocity of the coverage of the new lipid surfaces. The importance of the emulsifier for the quality of the lipid nanodispersion was also demonstrated on micro emulsion based SLN dispersions. The particle size of the SLN dispersion produced with the ionic surfactants was considerably smaller (7062 nm) compared to the nonionic formulation (20065 nm).

**Drug loading**

A variety of drugs, including agents for treating cancer, AIDS, fungal infections, high blood pressure, mental illness, skin disease, and imaging have been loaded into solid lipid nanoparticles. Following table lists several drugs that have been incorporated into lipid nanoparticles. For efficiency and efficacy reasons, the amount of drug that can be loaded is very important. Calculated as the ratio of drug weight to the sum of drug and lipid weight, loading capacity typically ranges from 1-5. The drug can locate between fatty acid chains, between lipid layers, in lipid crystal imperfections. As noted previously, the chemical properties of the lipid affect the crystallinity of solid particle. It has been suggested that lipids that form more perfect crystalline solids, such as monoacid triglycerides having a β-crystal structure, expel solubilized drugs and that those lipids that form less perfect crystalline structures, Such as triglyceride mixtures, possess higher loading capacities.

**Methods of Preparation of SLN**

Various methods have been developed for the preparation of aqueous dispersion of lipid nanoparticles. The different production methods use biocompatible lipids or lipid molecules with a history of safe use in medicine. The essential excipients of SLN are solid lipids as matrix material and amphipathic lipids as surface stabilizers. Solid lipids such as saturated monoacid triglycerides (tristearin, tripalmitin, trilaurin etc), hard fat, cetyl palmitate, fatty acids (stearic acid, behanic acid etc) and cholesteryl acetate are recommended to be used as matrix for solid lipid nanoparticles. Compatible emulsifiers such as phospholipids, bile salts and Poloxamers are preferred as stabilizers.

Requirements of a solid lipid nanoparticle synthesis process
1. Use only GRAS excipients.
2. Minimizes surfactant concentrations.
3. Ability to produce multiple particle sizes without significant formulation changes.
4. Permits surface functionalization.
5. Minimizes mechanical and thermal energy inputs.
6. Permits control of drug localization in nanoparticles to affect desired release kinetics.
7. Continuous operation.

**Three different methods are used for production of SLN**
- Melt-homogenization technique
- Micro emulsification–solidification
- Multiple micro emulsification solidification

**Melt-homogenization technique**

SLNs can be produced by homogenization of molten lipids in an aqueous phase. The preparation of solid lipid nanoparticles by this technique involves two steps. First, the lipids are heated at least 10ºc above their melting point. The melted lipids are then dispersed in hot aqueous medium using a suitable dispersing agent. Dispersion is accomplished using a suitable dispersing agent. Dispersion is accomplished using mechanical stirring or by ultrasonication. The pre-mix formed is then passed through a thermostatised high pressure homogenizer under optimum homogenization conditions. The second step involves the solidification of oil droplets by cooling the hot dispersion to room temperature. For drug loaded SLNs the drug is dissolved either in melted lipid or hot aqueous phase prior to emulsification. It should be kept in mind that optimum homogenization conditions differ for each nanoparticle system and cannot be generalized. The difference may be due to the difference in the velocity of the surfactant monomers from the bulk phase into the interphase. The limiting factor is the substitution of monomers removed from the bulk phase by monomers from micelles or undissolved surfactant. Diameter of SLNs has been found to decrease as the molar ratio of core/ coating material increases, until a plateau is reached. After this point the diameter of SLNs is unaffected by further increase in the molar ratio. Increase in surfactant concentration reduces the diameter of bulk population.
Micro emulsification- solidification
SLNs can be produced by micro emulsification of molten lipids as the internal phase and subsequent dispersion of the micro emulsion under mechanical stirring. Micro emulsions are clear, thermodynamically stable, microheterogeneous dispersions usually obtained by mixing oil, water, surfactant and co-surfactant. The diameter of the disperse phase droplet is always below 100nm. Moreover, their preparation doesn’t require energy. Rapid crystallization of oil droplets on dispersion in cold aqueous medium produces lipid nanoparticles with solid matrix. The micro emulsions require presence of a co-surfactant for their production. When lecithin alone is used as a single surfactant it will not produce balanced microemulsion. It favors the formation of reverse microemulsion over a very limited range of concentration. This is because the lecithin molecule is too lipophilic; it has a critical packing parameter, Cpp, of approx. 0.8 favoring the formation of lamellar phase or bilayers. The Cpp is further increased in a microemulsion if the oil phase of a microemulsion penetrates into the long alkyl chains of the lecithin. In order to produce a balanced lecithin microemulsion, it is necessary to reduce its effective Cpp. This can be achieved by the use of co-surfactants. They can alter the effective Cpp in one of two films. The co-surfactant can also have a third effect, in that it can reduce the tendency of lecithin to form highly rigid films thus allowing the interfacial film sufficient flexibility to take up the different curvature required to form balanced lecithin micro emulsion. So we can say that the co-surfactant acts in bulk aqueous phase (to decrease the effective Cpp) and in the interfacial layer (to decrease the effective Cpp and rigidity of the lecithin monolayer) interfacial surfactant layer, which would allow the infinite dilution of the microemulsion without destruction due to the dilution of the co-surfactant below effective levels.

Multiple micro emulsification solidification
Warm w/o/w multiple microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In second step, the formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant to obtain a clear w/o/w system. SLNs can be obtained by dispersing the warm micro multiple emulsions in cold aqueous medium in a fixed ratio, under mechanical stirring. The suspension of lipid particles is then washed with dispersion medium by ultra filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, coalescence of the oil droplets, and rupture of the layer on the surface of the internal droplets. In case of SLNs production, they have to be stable for few minutes, the time between the preparations of the clear multiple microemulsions and its quenching in cold aqueous medium, which is possible to achieve. This method of SLNs production needs to be investigated.

Instrumental techniques for SLN production
The IKA Ultra-Turrax T 18 rotorstator homogenizer
The lipid (lauric acid, stearic acid, trilaurin, or tristearin) was maintained at ~ 75 °C and allowed to melt completely. Separately, double distilled water was heated to 75 °C. Typically, surfactants were added to the water under magnetic stirring and allowed to equilibrate at 75 °C. Next, the water – surfactant solution was added to the melted lipid and once again allowed to equilibrate at 75 °C. If desired to create the emulsion (i.e., no spontaneous emulsification as in the case of micro emulsions), external mechanical energy then was added in the form of an IKA Ultra-Turrax T 18 rotor-stator homogenizer. The Ultra-Turrax T 18 homogenizer, equipped with the 19 mm dispersing tool, has a speed range of 6,000 – 30,000 rpm and an operational volume range of 10 – 2000 ml. The homogenizer motor produces 160 W of power. The homogenizer only was operated in a batch set-up. Fig. 4 shows the IKA Ultra-Turrax T 18 rotorstator homogenizer.

Laboratory scale production techniques
The discontinuous Micron LAB 40
Laboratory scale production of SLN and Disso Cubes is performed using a piston-gap homogenizer (Micron LAB 40, APV Homogenizer GmbH-1, Lubeek, Germany). Minimum batch size is 20 mL, maximum size is 40 mL. Pressures applied range from 100 bars to a maximum of 1500 bar. The aqueous dispersion is pressed by a piston through a small homogenization gap that is approximately 25 urns (at a pressure of 500 bars). The process is discontinuous, i.e., the system needs to be
dismantled and the dispersion poured back into the central cylinder for the next homogenization cycle. This is somewhat time consuming but the machine has the big advantage of an extremely low sample volume. This is of high interest for compounds that are expensive or of limited availability. Figure 5 shows the principle mode of operation and Fig. 6 a picture of the LAB 40 unit. The discontinuous Micron LAB 40 is highly suitable in case expensive drugs or compounds with limited availability are processed, but is very time consuming when performing a screening for optimized production parameters and optimized composition of the nanosuspension formulation. For example, screening of four production pressures (e.g., 100, 500, 1000, and 1500 bar) up to two homogenization cycles requires 40 homogenization steps. It gets even more complicated when different surfactants and surfactant mixtures at different concentrations in a nanosuspension need to be checked regarding optimized physical stability of the produced nanosuspension. For screening purposes, a continuous Micron LAB 40 is much more suitable.

The continuous LAB 40

The continuous LAB 40 has a feeding vessel and a product vessel of a typical size of 0.5 L (Fig. 7). It is only necessary to switch two tubes before running the next homogenization cycle. Product samples for size analysis can be drawn directly from the vessels between the homogenization cycles. This speeds up the screening procedure enormously but requires a sample volume of at least 200 mL. This minimum volume of suspension cannot be accepted in the case of very expensive drugs, e.g., paclitaxel (normal price for 1 g is approximately 10.000,-$ US). On the other hand the continuous LAB 40 provides the possibility of producing lab scale batches of up to 0.5—1 L (to fit larger vessels to the systems). Figure 8 shows a picture of the continuous LAB 40 machine.

The Micron LAB 60

The Micron LAB 60 is a homogenizer for continuous production with a production capacity of 60 L/h. It consists of two pumps yielding a product flow with minimized fluctuations in homogenization pressure. The dispersion is subsequently passed through two homogenization valves: a first main homogenization valve, and a second valve that creates a certain reverse pressure and is also in charge of redispersing coalesced droplets or aggregates in the case of solid suspensions. As a general rule, the homogenization pressure of the second valve should be about one-tenth of the pressure used in the first valve. The Micron LAB 60 was modified according to the needs of a Good Manufacturing Practices (GMP) production. The production unit with the LAB 60 requires a batch size of approximately 2 L (approximately 2 kg). It is not possible to run such a low volume in the discontinuous production mode because of the relatively large dead volume of the machine (0.5 L). About 25% of the suspension would remain in the machine without being homogenized prior to the next homogenization cycle. From this it is more sensible to run the unit in a continuous circulating mode, with the product feed back after having passed the homogenization tower directly to the feeding vessel.

Electro Hydrodynamic Aerosolisation [EHDA] as a novel approach for the preparation of SLN

The limited commercial development of solid lipid nanoparticle technology indicates that more development is required to realize the technology’s theoretical potential. Solid lipid nanoparticle research has been plagued by an inability to produce particles of desired sizes, a lack of particle stability over time, polydisperse distributions, limited drug loading, burst release kinetics, and the lack of an economically viable production process. This research aimed to address these shortcomings by simultaneously investigating the chemical formulation and a novel production process based on electro hydrodynamic aerosolization (EHDA). EHDA utilizes electric charge to aerosolize liquids by overcoming the liquid’s surface tension. The liquid to be aerosolized is delivered to a nozzle, often a stainless steel capillary, maintained at high electrical potential. As the fluid passes through the nozzle, the electric field induces free charge at the liquids surface. The free charge on the surface generates electric stress that causes the liquid to accelerate away from the nozzle, thereby producing a so-called Taylor cone and electric current at the liquid’s surface. At the cone apex where the free charge is highly concentrated, a liquid jet with high charge density is formed. At appropriate conditions, the jet will disintegrate into highly charged aerosol droplets. Three steps define EHDA: 1) acceleration of the liquid in the liquid cone and subsequent jet
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formation; 2) the jet disintegration into aerosol droplets; 3) droplet evolution after formation

**Design and Construction of EHDA System**

Without any existing designs to work from, several EHDA process design iterations were anticipated at the outset. The initial thinking was to charge a stainless steel capillary by an external power source to create an electric field at the nozzle outlet. A syringe pump was to supply the lipid solution to the stainless steel capillary. The lipids were to be melted using a controlled temperature water bath. The lipids were to be pre-mixed by either rotor-stator homogenization or simple impeller rotation. Flowing an inert gas such as air, carbon dioxide, or nitrogen concurrently around the stainless steel capillary possibly would help prevent aerosol build-up just downstream of the jet break up. The droplets rapidly decelerate after formation often causing disruption of the steady cone-jet operation. It was thought that a sheath gas flow may prevent this issue by carrying the droplets farther downstream by convection. The solidification process was least defined, but it was thought solidification could be accomplished a number of techniques such as reducing the temperature downstream of the aerosol formation, flashing volatile components like water and ethanol as a form of evaporative cooling, and discharging into a cold solution to create a suspension. Following fig. 11 & 12 shows a process flow diagram proposed at outset of design activities and a schematic representation of the process flow diagram, respectively. With the assistance of professional engineering staff, the ideas presented in above figures 11 &12 were transformed into CAD drawings (fig.13) and then real, functioning systems (fig. 14). In the 1st generation device, a stainless steel needle, 0.5 mm ID, served as the negative electrode and as the inlet cylinder introducing the lipid solution to the aerosolization chamber. A wire carrying negative charge from a power supply was attached to the needle. The maximum achievable potential was ~6 kV. Upstream, the Lipids were melted using heating tape or a jacketed tube kept at elevated temperatures. The lipophile to be delivered was mixed in the melted lipid, and then the lipid solution was delivered to the needle using a syringe pump. The ground and positive electrodes were attached to same power supply noted above, and the maximum positive potential was +6 kV. The exhaust consisted of a flexible tube attached to the outlet port that could be directed to any desired location. The housing was comprised of available cast acrylic.

**Possible problems in SLN preparation and SLN performance**

SLN offer several advantages compared to other systems (easy scaling up, avoidance of organic solvents, high content of nanoparticles). However, less attention has been paid to the detailed and appropriate investigation of the limitations of this carrier system. Points to consider include high pressure-induced drug degradation, the coexistence of different lipid modifications and different colloidal species, the low drug-loading capacity and the kinetics of distribution processes.

**High pressure-induced drug degradation**

HPH (High pressure homogenization) has been shown to decrease the molecular weight of polymers. High shear stress has been assumed to be the major cause and evidence of free radical formation was reported. This study also indicated that cavitations are less important for the mechanism of polymer degradation. Cavitations can be suppressed by the application of back pressure without significant changes of the homogenization efficiency. The molecular weight and the general molecular structure are the most important parameters for predicting the drug degradation. High molecular weight compounds and long chain molecules are more sensitive than low molecular weight drugs or molecules with a spherical shape. For example, it was found that HPH causes degradation of DNA and albumin. Almeida investigated the influence of HPH on the activity of the peptide lysozyme by means of sodium dodecyl sulphate–polyacrylamide gel electrophoresis and the rate of lysis of Mi-crococcus lysodeikticus. He reported that the peptide remained in its active form after cold homogenization. According to the data in the literature, it can be stated that HPH-induced drug degradation will not be a serious problem for the majority of the drugs. However, HPH might be not suitable for the processing of shear sensitive compounds (DNA, albumin, and erythropoietin).

**Lipid crystallization and drug incorporation**

Lipid crystallization is an important point for the performance of the SLN carriers. The relation between lipid modification and drug incorporation has been investigated for decades. The characterization of lipid modifications is well established. Methods...
are mainly based on X-ray and DSC measurements. However, most of the data have been extracted from investigations on bulk lipids. The behavior of SLN might differ considerably due to the very small size of the particles and the high amount of surfactant molecules which are necessary to stabilize the colloidal lipid dispersion. Therefore, surface-related phenomena and lipid–surfactant interactions may contribute to a great extent to the properties of the lipid particle. The following four key aspects should be considered in the discussion of drug incorporation into SLN:

1. The presence of several lipid modifications
2. The shape of lipid nanodispersions
3. Gelation phenomena

**Supercooled melts**

Supercooled melts are not unusual in SLN systems. They describe the phenomenon that lipid crystallization may not occur although the sample is stored at a temperature below the melting point of the lipid. Supercooled melts are emulsions. Special attention should be paid to supercooled melts, because the potential advantages of SLN over nanoemulsions are linked to the solid state of the lipid. The main reason for the formation of supercooled melts is the size dependence of crystallization processes. Crystallization requires a critical number of crystallization nuclei to start. This critical number of molecules is less likely to be formed in small droplets and therefore, the tendency of the formation of supercooled melts increases with decreasing droplet size. The range of supercooling (temperature difference between the melting and crystallization points) can reach 30–40°C in lipid dispersions. For example, the melting temperature of trilaurin is 40°C, but in phospholipid/tyloxapol stabilized nanodispersions the lipid recrystallizes at temperatures below the freezing point of water. In addition to size, crystallization can be affected by emulsifiers, incorporated drugs and other factors. It is therefore necessary to proof the solid state of the lipid by appropriate analytical techniques such as NMR, X-ray or DSC. Among these, NMR permits a very rapid and nondestructive analysis of the presence of supercooled melts.

**Lipid modifications**

It is not sufficient to describe the physical state of the lipid as crystallized or non-crystallized, because the crystallized lipid may be present in several modifications of the crystal lattice. In general, lipid molecules have a higher mobility in thermodynamically unstable configurations. Therefore, these configurations have a lower density and ultimately, a higher capability to incorporate guest molecules (e.g. drugs). The advantage of higher incorporation rates in unstable modifications is paid off by an increased mobility of the drug. During storage, rearrangement of the crystal lattice might occur in favor of thermo-dynamically stable configurations and this is often connected with expulsion of the drug molecules. The performance of the SLN system will be determined to a large extent by the lipid modification, because this parameter triggers drug incorporation and drug release. Aspects of reproducibility and drug safety demand the assurance of systems with defined and reliable characteristics. Therefore, the utilization of the higher drug-loading capacity in unstable configurations requires the development of strategies to prevent modification during storage. Further opportunities of modified drug release profiles will be open, if this problem will be solved. For example, Jennings has shown in vitro on skin that the evaporation of water leads to modification changes of SLN dispersions which cause drug expulsion from the lipid and result in increased penetration of the drug into the skin. Complexity further increases due to several subspecies and the interactions of the lipid with the emulsifiers. Furthermore, recent work of Westesen’s group demonstrates that the particle size itself is the decisive factor for the physical properties of SLN. Several sharp peaks were observed in DSC thermograms which correspond to a different number of lipid layers of the SLN particles.

**Particle shape**

The shape of lipid nanoparticles may significantly differ from a sphere. Lipids prefer to crystallize in the platelet form. Differences in shape between nanoemulsion (spheres) and SLN (platelets) have been observed by TEM. The shape of the lipid crystals is not only a theoretical matter of particle sizing (PCS and LD assume spherical shapes). Platelet shapes have much larger surface areas compared to spheres; therefore, higher amounts of surfactants are needed for stabilization. Particle sizes of 100 nm (measured by PCS or LD) translate into 20 lipid layers assuming a spherical shape. However, they translate into smaller values if a platelet structure exists. Cryo transmission electron
microscopy studies of trirystatin nanoparticles give clear evidence that PCS sizes of 130 nm correspond to only 1–5 (!) lipid layers. Therefore, a much higher amount of the drug will be localized directly on the surface of the particles, which is in conflict with the general aim of the SLN systems (drug protection and controlled release due to the incorporation of the drug in the solid lipid).

Gelation phenomena
Gelation phenomena describe the transformation of low-viscosity SLN dispersion into a viscous gel. This process may occur very rapidly and unpredictably. In most cases, gel formation is an irreversible process which involves the loss of the colloidal particle size. It can be stimulated by intense contact of the SLN dispersion with other surfaces and shear forces. A typical example is a syringe needle. Several mechanisms might be involved in the gelation process. All promoters of gelation (high temperature, light, shear stress) increase the kinetic energy of the particles and favor collision of the particles. The surfactant film might change his performance with temperature (especially PEG-surfactants!). Further aspects relate to the kinetics of crystallization and transformation between the lipids modifications which will be influenced by the factors mentioned above. Rapid crystallization of the lipid increases the gelation process. The presence of liquid phases promotes the crystallization in the stable form because unstable crystals may redissolve and crystallize in the stable modification. In this way, it is possible to accelerate the $\alpha \rightarrow \beta'$ transformation during storage at RT without melting of the Compritol. In most cases, triglycerides will crystallize in the $\alpha$ modification. The $\alpha \rightarrow \beta'$ transformation can be retarded by surfactants, e.g. poloxamer. A nitrogen atmosphere had similar effects. The retardation by nitrogen was attributed to the inhibition of the lipid hydrolysis (pH effect).

Coexistence of several colloidal species
The presence of several colloidal species is an important point to consider. Stabilizing agents are not localized exclusively on the lipid surface, but also in the aqueous phase. Therefore, micelle forming surfactant molecules (e.g. SDS) will be present in three different forms, namely: (i) on the lipid surface; (ii) as micelle; and (iii) as surfactant monomer. Only the detection of the presence of several colloidal species is not sufficient to describe the structure of colloidal lipid dispersions, because dynamic phenomena are very important for drug stability and drug release. Therefore, the kinetics of distribution processes has to be considered. Unstable drugs will hydrolyze rapidly in contact with water and, therefore, the distribution equilibrium of the drug between the different environments will be distorted. Carrier systems will be protective only if they prevent the redistribution of the drug.

Increasing the matrix viscosity will decrease the diffusion coefficient of the drug inside the carrier and, therefore, SLN are expected to be superior to lipid nanoemulsions. However, drug stabilization is a very challenging task for colloidal drug carriers, because of the very high surface area and the short diffusion pathways.

Mechanism of Drug Release from SLN
To develop controlled release SLN one needs to understand the drug release mechanism to allow a controlled development of formulations. At the very beginning of SLN development particles were produced using model drugs with different physiochemical properties, e.g. lipophilicity and hydrophilicity. Examples for lipophilic drugs studied were tetracain base\textsuperscript{29} and etomidate base\textsuperscript{30}, but also very hydrophilic drugs such as the x-ray contrast agent iotrolan produced by Schering AG in berlin\textsuperscript{31}. For tetracain and etomidate a burst release was observed. Study was done on the extent to which the burst release depends on particle size/ surface area. It was found that the burst release diminished with increasing particle size and prolonged release could be obtained when the particles were sufficiently large, i.e. lipid macroparticles. From this it was concluded the drug was enriched in an outer shell of the particles. This lead to the core shell model of SLN with enriched drug in an outer shell. The drug has a relatively short distance of diffusion and will be released in a burst. The formation of the shell is explained by the stepwise crystallization process of the drug-lipid mixture. After the hot homogenization step the produced o/w emulsion is cooled, the lipid precipitates first forming a more or less drug-free lipid core. The remaining liquid drug-lipid mixture will enrich continuously in drug content until the eutecticum is reached. Reaching the eutecticum leads to the simultaneous crystallization of lipid and drug, forming an outer shell surrounding the drug-free lipid core.
In addition, it must be considered that surfactant is present. This surfactant will interact with the outer shell and affect its structure. The existence of a shell can be proven by atomic force microscopy (AFM) measurements. With a special technique, noncontact imaging, the hardness of the particle is determined by pressing the cantilever of the AFM instrument into the particle. The force required to press the cantilever into the particle is a measure of the viscosity of the particle matrix. It can be shown that there is an outer shell of relatively low viscosity that is composed of lipid, drug and partially incorporated surfactant. That means the model could be specific to be the soft shell-hard core model. The prolonged release can be explained by molecular distribution of the drug in the lipid matrix. Figure 13 shows the release profile obtained with prednisolone loaded SLN of identical lipid composition but produced with different homogenization techniques (hot v. cold) and of SLN being produced under identical conditions (cold homogenization) but composed of different lipids (compritol v. cholesterol). The very interesting feature is that the release profile changes with production parameters and also changes by using a different lipid. A slow release without distinct burst was obtained by applying the cold homogenization technique. This was attributed to the presence of a solid solution, i.e., prednisolone was distributed in a molecular dispersed form homogeneously in the solid lipid matrix. This is very likely because cooling the drug-containing lipid will lead to the formation of a solid dispersion. This dispersion was just milled by high pressure homogenization, which means that no or limited melting occurred; the particles were just broken down and retained their structure of a solid dispersion. Of course, we all are aware of the fact that temperature peaks occur during the homogenization process. In addition, there will be a warming up of the dispersion by approximately 20°C. However, this does not lead to a melting if the difference between reached temperature and melting point of the lipid is sufficiently high. Based on these results, the existence of a solid dispersion model for SLN was proposed. Drug release is governed by diffusion of the drug in the solid matrix (solid phase diffusion). Producing prednisolone-loaded SLN by the hot homogenization technique led to a burst release followed by a prolonged release. The burst release was intensively investigated by changing the production parameters (temperature) and changing the composition of the SLN formulation (that means preferentially surfactant concentration). It was found that the extent of burst release increased with increasing temperature and increasing surfactant concentration (fig.15). With increasing temperature and increasing surfactant concentration, the solubility of the drug in the water phase increased. Applying the hot homogenization technique lead to an o/w emulsion. At high temperature the solubility of prednisolone in the outer aqueous phase was higher. Cooling down the emulsion lead to the precipitation of the drug-containing lipid core; simultaneously, the solubility of the prednisolone in the water phase led to the drug enrichment in the outer shell of the SLN. The better the prednisolone solubility in the water phase, the higher was the enrichment in the outer shell of the SLN. That means that burst release consequently needed to be increased with increased production temperature and increased surfactant concentration. When replacing the cold homogenization technique with the hot homogenization technique, one moves away from the solid dispersion again to the core shell type of SLN. This presents the possibility for an optimal design of drug release profile. If an initial dose is required, one can adjust the production parameters and/or the formulation composition (surfactant concentration) to obtain exactly the initial burst release required. Applying the hot homogenization technique and simultaneously using low surfactant concentration leads to the minimal burst and a prolonged drug release. Recently it was discovered that there is additionally the hard shell core model of SLN. Within an industrial product development the SLN were loaded with coenzyme Q10. The Q10-loaded SLN were routinely investigated by contact AFM. It was assumed that a solid dispersion of Q10 in lipid would be present. Contact AFM revealed that there was an outer shell of increased rigidity; the core was distinctly less rigid. Q10 was released relatively fast. Obviously the Q10 had accumulated in the outer shell but promoted crystallization of the lipid. Possibly Q10 and the lipid had structural properties such that they fitted together very well to form a solid structure (like brick layers). It could be possible that the molecule Q10 fitted into the imperfections of the lipid, leading to a more solid structure. Due to the location of Q10 in the outer shell the drug release was fast, but the presence of...
Q10 led to a more solid state of the lipid leading to a firm outer shell (fig.13).

To summarize, at present there are four different models of internal SLN structure proposed.

1) soft drug-containing shell core model
2) drug core/lipid shell model
3) solid dispersion model
4) Drug-free core/hard drug-containing shell model.

The different models shows that drug incorporation into SLN is complex, but at the same time the variety of models gives highest flexibility to modulate drug release if one is able to control the SLN structure formed during production. Knowledge of how to control this process is the major advantage of the companies having the adequate knowledge of SLN production.

Characterization of SLNs
In order to develop a drug product of high quality, a precise physico-chemical characterization of solid lipid nanoparticles is necessary. The parameters generally used to ensure that a standard product is made by the process in use include the particle size and its distribution, morphology and surface charge, the drug loading capacity, the drug release profile, and the physical state of the lipid particles.

Particle size, morphology, and zeta potential
Particle size characteristics are of great importance for dispersions suitable for parenteral administration. The limiting factor for i.v. administration is the number of large particles (greater than 5μm) which can partially block blood capillaries. The USP XXIII limits the particulate matter in small volume injections (100 ml or less) to 6000 particles per container equal or greater than 10μm. For i.v. use of SLN dispersions the presence of particles of average diameter above 5μm should in any case be avoided. To assess i.v. injectibility, the SLN dispersions are compares with emulsions for parenteral nutrition, with regard to the particles in the micrometer range.\[34\] The required maximum injection volume of SLN dispersions can be estimated by considering the necessary single dose of the drug, the typical loading capacity of the lipid matrix and the maximum lipid content of the SLN dispersion. Modification of the size significantly affects the physical stability and the biofate of the nanoparticles. The average size and size distribution of solid lipid nanoparticles is also important with respect to the release rate of the loaded drug. So the size of SLNs will have to be controlled within reasonable limits. The particle size depends on the matrix constituents as well as the type and amount of emulsifying agent. The choice of the lipid has been found to Affect SLNs diameter. It has been reported that the increase in the amount of oil and emulsifier. The size and the structure of the incorporated drug is also a factor affecting SLNs size and tend to increase the average diameter and PI of SLNs\[35\]. The size of the particles obtained from saturated monoacid triglycerides tend to increase with triglyceride chain length, which may be due to the increasing viscosity of the triglyceride melts. The choice of the emulsifying agent has been found to affect SLNs diameter. The phospholipid/ Tyloxapol (P/T) blend yields smaller particles than the phospholipids/ bile salt (P/Bs) blend. The smaller particle sizes observed in P/T stabilized dispersions may partially be attributed to the higher surfactant/triglyceride (S/T) ratio. Preparation of P/T stabilized lipid nanoparticles requires larger amounts of emulsifier to obtain dispersions with homogenous size distribution than preparation with P/Bs blends. The choice of the dispersion method is also found to affect the size of SLNs. Production of SLNs by high-pressure homogenization (HPH) proved to be most effective in reducing the number of large particles.

There are a number of methods used to determine the physical attributes of SLN. The spectroscopy (PCS) important methods are:
1) Photon Correlation Spectroscopy (PCS).
2) Atomic Force Microscopy (AFM).
3) Electron Microscopy.
4) Nuclear Magnetic Resonance (NMR).

Zeta Potential
It is a measure of charge on the surface of the particles. It imparts colloidal stability due to particle-particle repulsion. A zeta potential measurement also helps in designing particles with reduced reticuloendothelial system (RES) uptake. In order to divert SLNs away from the RES or lymphatic system, the surface of the particles should be hydrophilic and non-charged.

Determination of incorporated drug
It is of prime importance to measure the amount of drug incorporated in SLNs, since it influences the release characteristics. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium. This separation can be carried out using ultracentrifugation,
centrifugation, filtration or gel permeation chromatography. In centrifugation filtration the filters such as Ultrafree →MC (Milipore) or Utrasart→ 10 (Sartorius) are used along with classical centrifugation techniques. The degree of encapsulation can be assessed indirectly by determining in the supernatant after centrifugation filtration / ultracentrifugation of SLN suspension or alternatively by dissolution of the sediment in an appropriate solvent and subsequent analysis. Standard analytical techniques such as spectrophotometry, spectrofluorophotometry, high-performance liquid chromatography, or liquid scintillation counting can be used to assay the drug. In gel permeation chromatography Sephadex® and Sepharose® gels are used for removal of free drug from SLN preparations. First, preliminary calibration of column is carried out using SLNs and free drug. SLN preparations are applied to the column and washed with suitable buffer. Fractions containing SLNs can be collected and analyzed for the actual drug content after dissolution/extraction with appropriate solvent. Drug content can also be determined directly in SLNs by extracting the drug with suitable solvent under optimum conditions and subsequent analysis of aqueous extract.

**In vitro drug release studies**

In vitro drug release studies are mainly useful for quality control as well as for the prediction of in-vivo kinetics. Unfortunately, due to the very small size of the particles, the release rate observed in vivo can differ greatly from the release obtained in a buffer solution. However, in vitro release studies remain very useful for quality control as well as for evaluation of the influence of process parameters on the release rate of active compounds. In vitro drug release profile from SLNs can be evaluated by various experimental methods. Release profile of drug can be conducted in dialysis tubing or without tubing. In dialysis SLN is introduced into prewashed dialysis tubing, which is then hermetically sealed. The dialysis sac is dialyzed against dissolution medium at constant temperature with constant stirring. The released drug diffuses through the dialysis membrane. Samples from dissolution medium are taken at discrete times, centrifuged, and assayed for drug content. The sink conditions must be maintained during release studies. Criticized this method and claimed that perfect sink conditions are not maintained during release studies, since SI .N dispersions are not directly diluted in the dissolution medium. As result, the rate of drug appearance in the dissolution medium does not reflect its real release rate, but rather the concentration gradient between the continuous phase of the SLN dispersion and the dissolution medium. The potential drawback of this method is that it is not ‘sensitive' enough to characterize rapid release rate of drug from colloidal carrier. However it can be assumed that if the drug is released over much more than one hour, then this method can be used for in vitro release profile investigation from colloidal carriers. The in vitro kinetic methods based on dilution and separation can be used to assay the drug. In gel permeation chromatography Sephadex® and Sepharose® gels are used for removal of free drug from SLN preparations. First, preliminary calibration of column is carried out using SLNs and free drug. SLN preparations are applied to the column and washed with suitable buffer. Fractions containing SLNs can be collected and analyzed for the actual drug content after dissolution/extraction with appropriate solvent. Drug content can also be determined directly in SLNs by extracting the drug with suitable solvent under optimum conditions and subsequent analysis of aqueous extract.

At specified time intervals, samples of the diluted dispersion solution are withdrawn. After separation of solution from the SLNs the amount of drug released in the solution can be assessed. This method is efficient only if successful and rapid separation of the SLNs from the aqueous phase is achieved to prevent further drug release in release medium after sampling. Because of small size of the SLNs this is likely to be difficult.

**Rheology**

Rheological measurements of formulations can be conducted in a Brookfield Viscometer, using an appropriate spindle number. The viscosity depends upon the dispersed lipid content. Usually flow is Newtonian but becomes non-Newtonian for high lipid content.

**Storage stability**

The physical stability of the SI.Ns during prolonged storage can be determined by monitoring changes in panicle size, ding content, appearance, and viscosity as a function of time. Since with the passage of time the PC components can be hydrolyzed to lyso-PCs, the chemical changes also need to be monitored. This can be accomplished by thin -layer chromatography.

**Pharmacological Performance of SLN Systems**

Due to their nanoscale size, lipid nanoparticles can be administered intravenously. Without proper surface modification the cells of the reticuloendothelial system, particularly the liver and spleen, rapidly clear colloidal particles. To increase circulation times, reticuloendothelial system avoidance (‘stealth’) can be accomplished by incorporating polyoxyethylene, utilized extensively in liposomal and polymeric. Microparticle technologies. To accomplish the incorporation, researchers add polyoxyethylene (hydrophilic) and polypropylene (hydrophobic) block copolymers into the formulation. Incorporation of polyoxyethylene and polypropylene block copolymers has increased lipid nanoparticle tumor accumulation, antibacterial
activity of antifungal drugs, and extravasations of the blood brain barrier (BBB) of anticancer drugs normally incapable of crossing the BBB. Lipid nanoparticle drug formulations have shown to produce improved pharmacokinetic profiles versus traditional drug formulations. When formulated in lipid nanoparticles, doxorubicin plasma concentrations increased 3-5 times, showed a bi-exponential curve with high Area under the curve (AUC), exhibited longer circulation half-lives, decreased the volume of distribution, and reduced toxic side effects in rats. Surprisingly, similar circulation half-lives and pharmacokinetics were observed for stealth and non-stealth lipid nanoparticle formulations of doxorubicin. Drug targeting can be accomplished by ligand mediated attachment, exploiting physiological conditions as in cancer’s leaky vasculature, and utilizing the immune system’s affinity for hydrophobic colloidal particles. As noted earlier, a role of Kupffer cells in the liver is the removal of hydrophobic colloidal particles. If liver targeting is desirable, passive targeting can be accomplished in the case of nonstealth nanoparticles. Similarly, macrophages throughout the circulation naturally remove nanoparticles, offering a passive targeting opportunity. Typically, however, targeting of the liver and macrophages is undesirable and is avoided through the use of stealth technology. Passive targeting of cancer tumors is made possible by the leaky vasculature associated with cancer. The leaky vasculature generated during cancer driven angiogenesis (to feed the tumor cells) allows extravasation of colloidal paritculates. Interestingly, stealth lipid nanoparticles have demonstrated a strong propensity to accumulate in the brain.BBB penetration is extremely difficult and one of the critical challenges facing pharmaceutical therapeutics and imaging today. Lipid nanoparticle accumulation in the brain may be blood protein mediated. Adsorption of blood proteins such as lipoproteins on lipid nanoparticle surfaces may lead to interactions with endothelial cells that facilitate crossing the BBB. Diminazen aceturate alone does not cross the BBB because of its hydrophilicity. Lipid nanoparticle enhanced BBB transport also has been demonstrated for tobramycin, doxorubicin, and idarubicin. Drug delivery to the brain is an exciting area of possible application for lipid nanoparticle technology.

**Applications of SLN**

**Per oral administration**

Per oral 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 favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance, and however, no experimental data have been published on this issue. The question concerning the influence of the stomach and pancreatic lipases on SLN degradation in vivo remains open, too. The plasma levels and body distribution were determined after administration of CA-SLN suspension versus a CA solution (CA-SOL). Two plasma peaks were observed after administration of CA-SLN. The first peak was attributed to the presence of free drug; the second peak can be attributed to controlled release or potential gut uptake of SLN. These two peaks were also found in the total CA concentration–time profiles of all measured organs. It was also found that the incorporation into SLN protected CA from hydrolysis. The conclusion from this study was that SLN are a promising sustained release system for CA and other lipophilic drugs after oral administration. Increased bioavailability and prolonged plasma levels have been described after per oral administration of cyclosporine containing lipid nanodispersions to animals. An increased uptake of SLN into the lymph has been described by Bargoni after intraduodenal administration.

**Parenteral administration**

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. Parenteral application is a very wide field for SNL. Subcutaneous injection of drug loaded SLN can be employed for commercial aspect, e.g., erythropoietin (EPO), interferon-β. Other routes are intraperitoneal and also intra-articular. Intraperitoneal application of drug-loaded SLN will prolong the release because of the application area. In addition, incorporation of the drug into SLN might reduce irritancy compared to injecting drug micro particles. Possible applications...
for intra-articular applications are treatment of arthritis. Arthritis inflammation in joints is caused by hyper activation of the macrophages releasing inflammation mediators. The basic concept is to give corticoids to the macrophages to reduce their hyperactivity. Corticoids are generally poorly soluble in water; incorporation in a lipophilic matrix is therefore possible. Macrophages can internalize the SLN. Release of corticoid will follow, leading to a reduction in hyperactivity and consequently inflammation of the joint. Another broad application area is intra venous injection. Critical excipients like Cremophor EL can lead to anaphylactic reactions; administration of the product can only be performed by applying medical precautions. The adsorption of a blood protein onto particle surfaces is supposed to be responsible for the uptake of SLN by the brain by mediating the adherence to the endothelial cells of the blood–brain barrier.

**Transdermal application**

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin. Unfortunately, in most cases, the increase in lipid content is connected with a large increase of the particle size. Surprisingly it has been found that very high concentrated (30–40%), semisolid cetyl palmitate formulations preserve the colloidal particle size. A dramatic increase of the elastic properties was observed with increasing lipid content. The rheological properties are comparable to typical dermal formulations. The results indicate that it is possible to produce high concentrated lipid dispersions in the submicron size range in a one-step production. Therefore, further formulation steps (e.g. SLN dilution in cream or gel) can be avoided. The cosmetic field offers interesting applications. It has been found in vitro that SLN have UV reflecting properties. The UV reflectance is related to the solid state of the lipid and was not evident in nanoemulsions of comparable composition. These observations open the possibility of the development of SLN-based UV protective systems. The use of physiological components in SLN is a clear advantage over existing UV protective systems (UV blockers or TiO₂) with respect to skin penetration and potential of skin toxicity. SLN have also been found to modulate drug release into the skin and to improve drug delivery to particular skin layers in vitro. The loss of water after application on the skin causes changes of the lipid modification and SLN structure. Electron microscopy indicates that dense films are formed after drying (32°C) of SLN dispersions in contrast to spherical structures which have been proposed previously. The formation of the dense structure will favor occlusive effects on skin. It is interesting to note that the films made from melts of the lipid bulk do not form close films as dried SLN dispersions do. The surfactant plays a significant role in preventing pore formation.

**Topical application**

Regarding the regularity aspect, topical application is relatively unproblematic. The major advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin. Especially in the area of cosmetics there are many compounds such as retinol or vitamin C which cannot be incorporated because of the lack of chemical stability. Incorporation of retinol is only possible when applying certain protective measures during production (e.g. noble gasing) and using special packing materials (e.g. aluminium). This increases production costs and it would be better to achieve the protection against degradation by the SLN and use a normal production process and a highly acceptable packing material (e.g. polyethylene elastic tube). It could be shown that incorporation of cosmetic ingredients into SLN can change their penetration profile. By choosing a controlled composition of the cream the release of the active ingredient/drug can be triggered. In addition, the occlusion effect of the SLN film formed onto the skin promotes penetration of the active ingredients. In vitro occlusion tests showed a superior effect of solid lipid nanoparticles v. solid lipid microparticles and demonstrated the increase in occlusion by admixing SLN to traditional creams. Apart from the change in penetration, the occlusion can lead to an increased hydration and the smoothing of wrinkles.
Ophthalmic administration

Many investigations have been made to use nanoparticles for the prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at the desired site of action. However, the basic problem was that the nanoparticles are of limited toxicological acceptance, e.g., polyalkylcyanoacrylate nanoparticles which lead to the release of potentially cancerogenic formaldehyde. Other particles are too slowly biodegradable and therefore are not acceptable to the regulatory authorities. It was shown by Gasco that SLN have a prolonged retention time at the eye. This was confirmed by using radiolabeled formulations and γ-scintigrapy. The lipids of the SLN are easy to metabolize and open a new potential for ophthalmological drug delivery without impairing vision.

Pulmonary administration

A very interesting application appears to be the pulmonary administration of SLN. SLN powders cannot be administered to the lung because the particle size is too small and they will be exhaled. A very simple approach is the aerosolization of aqueous SLN dispersions. The important point is that the SLN should not aggregate during the aerosolization. The nebulizer employed was a periboy. The aerosol droplets were collected by collision of the aerosol with a glass wall of a beaker. This basically demonstrates that SLN are suitable for lung delivery. After localization into the bronchial tube and in the alveoli, the drug can be released in a controlled way from the lipid particles. After special feature of SLN is that they are susceptible to nonspecific hydrolysis. This could be shown by degrading SLN produced from a wax, cetylpalmitate. In vivo the cetylpalmitate, despite being a no physiological wax, was much more quickly degraded than the glyceride mixture of behanic acid.

References

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Fig. 2: SLN made from triglycerides and nonionic surfactant.

Fig. 3: IKA Ultra-Turrax T 18 rotor-stator homogenizer.

Fig. 4: Production node of discontinuous Micron LAR 40.

Fig. 5: The LAB 40 with self-built temperature jacket.

Fig. 6: Schematic setup of continuous LAB 40.

Fig. 7: Continuous version of the Micron LAB 40.

Fig. 8: LAB 60 for production under laminar airflow.

Fig. 9: Force balance in EHDA flow.
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Fig. 10: Schematic of 1st generation EHDA process

Fig. 11: Front and 45° views of CAD depiction of 1st generation EHDA device

Fig. 12: 1st generation EHDA device

Fig. 13: Release of etomidate from lipid nanoparticles (SLN)

Fig. 14: Proposed models for the internal structure of SLN