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Review article

Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art

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Abstract

Solid lipid nanoparticles (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 paper 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. References of the most relevant literature published by various research groups around the world are provided.

Keywords: Solid lipid nanoparticles; Controlled release; Bioavailability enhancer; Vaccine adjuvant; Colloidal drug carrier

1. Introduction

Particulate drug carriers investigated for many years include oil-in-water (O/W) emulsions, liposomes, microparticles and nanoparticles based on synthetic polymers or natural macromolecules [1]. The O/W emulsions have been introduced successfully to the clinic for parenteral nutrition in the fifties. Based on these emulsions for parenteral nutrition, drug-containing emulsion formulations have been developed, e.g. containing diazepam and etomidate [2]. Trade products are Diazemuls, Diazepam-Lipuro and Etomidate-Lipuro. The only intention of these emulsions was to reduce drug side effects, e.g. pain of injection and inflammation at the injection site (e.g. diazepam). Despite the excellent tolerability of these O/W emulsions the number of products on the market is relatively low, indicating their limited success. One of the reasons preventing a broader introduction of emulsions for drug delivery is the physical instability which can be caused by the incorporated drug. In addition, the registered oils such as soybean oil, MCT and LCT and mixtures thereof show an insufficient solubility for drugs of possible interest to be incorporated into emulsions. Despite the fact that the emulsion is a very interesting delivery system, one has the impression that pharmaceutical companies are reluctant to pursue this delivery system further. A possible reason for this might be the necessity to search for new oils with improved solubility properties which would of course also require an expensive toxicity study.

Phospholipid vesicles rediscovered as 'liposomes' in 1965 by Bangham found their way to the cosmetic market in 1986 [3]. It was the anti-aging product Capture (Dior) which smoothed the way for liposome-based pharmaceutical products. Having the first liposome product on the market strengthened at least the morale of researchers in the pharmaceutical area working intensively for so many years with this delivery system. Finally, the first pharmaceutical products came to the market at the end of the eighties and beginning of the nineties, and include the synthetic lung surfactant Alveofact® (Dr Karl Thomae GmbH/Biberach in Germany) for pulmonary instillation, Epi-Pevaryl®, a topical product for anti-mycotic therapy (drug: econazole) and other products for intravenous injection (e.g. Ambisome® with amphotericin and cytotoxic-containing formulations like Doxil® and Daunosome®) [1]. However, the total number of products on the market is still limited. One of the reasons for this – apart from possible technolo-

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gical problems – is the non-availability of a 'cheap' pharmaceutical liposome.

The number of products based on polymeric microparticles on the market is limited. After the introduction of the first wave of products (e.g. Enantone Depot®, Decapeptyl Depot®, Parlodel LA®, Parlodel LAR®) [4], there was only a limited increase in the number of microparticulate products. The situation is even worse for polymeric nanoparticles, after more than 30 years of research, this delivery system practically does not exist. An exception is the product Abdoscan produced by the company Nycomed, however, this is not a formulation for chronic treatment, it is a diagnostic agent.

There are quite a few well-known reasons for this, of which two should be highlighted: the cytotoxicity of polymers and the lack of a suitable large scale production method. Polymers accepted for use as implants are not necessarily also of good tolerability in the form of nanoparticles. In the nanometer size range and having a size of a few micrometers, the polymer can be internalized by cells (e.g. macrophages) and degradation inside the cell can lead to cytotoxic effects, e.g. as reported for polyester polymers [5]. A hundred percent mortality was found in cell cultures when incubating the cells with 0.5% PLA/GA nanoparticles [6]. A prerequisite to introducing a product to the pharmaceutical market is the availability of a suitable large scale production method, suitable means a method being cost-effective and leading at the same time to a product having a quality being acceptable by the regulatory authorities. There are still problems in the production of polymeric nanoparticles on large scale.

Since the beginning of the nineties attention from various research groups has focused on an alternative to polymeric nanoparticles, the solid lipid nanoparticles (SLN) [7–37]. The use of solid lipids as a matrix material for drug delivery is well-known from lipid pellets for oral drug delivery (e.g. Mucosolvan® retard capsules). The production of lipid microparticles by spray congealing was described by Speiser at the beginning of the eighties [38] followed by lipid nanopellets for peroral administration [39]. Basically, lipids can be used which are well tolerated by the body (e.g. glycerides composed of fatty acids which are present in the emulsions for parenteral nutrition). Large scale production can be performed in a cost-effective and relatively simple way using high pressure homogenization leading to SLN [7]. An alternative approach is the production of SLN via microemulsions [8]. This paper reviews the present state of the art in drug delivery using solid lipid nanoparticles and highlights the potential future perspectives.

2. Preparation techniques for lipid particles

2.1. Preparation of SLN by high pressure homogenization

SLN are particles made from solid lipids with a mean photon correlation spectroscopy (PCS) diameter between approximately 50 and 1000 nm. One can derive them from the emulsions for parenteral nutrition just by replacing the liquid lipid (oil) of the emulsion droplets by a solid lipid. In contrast to emulsions for parenteral nutrition which are normally stabilized by lecithin, the SLN can be stabilized by other surfactants or polymers and their mixtures. However – as a distinct advantage of SLN compared to polymeric nanoparticles – they can be produced by high pressure homogenization identical to parenteral O/W emulsions. This is a technique well established on the large scale since the fifties and already available in the pharmaceutical industry. The production lines for parenteral emulsions are in most cases equipped with temperature control units because an increased temperature facilitates emulsion production, this means that existing production lines can be used for producing SLN by the hot homogenization technique.

The two basic production methods for SLN are the hot homogenization technique and the cold homogenization technique [7,40]. For both techniques the drug is dissolved or solubilized in the lipid being melted at approximately 5–10°C above its melting point. For the hot homogenization technique the drug-containing melt is dispersed under stirring in a hot aqueous surfactant solution of identical temperature. Then the obtained pre-emulsion is homogenized using a piston-gap homogenizer (e.g. Micron LAB40), the produced hot O/W nanoemulsion is cooled down to room temperature, the lipid recrystallizes and leads to solid lipid nanoparticles (Fig. 1). Of course, care needs to be taken that recrystallization of the lipid occurs. For glycerides being composed of short chain fatty acids (e.g. Dynasan 112) and glycerides with a low melting point (too close to room temperature) it might be necessary to cool the nanoemulsions to even lower temperatures to

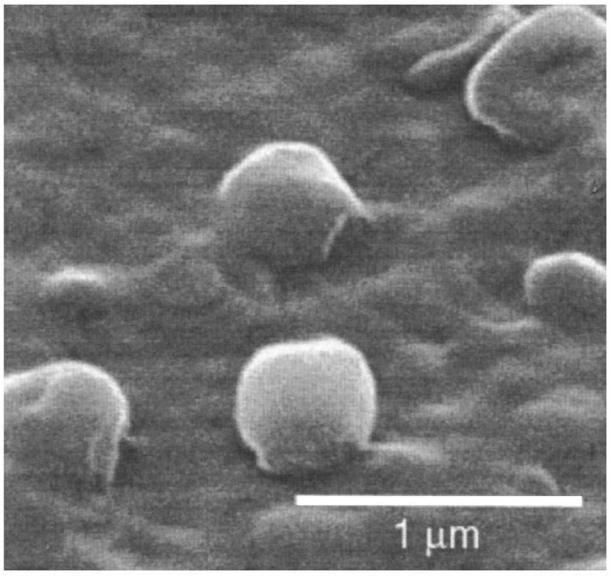

Fig. 1. REM picture of solid lipid nanoparticles made from Compritol stabilized with Poloxamer 188, diameter 400 nm (after [78]).

initiate recrystallization. Recrystallization can also be initiated, e.g. by lyophilization.

The hot homogenization technique is also suitable for drugs showing some temperature sensitivity because the exposure to an increased temperature is relatively short. In case of highly temperature-sensitive compounds the cold homogenization technique can be applied. It is also necessary to use this technique when formulating hydrophilic drugs because they would partition between the melted lipid and the water phase during the hot homogenization process. For the cold homogenization technique the drug-containing lipid melt is cooled, the solid lipid ground to lipid microparticles (approximately 50–100 μm) and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the cavitation forces are strong enough to break the lipid microparticles directly to solid lipid nanoparticles. This process avoids, or minimizes, the melting of the lipid and therefore minimizing loss of hydrophilic drugs to the water phase. Of course, the difference between the melting point of the lipid and the homogenization temperature needs to be large enough to avoid melting of the lipid in the homogenizer. The homogenization process itself increases the product temperature (e.g. 10–20°C per homogenization cycle). There are also temperature peaks in the homogenizer. To further minimize the loss of hydrophilic compounds to the aqueous phase of the SLN dispersion, water can be replaced by liquids with low solubility for the drug, e.g. oils or PEG 600. Production of SLN in oil or PEG 600 is advantageous for oral drug delivery because this dispersion could be directly filled into soft gelatine capsules.

2.2. SLN produced by microemulsion technique

Microemulsions are clear or slightly bluish solutions being composed of a lipophilic phase (e.g. lipid), a surfactant and in most cases also a co-surfactant and water. The term microemulsion is controversially discussed. Nowadays one considers microemulsions not as a real emulsion with very fine droplets but as a 'critical solution' [41]. The microemulsions show properties of real macroemulsions (e.g. small particle sizes can be measured by laser light scattering) and simultaneously properties of a real solution (e.g. drugs possess a saturation solubility in a microemulsion and do not show a distribution coefficient as in macroemulsions). Addition of a microemulsion to water leads to precipitation of the lipid phase forming fine particles. This effect is exploited in the preparation method for SLN developed by Gasco [8].

To form a microemulsion with a lipid being solid at room temperature, the microemulsion needs to be produced at a temperature above the melting point of the lipid. The lipid (fatty acids and/or glycerides) are melted, a mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipid and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratio for microemulsion formation. This microemulsion is then dispersed in a cold aqueous medium (2–3°C) under mild mechanical mixing, thus ensuring that the small size of the particles is due to the precipitation and not mechanically induced by a stirring process [42,43]. Surfactants and co-surfactants include lecithin, biliar salts, but also alcohols such as butanol [44]. Excipients such as butanol are less favourable with respect to regulatory aspects. From the technical point of view precipitation of the lipid particles in water is a dilution of the system, that leads to a reduction of solid content of the SLN dispersion. For some technological operations it is highly desirable to have a high lipid solid content, e.g. 30%. An example is the transfer of the SLN dispersion to a dry product (e.g. tablet, pellet) by a granulation process. The SLN dispersion can be used as granulation fluid, but in the case of low particle content too much water needs to be removed.

Large scale production of SLN by the microemulsion technique also appears feasible and is at present under development at Vectorpharma (Trieste, Italy). The microemulsion is prepared in a large, temperature-controlled tank and then pumped from this tank into a cold water tank for the precipitation step [45]. Important process parameters during the scaling up are e.g. the temperatures of the microemulsion and the water, but also temperature flows in the water medium and the hydrodynamics of mixing which should change as little as possible during scaling up to maintain the same product characteriztics.

2.3. Lipid nanopellets and lipospheres

The lipid nanopellets for oral delivery developed by Speiser are produced by dispersing a melted lipid in a surfactant solution by stirring or sonication. The obtained particle size is determined by the power density of the stirrer. In general, a mixture of nanoparticles and microparticles is obtained [36,46]. To preferentially obtain nanoparticles, relatively high surfactant concentrations are employed (i.e. one moves towards solubilization of the lipid). However, during the production of lipid particles, surfactant is also incorporated into the lipid phase, the more surfactant is present the more it is incorporated leading to a reduced crystallinity of the lipid particles (unpublished data). Higher surfactant concentrations might be acceptable for oral administration, the route that nanopellets were intended for according to the patent [39], but might cause some problems for other administration routes such as intravenous.

The lipospheres developed by Domb are 'solid, water-insoluble microparticles that have a layer of a phospholipid embedded on their surface' [47–49]. According to the patent claims, lipospheres comprise a core formed of a hydrophobic material solid at room temperature and a phospholipid coating surrounding the core. The average particle diameter is between 0.3 and 250 μm. The particles are prepared by

melting the core material, adding phospholipid along with an aqueous medium and dispersing the melted material at increased temperature by mixing techniques, such as mechanical stirring or sonication. Cooling leads to solid lipospheres. The liposphere is restricted to one stabilizing material, that means the phospholipid layer. For SLN it has been reported that suspensions stabilized only with phospholipid can tend to form semi-solid ointment-like gels [50]. Gel formation can be prevented by adding a co-emulsifier which is not covered by the liposphere patent. The SLN produced by our group are in most cases stabilized by binary or ternary surfactant mixtures providing optimal physical long-term stability.

2.4. Precipitated lipid particles

Solid lipid particles can also be produced by a precipitation method comparable to the production of polymeric nanoparticles by solvent evaporation. In contrast to SLN this method is characterized by the need for solvents. The glyceride is dissolved in an organic solvent (e.g. chloroform) and this solution is emulsified in an aqueous phase. After evaporation of the solvent the lipid precipitates forming nanoparticles [51]. A clear disadvantage is the need to use organic solvents. In addition, other problems arise similar to when scaling up production of polymeric nanoparticles on the basis of solvent evaporation. In contrast, SLN produced by high pressure homogenization have the advantage of avoiding the use of solvents.

3. Drug incorporation and loading capacity

Many different drugs have been incorporated in SLN, examples are given in Table 1. A very important point to judge the suitability of a drug carrier system is its loading capacity. The loading capacity is generally expressed in percent related to the lipid phase (matrix lipid + drug). Westesen et al. studied the incorporation of drugs using loading capacities of typically 1–5%, for Ubidecarenone loading capacities of up to 50% were reported [52]. For Tetracaine and etomidate capacities of 10–20% are reported [34,53,54], for retinol up to 5% [55–57], for coenzyme Q10 20% [58] and for cyclosporin 20–25% [59,60].

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

1. solubility of drug in melted lipid;
2. miscibility of drug melt and lipid melt;
3. chemical and physical structure of solid lipid matrix;
4. polymorphic state of lipid material.

The prerequisite to obtain a sufficient loading capacity is a sufficiently high solubility of the drug in the lipid melt. Typically, the solubility should be higher than required because it decreases when cooling down the melt and might even be lower in the solid lipid. To enhance the solubility in the lipid melt one can add solubilizers. In addition, the presence of mono- and diglycerides in the lipid used as matrix material promotes drug solubilization.

The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice (e.g. monoacid triglycerides) lead to drug expulsion [52]. More complex lipids being mixtures of mono-, di- and triglycerides and also containing fatty acids of different chain length form less perfect crystals with many imperfections offering space to accommodate the drugs [61]. Chemi-

Table 1
Examples of drugs incorporated in SLN, all SLN were prepared by high pressure homogenization apart from the SLN by Gasco (microemulsion technique)

Drug	Corresponding author/ research group	Reference
Timolol		[102,104]
Deoxycorticosterone		[103]
Doxorubicin		[106]
Idarubicin		[106]
[D–Trp–6]LHRH		[107]
Pilocarpine	Gasco	[108]
Thymopentin		[109]
Diazepam		[15]
Gadolinium (III) complexes		[44]
Progesterone		[66]
Hydrocortisone		[66]
Paclitaxel		[125]
Retinol		[55,56]
Coenzyme Q10	Gohla	[58]
Vitamin E palmitate		[85]
Aciclovir	Lukowski	[24,26]
Prednisolone		[37,61]
Tetracaine	Mehnert	[61,68]
Etomidate		[53,61,68]
Cyclosporin		[60]
Sunscreens	Müller	[84]
Nimesulide	Patravale	[126]
3′-Azido-3′deoxythymidine palmitate	Phillips	[19,20]
Azido thymidine palmitate		[21]
Oxazepam Diazepam Cortisone Betamethasone valerate Prednisolone Retinol Menadione Ubidecarenone	Westesen	[52]
Camptothecin	Yang	[22,23]
Piribedil	Yazan	[28]

cally polydisperse lipids such those used in cosmetics showed very good drug incorporation capacities.

Crystalline structure – of course related to the chemical nature of the lipid – is a key factor to decide in determining whether a drug will be expelled or firmly incorporated in the long-term. Therefore, for a controlled optimization of drug incorporation and drug loading, intensive characterization of the physical state of the lipid particles by NMR, X-ray and other new techniques in this area such as ESR is highly essential (cf. Section 5).

The polymorphic form is also a parameter determining drug incorporation. Crystallization of the lipid in nanoparticles is different to the bulk material, lipid nanoparticles recrystallize at least partially in the α-form, whereas bulk lipids tend to recrystallize preferentially in the β'-modification and transforming rapidly into the β-form [62]. With increasing formation of the more stable modifications the lattice is getting more perfect and the number of imperfections decreases, that means formation of β'/β_i-modifications promotes drug expulsion. In general the transformation is slower for long-chain than for short-chain triglycerides [63]. An optimal SLN carrier can be produced in a controlled way when a certain fraction of α-form can be created and preserved during the storage time. By doing this the normal SLN carrier transforms to an intelligent drug delivery system by having a built-in trigger mechanism to initiate transformation from α- to β-forms and consequently controlled drug release [64,65]. Triggering factors for the lipid transformation are, e.g. temperature and water loss of the SLN dispersion, e.g. after topical administration (cf. Section 8 below).

4. Drug release from SLN

As can be seen from Table 1 there are many studies dealing with drug incorporation, however, there are distinctly less data available about drug release [23,37,66], especially information about the release mechanisms. Most of the data about in vitro drug release mechanisms were generated by Mehnert et al. studying the model drugs tetracaine, etomidate and prednisolone [34,37,53,54,67,68].

A major problem during the work with lipid nanopellets was the burst release observed with these systems. A similar burst release was obtained when incorporating tetracaine and etomidate into SLN independent on the production method (hot vs. cold homogenization) [69]. A prolonged drug release was first obtained when studying the incorporation of prednisolone. This demonstrated the principle suitability of the SLN system for prolonged drug release [37]. Even more important it was possible to modify the release profiles as a function of lipid matrix, surfactant concentration and production parameters (e.g. temperature) [37,67]. In vitro drug release could be achieved for up to 5–7 weeks. The profiles could be modulated showing prolonged release without any burst at all, but also generating systems with different percentages of burst followed by prolonged release (Fig. 2a,b). The burst can be exploited to deliver an initial dose when desired.

It is highly important that it could be shown that the release profiles are not or only slightly affected by the particle size, dominant factors for the shape of the profiles are the production parameters (surfactant concentration, temperature) and also the nature of the lipid matrix. The profiles obtained in Fig. 2 could be explained by partitioning effects of the drug between the melted lipid phase and the aqueous surfactant phase during particle production. During particle production by the hot homogenization technique, drug partitions from the liquid oil phase to the aqueous water phase (Fig. 3). The amount of drug partitioning to the water phase will increase with the solubility of the drug in the water phase, that means with increasing temperature of the aqueous phase and increasing surfactant concentration. The higher the temperature and surfactant concentration, the greater is the saturation solubility of the drug in the water phase. During the cooling of the produced O/W nanoemulsion the solubility of the drug in the water phase decreases continuously with decreasing temperature of the water phase, that means a re-partitioning of the drug into the lipid phase occurs. When reaching the recrystallization temperature of the lipid, a solid lipid core starts forming including the drug which is present at this temperature in this lipid phase. Reducing the temperature of the dispersion

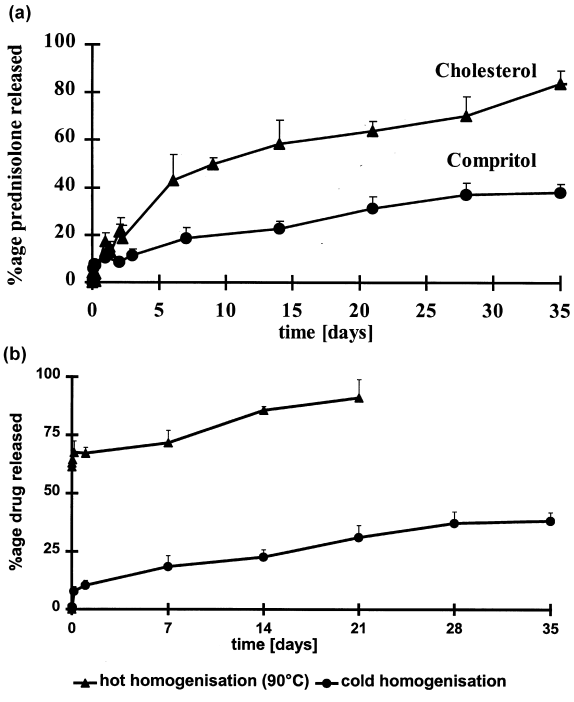

Fig. 2. (a) In vitro release profiles of prednisolone from SLN made from different lipids (compritol, cholesterol), but produced with the identical method (hot homogenization technique) (modified after [68]). (b) In vitro release profiles of prednisolone from compritol SLN produced by the hot homogenization technique (upper) and by the cold homogenization technique (lower) (modified after [37]).

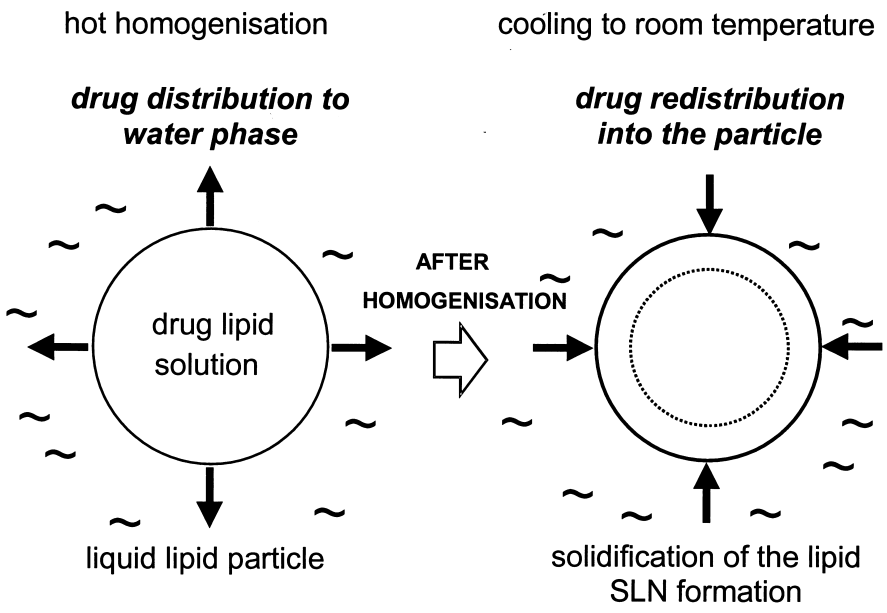

Fig. 3. Partitioning effects on drug during the production of SLN by the hot homogenization technique. Left: Partitioning of drug from the lipid phase to the water phase at increased temperature. Right: Re-partitioning of the drug to the lipid phase during cooling of the produced O/W nanoemulsion (modified after [37]).

further increases the pressure on the drug because of its reduced solubility in water to further re-partition into the lipid phase. The already crystallized core is not accessible anymore for the drug, consequently the drug concentrates in the still liquid outer shell of the SLN and/or on the surface of the particles. The amount of drug in the outer shell and on the particle surface is released in the form of a burst, the drug incorporated into the particle core is released in a prolonged way. Therefore, the extent of burst release can be controlled via the solubility of the drug in the water phase during production, that means via the temperature employed and the surfactant concentration used. Higher temperatures and higher surfactant concentrations increase the burst, production at room temperature avoids partitioning of drug into the water phase and subsequent re-partitioning to the oil phase, thus showing no burst at all (Fig. 2b). To avoid or minimize the burst, SLN can be produced surfactant free or using surfactants which are not able to solubilize the drug. Fig. 4 shows the extent of burst as a function of production temperature and surfactant concentration. No burst occurs at room temperature and 0% surfactant, the burst increases with increasing temperature and also with increasing surfactant concentration at a given temperature.

Based on the data published by the group of Mehnert [37,61,67,69] three drug incorporation models resulted:

1. solid solution model;
2. core-shell model, drug-enriched shell;
3. core-shell model, drug-enriched core.

The SLN matrix is a solid solution (i.e. drug molecularly dispersed in the lipid matrix) when the particles are produced by the cold homogenization technique and using no surfactant or no drug-solubilizing surfactant. The core-shell model with a drug-enriched shell will be obtained when performing the production as described in Fig. 3, that means re-partitioning of the drug during cooling. A drug-enriched core will be found in case the drug precipitates first before the lipid recrystallizes. This should be obtained when dissolving a drug (e.g. prednisolone) in the lipid melt at or close to its saturation solubility [67]. Cooling of the nanoemulsion will lead to a supersaturation of drug in the melted lipid and subsequently to drug crystallization prior to lipid crystallization. Further cooling will finally lead to the recrystallization of the lipid surrounding the

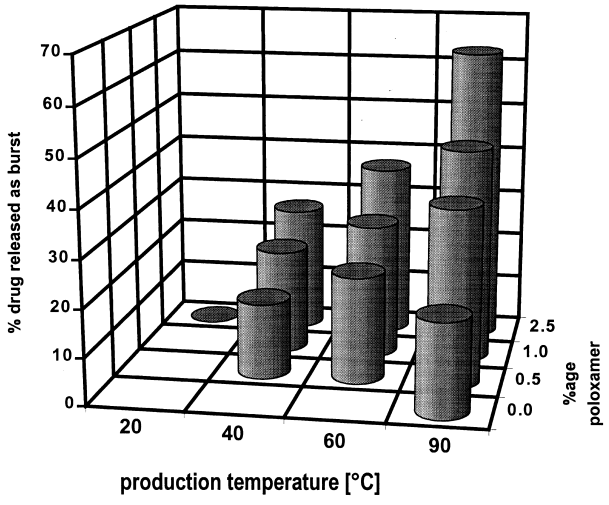

Fig. 4. Extent of burst release from prednisolone-loaded SLN as a function of production temperature and surfactant concentration. The burst release was not a function of particle size (modified after [37]).

drug core as a membrane. This lipid membrane will contain only drug in such a concentration corresponding to the saturation solubility of the drug at the recrystallization temperature of the lipid. That means it will result in a drug-enriched core surrounded by a lipid shell (Fig. 5).

5. Analytical characterization of SLN

As described before, SLN are made by homogenizing an aqueous dispersion of lipids and emulsifiers. An adequate characterization of the resulting dispersion is a prerequisite for the control of the quality of the product. Characterization of SLN is a serious challenge due to the small size of the particles and the complexity of the system, which includes also dynamic phenomena. Several parameters have to be considered which have direct impact on the stability and release kinetics:

1. particle size and zeta potential;
2. degree of crystallinity and lipid modification;
3. co-existence of additional colloidal structures (micelles, liposomes, supercooled melts, drug-nanoparticles) and dynamic phenomena.

5.1. Measurement of the particle size and zeta potential

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

PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 μm. This means PCS is a good tool to characterize nanoparticles, but it is not able for the detection of larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependency of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. The development of phase-sensitive-intensity-difference-scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. However, despite this progress, it is highly recommended to use PCS and LD simultaneously. It should be kept in mind, that both methods are not 'measuring' particle sizes. Rather they detect light scattering effects which are used to calculate particle sizes. For example, uncertainties may result from nonspherical particle shapes. Platelet structures commonly occur during lipid crystallization [70] and have been also suggested in the SLN literature [9]. Furthermore, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication about the presence and the character of microparticulates (microparticles of unit form or microparticles consisting of aggregates of smaller particles). Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artifacts which may be caused by the sample preparation. For example, solvent removal may cause modification changes which will influence the particle shape [70]. The same cautionary note applies for atomic force microscopy (AFM), because an immobilization of the SLN is required to assess their shape by the very tiny AFM tip.

Rapid progress in the development of field-flow-fractionation (FFF) has been observed during the last years. The separation principle of FFF is based on the different effect of a perpendicular applied field on particles in a laminar flow [71–74]. The separation principle corresponds to the nature of the perpendicular field and may for example be based on

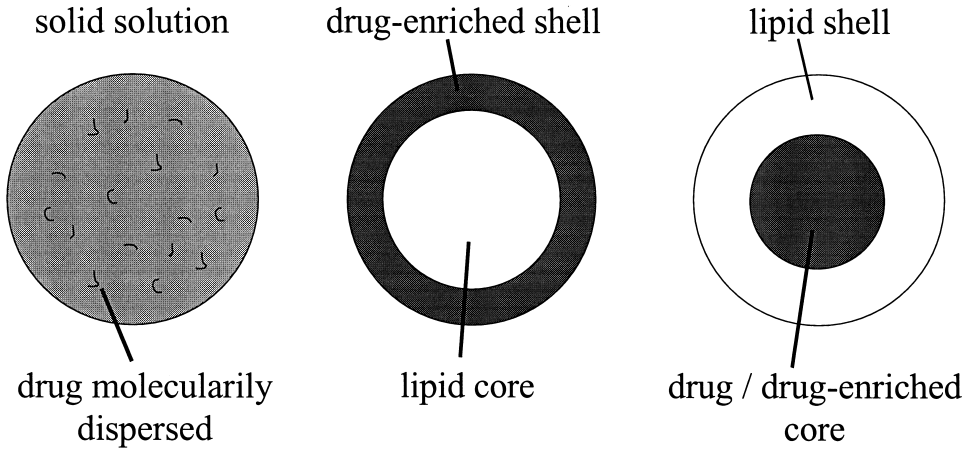

Fig. 5. Three drug incorporation models (solid solution model (left), core-shell models with drug-enriched shell (middle) and drug-enriched core (right)).

different mass (sedimentation-FFF), size (cross-flow-FFF), charge (electric-field-FFF). A combination of different FFF-separation principles may give unique resolution. A certain advantage of FFF over PCS is the high resolution of small particle size differences. Pilot studies with lattices of different size demonstrate that particles with a size difference of 30 nm are well resolved. Furthermore, FFF leads to a separation of the particles which means that the separated particles may be subjected to further characterization. The high dilution of the sample by FFF may cause potential problems because it may disturb the sample characteriztics (e.g. dilution with pure water may cause removal of the surfactant from the particle surface). Current studies investigate the influence of the dilution media on the particle characteriztics. Due to the advantages of FFF and the development of commercial FFF-product lines it can be anticipated that FFF will be a key tool for the characterization of colloidal dispersions like SLN in the future.

The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersion [75]. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. However, this rule cannot not strictly applied for systems which contain steric stabilizers, because the adsorption of steric stabilizer will decrease the zeta potential due the shift in the shear plane of the particle (for detailed discussion see [75]).

Degree of crystallinity and lipid modification: Particle size analyzis is a necessary, but not a sufficient step to characterize SLN quality. Special attention must be paid to the characterization of the degree of lipid crystallinity and the modification of the lipid, because these parameters are strongly correlated with drug incorporation and release rates. Thermodynamic stability and lipid packing density increase, and drug incorporation rates decrease in the following order:

supercooled melt $<$ α-modification
$<$ β'-modification $<$ β-modification

Due to the small size of the particles and the presence of emulsifiers, lipid crystallization and modification changes might be highly retarded. For example, it has been observed, that polymorphic transitions might occur very slowly and that Dynasan 112-SLN – if crystallization is not artificially induced – may remain as a supercooled melt over several months [62].

Differential scanning calorimetry (DSC) and X-ray scattering are widely used to investigate the status of the lipid. DSC uses the fact that different lipid modifications possess different melting points and melting enthalpies. By means of X-ray scattering it is possible to assess the length of the long and short spacings of the lipid lattice. It is highly recommended to measure the SLN dispersion themselves because solvent removal will lead to modification changes. Sensitivity problems and long measurement times of conventional X-ray sources might be overcome by synchrotron irradiation [62]. However, this source has limited accessibility for most investigators.

Infrared and Raman spectroscopy are useful tools to investigate structural properties of lipids [70]. However, their potential to characterize SLN dispersions remains to be investigated.

5.2. Co-existence of additional colloidal structures (micelles, liposomes, supercooled melts, drug-nanoparticles) and dynamic phenomena

The magnetic resonance techniques, NMR and ESR, are powerful tools to investigate dynamic phenomena and the characteriztics of nanocompartments in colloidal lipid dispersions. Due to the non-invasiveness of both methods, repeated measurements of the same sample are possible.

NMR active nuclei of interest are ^{1}H, ^{13}C, ^{19}F and ^{35}P. Due to the different chemical shifts it is possible to attribute the NMR signals to particular molecules or their segments. For example, lipid methyl protons give signals at 0.9 ppm while protons of the polyethyleneglycol chains give signals at 3.7 ppm. Simple ^{1}H-spectroscopy permits an easy and rapid detection of supercooled melts [76]. It permits also the characterization of liquid nanocompartments in recently developed lipid particles, which are made of blends from solid and liquid lipids [57,65]. This method is based on the different proton relaxation times in the liquid and semisolid/solid state. Protons in the liquid state give sharp signals with high signal amplitudes, while semisolid/solid protons give weak and broad NMR signals under these circumstances. The great potential of NMR with its variety of different approaches (solid-state-NMR, determination of self-diffusion coefficients etc.) has scarcely been used in the SLN field, although it will provide unique insights into the structure and dynamics of SLN dispersions.

ESR requires the addition of paramagnetic spin probes to investigate SLN dispersions. A large variety of spin probes is commercially available. The corresponding ESR spectra give information about the microviscosity and micropolarity. ESR permits the direct, repeatable and non-invasive characterization of the distribution of the spin probe between the aqueous and the lipid phase. Experimental results demonstrate that storage induced crystallization of SLN leads to an expulsion of the probe out of the lipid into the aqueous phase [77]. Furthermore, using an ascorbic acid reduction assay it is possible to monitor the time scale of the exchange between the aqueous and the lipid phase. The development of low-frequency ESR permits non-invasive measurements on small mammals. ESR spectroscopy and imaging will give new insights about the fate of SLN in vivo.

6. Sterilization of SLN

Sterilization of SLN is an issue in the case of pulmonary or parenteral administration. For lecithin-stabilized SLN it

could be shown that autoclaving is possible [53]. The SLN melt during the autoclaving and recrystallize during the cooling down. However, autoclaving is not possible when a certain structure has been given to the SLN in a controlled way by adjusting the production parameters (cf. Section 4). This special structure – leading to the desired modulated release profile – would be lost when the particles melt again during the autoclaving and recrystallize in a non-controlled way.

Autoclaving at 121°C cannot be performed when using sterically stabilizing polymers, e.g. poloxamer series [15,53,54]. The autoclaving temperature seems to be too close to the critical flocculation temperature (CFT) of the polymers, at least the polymer adsorption layer seems partially to collapse leading to insufficient stabilization and particle aggregation. This can be avoided by reducing the autoclaving temperature (e.g. 121° to 110°C, but simultaneously prolonging the autoclaving time).

The physical stability during autoclaving cannot be stated in a general manner, it depends very much on the composition of the SLN formulation. Therefore, the above two statements can only be seen as a rough guideline.

SLN dispersions can also be sterilized by filtration similar to emulsions for parenteral nutrition. It is highly important to filter them in the liquid state, this allows even particles with a size larger than the pores in the filter to be filtered [78]. This technology is well known from parenteral emulsions and easy to apply to SLN. Alternatively, the SLN can be produced aseptically, again identical to parenteral emulsions.

To sum up, SLN dispersions can be sterilized or prepared aseptically using already established techniques in the pharmaceutical industry.

7. Toxicity and status of excipients

Toxicity and the status of excipients are a major issue for the use of a delivery system. One can have a very neat delivery system, but if there is a necessity to undertake toxicity studies this will be a major obstacle for its introduction into the clinic and the pharmaceutical market.

The status of excipients for SLN has to be discussed as a function of the administration routes. Topical and oral administration of SLN are absolutely non-problematic regarding the excipients. For topical SLN, all excipients can be used which are currently employed for the formulation of pharmaceutical and cosmetic ointments and creams. For oral SLN, all the lipids and surfactants used in traditional dosage forms such as tablets, pellets and capsules can be exploited. In addition all compounds of GRAS status or accepted GRAS status can be employed. There is also the option to use lipids and surfactants from the food industry. Of course, use in the food industry does not allow directly its use in pharmaceutical products. However, the toxicity material available for the food area can be used for submission to the pharmaceutical regulatory authorities, that means it is a relatively easy case.

The situation is slightly different for parenteral administration. Up to now there are no products on the market containing solid lipid particles for parenteral injection. Therefore, a toxicity study would be necessary. However, one can use glycerides composed of fatty acids which are contained in oils of parenteral fat emulsions. Therefore, no toxic effects are expected from the SLN degradation products. In addition, one has to consider that a toxicity study with the parenteral new product has to be made anyway, that means the lipid itself might contribute very little to the total costs of the study required. To formulate parenteral SLN, surfactants accepted for parenteral administration can be used, that means, e.g. lecithin, Tween 80, Poloxamer 188, PVP, sodium glycocholate, Span 85 etc. For the intravenous route it is recommended to focus on the i.v. accepted surfactants (e.g. lecithin, Tween 80, Poloxamer 188, sodium glycocholate).

The good tolerability of SLN has been confirmed in both in vitro and in vivo studies. In cell cultures SLN were compared with polyester nanoparticles (PLA, PLA/GA). At 0.5% of PLA/GA nanoparticles 100% of the cells died, at 10% SLN in the cell suspension the viability remained at around 80% [6,79].

Good tolerability was also found when performing bolus injections into mice. The administered dose was 1.33 g lipid/kg body weight, 6 bolus injections were performed. There was no acute toxicity, for cetyl palmitate, no increase in liver and spleen weight was observed. Histopathology was also performed giving no critical evidence, for details compare [46,80]. SLN were also injected intravenously in studies performed by other research groups [22,81].

8. SLN for topical application

An area of big potential for SLN and with a short time-to-market are topical products based on the SLN technology, that means pharmaceutical but also cosmetic formulations. SLN are considered as being the next generation of delivery system after liposomes [82,83]. Similar to liposomes they are composed of well-tolerated excipients and due to their small particle size they possess similar adhesive properties leading to film formation on the skin. Distinct advantages of SLN are their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition and the possibility to modulate drug release.

Apart from technological benefits the solid state of SLN has also an advantage with regard to product registration for pharmaceuticals but also cosmetics. For example, in Japan even for cosmetic products it needs to be proven that liposomes are present not only qualitatively but also quantitatively. For liposomes a qualitative proof is easy by electron microscopy, however it is extremely difficult to quantify them and to show that they are still present in a sufficient

amount (e.g. > 90%) during the storage of the product. This is a major obstacle to the introduction of liposomal cosmetic products to the potentially lucrative Japanese market. In contrast to this, quantitative analyzis of SLN in creams is very simple and straightforward. Many cream bases do not exhibit a melting peak below 100°C, that means the content of SLN in a cream can be quantified by their melting peak determined by DSC. The stability during storage can easily be monitored just by looking at the change in melting enthalpy. Analyzis is even possible in cases where a cream contains a fraction which melts below 100°C. It is no problem if the peaks are separated. If there is an overlapping, one can determine the total melting energy as a function of time. This special property of SLN opens new markets for topical products containing colloidal carriers for active ingredients.

Adhesiveness is a general property of very fine particles, that means nanoparticles of different kinds. A nice example from practical life is iced sugar which sticks much better to bakery products than crystalline sugar. Similar to liposomes the SLN are forming adhesive films onto the skin [82,83]. Previously it was assumed that SLN would be forming films of densely packed spheres, recent results suggest that under the pressure of application the spheres form a coherent film [84]. Such a lipid film formation will be able to restore a damaged protective lipid film on the skin. In addition such a film can have an occlusive effect.

Such an occlusive effect was shown by in vitro measurements [31,82,83]. Data obtained from porcine skin support this. SLN were incorporated into a commercial cosmetic O/W cream and tested in the Franz cell regarding their effect on drug penetration but also occlusiveness. Cream base and SLN-containing cream base were applied to the skin and analyzis was performed after 24 h of incubation. The occlusive effects were assessed by staining vertical skin slices by hematoxylin/eosin. Fig. 6 shows the microscopic pictures of untreated skin, skin treated with cream base and with SLN-containing cream base. Untreated skin showed a compact stratum corneum with corneocyte layers closely conjuncted. Application of the conventional SLN-free cream only slightly changed the structure. A different result was obtained for the SLN cream, the stratum corneum appeared swollen and overall thickness had increased.

Of course it is difficult to make a quantitative assessment based on microscopic skin slices. In addition, transepidermal water loss (TEWL) was determined. The most pronounced – but not significantly different – effect was obtained by SLN. The discussion about the in vivo occlusive effect of SLN is somewhat controversial which is partially attributed to the differences in the formulations tested. From the results obtained to date it can be concluded that SLN added to a formulation do not have an additional occlusive effect when the formulation itself is already highly occlusive (e.g. petrolatum or night creams of O/W type being already highly occlusive). An enhancement of occlusiveness can be achieved by adding SLN of suitable composition to light O/W day creams, thus increasing the moisturing effect without having the glossiness of a night cream.

The only parameter to assess the ability of a delivery system is its effect on drug/active ingredient penetration into skin and consequently its therapeutic effect and in cosmetic applications the effect on skin appearance. A range of cosmetic ingredients like coenzyme Q10, vitamin E and its derivatives and retinol [55,56,58,65,85,86] have been incorporated into SLN. The skin caring properties of a commercial retinol cream have been compared to the same cream containing retinol-loaded SLN, reference was

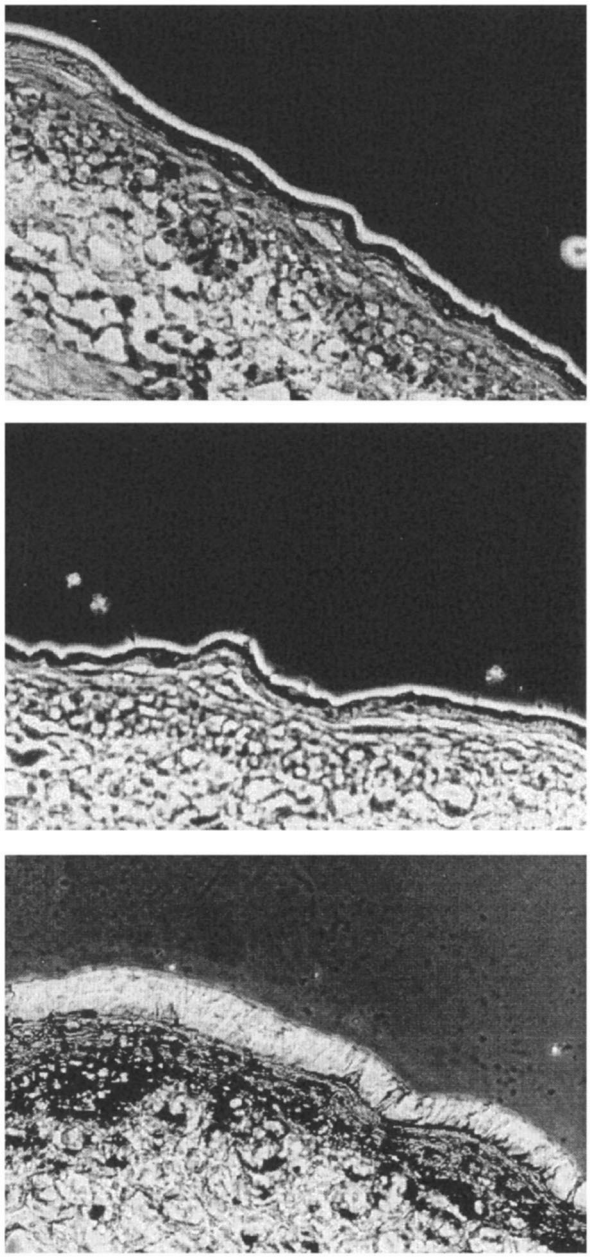

Fig. 6. Microscopic pictures of untreated porcine skin (upper), skin treated with cream base (middle) and with SLN-containing cream base (lower) (after [57] with permission).

untreated skin. Parameters assessed were skin elasticity, moisture state and skin roughness as standard read out parameters. The moisture level of the SLN-containing formulation was raised by 33% (SLN-free base 23%) after a 1-week period of treatment compared to untreated skin. Besides this the cream containing retinol-loaded SLN improved the skin smoothness by 10.3%, the SLN-free cream achieved only 4.1% (Fig. 7).

Incorporation of active ingredients into the solid SLN matrix protected them against chemical degradation. Stability enhancement was reported for coenzyme Q10 [58] and also for the very sensitive retinol [57,86]. Cosmetic products containing retinol, which recently entered the market, have to be produced applying special, cost-intensive safety conditions (e.g. yellow light during production, protective gassing using inert or noble gas) and also special, less aesthetic packing (e.g. aluminium instead of polyethylene tube). The stabilization of retinol incorporated into SLN offers more cost-effective ways of production and the use of more appealing, consumer-orientated packaging.

A major step forward was the development of the 'intelligent' SLN (ISLN) which can be exploited for topical but also for all other delivery routes. Intelligent SLN means that the SLN releases in a controlled way the incorporated drug/active ingredient after it receives a triggering impulse. Such triggering impulses are the increase in temperature or the loss of water from an SLN dispersion or an SLN-containing cream. As mentioned above it is well known from the literature that formation of the more stable lipid modifications leads to drug expulsion, that means the release of the drug from the SLN. This natural effect can be exploited in a controlled way by setting this triggering effect when release of the drug is desired. It is also known that a certain fraction of α-modification and imperfections in the crystal lattice promote drug inclusion. That means during the storage of the SLN formulation the lipid carrier should be preserved in its high energy modifications, when it is applied to the skin or administered to the body transformation from α to the more stable β'-/β_i and/or β-modifications will be triggered. This transformation leads to a more ordered structure

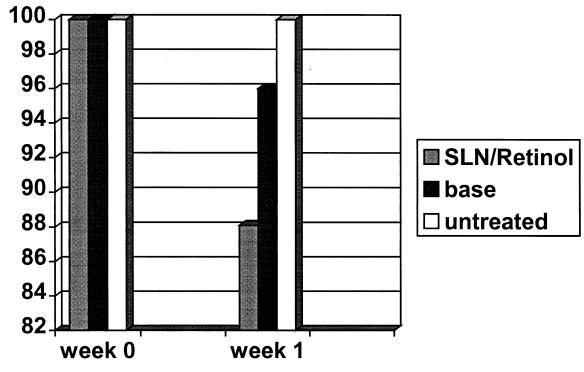

Fig. 7. Microtopographical evaluation of retinol/SLN, cream base and untreated. The degree of reduction expresses the degree of roughness reduction as a mean value of 24 measurements.

and less imperfections, thus leading consequently to the expulsion or release of the drug from the carrier. This effect was exploited for the controlled release of retinol from SLN incorporated into creams and hydrogels [54,57].

A completely new, recently discovered area of application is the use of SLN in sun-protective creams. Due to the reduction of the protective ozone layer there is a steep increase in skin cancer, melanoma is the form of cancer showing the strongest increase world-wide, especially in countries like Australia [84]. Side effects of molecular sunscreens (UV-blockers) are penetration into the skin and consequently irritation. Particulate sunscreens like titanium dioxide were also found to possibly penetrate into the skin. This can be avoided or minimized by entrapping molecular and particulate sunscreens into the SLN matrix. Surprisingly it was found that the SLN themselves have also a sun-protective effect [84]. Due to their particulate character they are protective due to scattering of UV-light (similar to titanium dioxide). In addition it was found that molecular sunscreens and SLN in combination show a synergistic effect. Molecular sunscreens are much more effective after incorporation into SLN and at the same time side effects are reduced. This opens the perspective to a new class of sun-protective creams.

9. SLN for oral administration

Oral administration of SLN is possible as aqueous dispersion or alternatively after transform into a traditional dosage form, i.e. tablets, pellets, capsules or powders in sachets [87]. For the production of tablets the aqueous SLN dispersion can be used instead of a granulation fluid in the granulation process. Alternatively SLN can be transferred to a powder (e.g. by spray-drying) and added to the tabletting powder mixture. For the production of pellets the SLN dispersion can be used as wetting agent in the extrusion process [88]. SLN powders can be used for the filling of hard gelatine capsules, alternatively, the SLN can be produced directly in liquid PEG 600 and filled into soft gelatine capsules. Sachets are also possible using spray-dried or lyophilized powders. In both cases it is beneficial to have a higher solid content to avoid the necessity of having to remove too much water. For cost reasons spray-drying might be the preferred method for transferring SLN dispersions into powders.

An example for orally administered SLN are Camptothecin (CA)-loaded particles [23]. The CA-SLN were produced from stearic acid and stabilized with Poloxamer 188. Particle size was 197 nm, zeta potential −69 mV, the encapsulation efficiency of CA was 99.6%, in vitro drug release was achieved up to a week. The plasma levels and body distribution were determined after administration of CA-SLN suspension vs. 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 incorporation of CA into SLN prevented it 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.

The bioavailability and plasma profiles of orally administered piribedil-loaded SLN were studied by Yazan et al. [28]. Incorporation of piribedil into lipid particles increased bioavailability and prolonged the plasma levels. This is in agreement with the data for CA, in addition the prolonged blood levels suggest also some adhesion of the particles to the mucosal wall. It opens the perspective to develop mucoadhesive SLN.

Cyclosporin has also been formulated as SLN. A loading capacity of 20% cyclosporin in the lipid Imwitor 900 was achieved. The SLN were stabilized using a mixture of Tagat S and sodium cholate [59,60]. The present situation regarding cyclosporin formulations on the market is:

1. the old Sandimmun shows no nephrotoxic plasma peak, but has a high variability in the bioavailability/blood levels;
2. the new Sandimmun microemulsion shows reproducible plasma profiles, but exhibits a peak above 1000 ng/ml being problematic regarding toxic side effects.

Target of the SLN formulation was to combine the advantages of the old and new Sandimmun formulations, that means achieving good reproducible prolonged blood levels and simultaneously having no nephrotoxic plasma peak. An in vivo study was performed (three pigs) comparing the cyclosporin SLN dispersion with the commercial product Sandimmun Neoral/Optoral. In the pigs the Sandimmun Neoral/Optoral showed the typical blood profile well-known with the typical initial peak and little variation, the aqueous SLN dispersion showed no peak above 1000 ng/ml and similar low variations in the blood levels combined with prolonged release [60].

10. Pulmonary administration of SLN

Until now the SLN system has not yet been fully exploited for pulmonary drug delivery, very little has been published in this area [89]. To demonstrate the suitability in principle of SLN for pulmonary delivery, aqueous SLN dispersions were nebulized with a Pari-Boy, the aerosol droplets were collected and the size of SLN analyzed. It could be shown that the particle size distributions of SLN before nebulization and after nebulization were almost identical, only very little aggregation could be detected which is of no significance for pulmonary administration (Fig. 8).

Alternatively SLN powders might be used in dry powder inhalers. SLN could be spray-dried using, e.g. lactose as excipient in the spray-drying process.

Basic advantages of drug release from SLN in the lung are control of the release profile, achievement of a prolonged release and having a faster degradation compared to particles made from some polymeric materials. In addition, SLN proved to possess a high tolerability, one might also consider drug targeting to lung macrophages. Particles in the lung are easily accessed by lung macrophages, that means one could use the SLN system for treating infections of the MPS system. In particular parasites such as mycobacteria are difficult to reach with a normal treatment. Within the MPS macrophages, liver and spleen macrophages are more accessible than the parasites in the lung macrophages. To sum up, there could be a huge potential waiting to be exploited.

11. SLN for parenteral administration

Basically SLN can be used for all parenteral applications suitable for polymeric nanoparticles. This ranges from intraarticular to intravenous administration. Studies using intravenously administered SLN have been performed by various groups [22,66]. Gasco et al. produced stealth and non-stealth solid lipid nanoparticles and studied them in cultures of macrophages [16,17] and also after loading them with Paclitaxel in vivo. The i.v. administered SLN led to higher and prolonged plasma levels of Paclitaxel. Interestingly both non-stealth and stealth SLN showed a similar low uptake by the liver and the spleen macrophages, a very interesting point was the increased uptake observed in the brain [81]. This study demonstrates nicely the potential of SLN to achieve prolonged drug plasma levels. The observed similar low uptake by the liver and spleen macrophages might be explained by a similar low surface hydrophobicity of both types of particles avoiding the adsorption of any blood proteins mediating the uptake by liver and spleen macrophages. The uptake of the SLN by the brain might be explained by adsorption of a blood protein mediat-

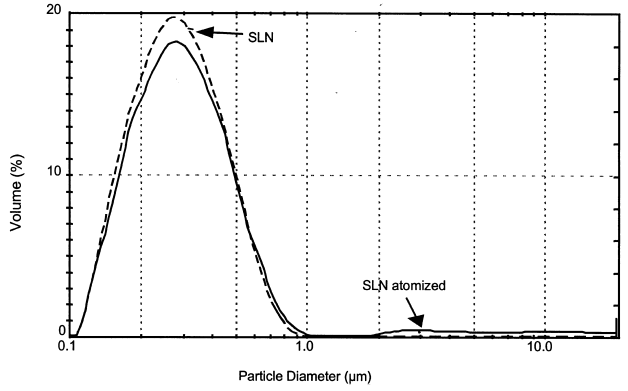

Fig. 8. Particle size distribution of SLN before nebulization and after nebulization with a Pari-Boy (laser diffractometry data, Coulter LS 230) (after [89]).

ing the adherence to the endothelial cells of the blood brain barrier, an effect described previously by Kreuter [90,91].

These data are very well in agreement with body distribution data of Camptothecin-loaded SLN [22]. The authors found also an increased uptake in some organs, especially in the brain. The SLN employed were composed of stearic acid, soybean lecithin and Poloxamer 188 and prepared by high pressure homogenization.

There are many other parenteral applications which appear to be feasible and of therapeutical value, an example is treatment of arthritis of joints. In the 1980s, Boots PLC (Nottingham, UK) was working on a polymeric microparticulate delivery system for corticoids to treat arthritis. The microparticles loaded with a corticoid were to be injected into the joint and the macrophages would phagocytose the particles. The drug released inside the macrophages would reduce their hyperactivity which was causing the inflammation. Unfortunately, the polymer particles proved to be cytotoxic in the concentrations necessary for the treatment [5]. As an alternative the lipophilic corticoids could be incorporated into SLN. To sum up, SLN can be used parenterally everywhere where polymeric particles can be employed.

12. SLN as potential new adjuvant for vaccines

Adjuvants are used in vaccination to enhance the immune response. The more safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required [92]. Increase the amount of antigen delivered is not a solution because this also increases the costs. Especially with regard to the third world such a solution prohibits the desired broad vaccinations in these countries. The side effects of Freund's complete adjuvant (FCA) and Freund's incomplete adjuvant (FIA) are too strong to be employed, but Freund's complete adjuvant is still considered as a 'gold standard' when developing new adjuvants. The adjuvant frequently used for many years consist of aluminium hydroxide particles, however they can also exhibit side effects. New developments in the adjuvant area are emulsion systems, for example SAF 1 and MF 59 [92]. They are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLN will be degraded more slowly providing a longer lasting exposure to the immune system. Degradation can be slowed down even more when using sterically stabilizing surfactants that hinder the anchoring of enzyme complexes [93–95]. In a first study SLN have been tested as adjuvant in comparison to FIA in sheep. The two unoptimized SLN formulations exhibited 43 and 73% of the immune response (antibody titer) of FIA investigated as standard [92]. These data are promising and currently the SLN are being optimized regarding their surface properties to give a maximum immune response. Advantages compared to traditional adjuvants are the biodegradation of SLN and their good tolerability by the body.

13. Clinical batch production and large scale production of SLN

An important step towards a pharmaceutical product are first human trials, a prerequisite for this is the availability of a GMP production unit to provide first clinical batches. A GMP production unit was developed to produce clinical batches between 2 kg up to a maximum of 10 kg SLN dispersion [58,96,97]. Such a unit exists at the company Pharmatec (Milan, Italy) and will be very soon available also at SkyePharma (Muttenz/Basel, Switzerland).

For topical products, i.e. creams containing SLN, a batch size of approximately 50 kg to a few hundred kg is required. For this batch size a production line was developed having a capacity of 50 kg SLN dispersion/h [97]. It consists of two homogenizers being placed in series, that means instead of running a dispersion twice through one homogenizer (two homogenization cycles), the product is run continuously through two homogenizers placed in series (APV LAB60, Gaulin 5.5). Such solutions are possible because it is low-cost equipment from the shelf. The size of the batch is given by the size of the feeding vessel and product container, respectively.

Meanwhile a production line has been designed running on a continuous basis and having a capacity of 150 kg/h. The melted lipid and the hot aqueous surfactant solution are mixed by static blenders instead of mixing them batchwise in a large feeding container. A basic advantage of the homogenizers employed is their ability to be cleaned in place (CIP) and sterilized in place (SIP). The homogenizers can be sterilized by streaming steam, the product containers (e.g. employed for cosmetic batches) can be autoclaved.

14. Perspectives of the delivery system SLN

The last article providing an overview of SLN technology has been written by our group for this journal in 1995 and been published in the special theme issue 'colloidal drug carriers' [10]. During the last 5 years the number of research groups working with SLN has distinctly increased as well as the number of publications in this area. It reflects that more and more scientists in academia have realised the potential of the SLN system and started to develop it. Research groups are placed all over the world in countries like Germany, Canada, China, but also countries such as Slovenia and Poland. For further information about their activities the reader is referred to selected additional publications [98–126].

There is no break through for a delivery system if only academic research groups are developing it. Success can only be possible if also pharmaceutical industry takes up developments. To guarantee a broad application of a carrier system it is highly desirable that companies specialized in drug delivery systems engage themselves in the new technology. Drug delivery companies develop pharmaceutical

solutions adapted to the needs of many different pharmaceutical companies, that means the technology will spread to many companies and not only be localized inside one company using this new technology just limited to their own drugs. In 1999, the complete patent rights for production of SLN by high pressure homogenization have been acquired by SkyePharma AG (Muttenz, Switzerland), a drug delivery company specialized in oral delivery, but also having the potential for parenteral production. The company Vectorpharma (Trieste, Italy) is developing SLN produced by microemulsion technology. That means the SLN system has successfully found its way to pharmaceutical industry, a prerequisite for the introduction of new SLN-based formulations into clinic and the pharmaceutical market.

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