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Research paper

Solid lipid nanoparticles (SLN) for controlled drug delivery – Drug release and release mechanism

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Abstract

Solid lipid nanoparticles (SLN) are particulate systems for parenteral drug administration with mean particle diameters ranging from 50 up to 1000 nm. The model drugs tetracaine, etomidate and prednisolone were incorporated (1, 5 and 10%) to study the drug load, effect of drug incorporation on the structure of the lipid matrix and the release profiles and mechanism. SLN were produced by high pressure homogenization of aqueous surfactant solutions containing the drug-loaded lipids in the melted or in the solid state (500/1500 bar, 3/10 cycles). In case of tetracaine and etomidate, high drug loadings up to 10% could be achieved when using Compritol 888 ATO and Dynasan 112 as matrix material. The melting behavior of the drug loaded particles revealed that little or no interactions between drug and lipid occured. A burst drug release (100% release $<$ 1 min) was observed with tetracaine and etomidate SLN, which was attributed to the large surface area of the nanoparticles and drug enrichment in the outer shell of the particles. In contrast, prednisolone loaded SLN showed a distinctly prolonged release over a monitored period of 5 weeks. Depending on the chemical nature of the lipid matrix, 83.8 and 37.1% drug were released (cholesterol and compritol, respectively). These results demonstrate the principle suitability of SLN as a prolonged release formulation for lipophilic drugs. © 1998 Elsevier Science B.V.

Keywords: Solid lipid nanoparticles; Drug incorporation; Intravenous drug delivery; Crystallization

1. Introduction

Nanoparticles made from solid lipids are attracting increasing attention as colloidal drug carriers for i.v. application [1–3]. The nanoparticles are in the submicron size range (50–1000 nm) and they are composed of physiological lipids. At room temperature the particles are in the solid state. Therefore, the mobility of incorporated drugs is reduced, which is a prerequisite for controlled drug release. They are stabilized with non-toxic surfactants like poloxamer and lecithin [4]. Due to the production by high pressure homogenization they can be produced on large industrial scale. In addition, this production method avoids the use of organic solvents. Compared to traditional carriers the SLN combine advantages of polymeric nanoparticles and o/w fat emulsions for parenteral administration.

To-date, several studies concerning optimization of production parameters [5], long term stability [6], recrystallization behaviour [7], morphological characterization [8] and in vivo toxicity [9] have been undertaken. In addition, investigations about drug incorporation and release are an important tool in the design and evaluation of a potential drug carrier system. A basic problem in early work with lipid particles in the nanometer range was the generally observed burst release of drugs, a prolonged release could not be achieved [10]. The lack of a prolonged release would severely limit the applicability of the system for drug delivery. The aim of this investigation was therefore, to assess if a prolonged release is basically possible. Tetracaine (base), etomidate (base) and prednisolone were used as lipophilic model drugs. The crystalline state of the particles was ana-

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lyzed and a mechanism suggested leading to the observed differences in release behavior of the drug-loaded particles.

2. Materials and methods

2.1. Materials

Dynasan 112 (glycerol trilaurate) was provided by Hüls AG (Witten, Germany) and Compritol 888 ATO (glycerol behenate) by Gattefossé (Weil a. R., Germany). Pluronic F 68 (poloxamer 188) was a gift from BASF AG (Luwigshafen, Germany) via the distributor Tensidchemie (Düren, Germany). Lipoid S 75 (soy lecithin) was provided by Lipoid KG (Ludwigshafen, Germany). All other chemicals (e.g. tetracaine) were purchased from Sigma (Deisenhofen, Germany).

2.2. Methods

Solid lipid nanoparticles were produced by high pressure homogenization either at increased temperature (hot homogenization technique, tetracaine and etomidate) or at room temperature (cold homogenization technique, prednisolone) [6] using a Micron LAB 40 homogenizer (APV Gaulin, Lübeck, Germany).

Hot homogenization technique: the drugs were dissolved in the melted lipid (5–10°C above the melting point) and the drug-loaded lipid dispersed in a hot aqueous surfactant solution to form a pre-emulsion, which was subsequently homogenized (500 bar, 3 cycles with poloxamer as surfactant, 1500 bar, 3 cycles with Lipoid S 75).

Cold homogenization technique: after dissolving the drug in the lipid, solidification was performed by pouring the drug-loaded lipid in liquid nitrogen. This lead to the formation of a solid solution (molecular dispersion) of the drug in the lipid matrix. The solid solution was ground, the microparticles suspended in a poloxamer solution (2.5%) and this suspension homogenized at room temperature (1500 bar, 10 cycles).

The SLN dispersions had a matrix (lipid or lipid-drug mixture) content of 5–10%, stabilized by 2.5–5% surfactant (poloxamer 188, Lipoid S 75). The drugs were generally incorporated in percentages of 1, 5 and 10%. The drug was calculated as a percentage of the solid matrix, e.g. 100 g of a 10% SLN dispersion loaded with 5% drug contained 10 g solid consisting of 9.5 g lipid and 0.5 g drug. An overview of the SLN formulations is given in Table 1.

When incorporating tetracaine and etomidate, between 90 and 100% was entrapped in the nanoparticles. Therefore, in the tables, the nominal percentages 1, 5 and 10% are quoted. For prednisolone (nominal drug percentage in the dispersion: 1%), 71% of drug was entrapped in case of the cholesterol SLN and 80% in case of Compritol SLN formulations. In case of prednisolone loaded cholesterol and Compritol SLN formulations, which were used in this investigations, the SLN contained therefore 0.71 and 0.85% drug in the matrix, respectively (Table 1).

Table 1
Overview of aqueous SLN dispersions made from Dynasan 112, Compritol and Cholesterol[a]

	Lipid content in aq. dispersion (%)	Drug content in lipid matrix		
		Tetracaine (%)	Etomidate (%)	Prednisolone (%)
Dynasan-SLN	10	1	–	–
	10	5	–	–
	10	10	–	–
	10	–	1	–
	10	–	5	–
	10	–	10	–
Compritol-SLN	10	1	–	–
	10	5	–	–
	10	10	–	–
	10	–	1	–
	10	–	5	–
	10	–	10	–
	5	–	–	0.8
Cholesterol-SLN	5	–	–	0.7

[a] The drug load is calculated as % of the lipid mass (Section 2.2).

Particle size distribution was determined by photon correlation spectroscopy (PCS) (Malvern Zetasizer IV, Malvern Instruments, UK). From the PCS data, the mean particle diameter of the bulk population and the polydispersity index (PI) of the SLN dispersions could be calculated. The percentage of incorporated drug in the lipid matrix (entrapment efficacy) was determined by filtration of the SLN dispersion using an ultrafiltration cell (Amicon, Witten, Germany) and subsequent photometric determination of the free drug in the aqueous phase (wavelengths: 307 nm for tetracaine, 242 nm for etomidate and 247 nm for prednisolone, Uvikon 940, Kontron, Eching, Germany).

Partition coefficients were determined by equilibration of drug partitioning between a water phase and a phase of melted lipid. After cooling down and solidification, the drug content was analyzed in the water phase.

Lipid microparticles were prepared by dissolving the drug in the melted lipid, pouring the molten lipid–drug solution into liquid nitrogen and subsequent grinding of the solidified mould using a mortar mill (Retsch, Haan, Germany). The particles were fractionated by sieving.

To study the drug release from SLN and from microparticles, the paddle method USP XXII was employed. In case of tetracaine and etomidate loaded SLN drug release was investigated at 37°C in phosphate–citrate buffer after Mc Ilvaine, pH 7.4. To improve the wetting of the microparticles by the dissolution medium, 0.1% poloxamer 188 was added. The release behavior of prednisolone loaded SLN was performed in distilled water, pH 5.5–6. Samples were

drawn and filtered using polyamide filters (Sartorius, Göttingen, Germany), pore size 100 nm for SLN and 200 nm for the microparticles. The filters were validated with regard to drug adsorption. Analysis was performed spectrophotometrically.

Differential Scanning Calorimetry (DSC) measurements were performed using a TA 3000 (Mettler-Toledo GmbH, Gießen, Germany) under nitrogen. Heat rate: 5°C/min (40 μl pans). The enthalpies were calculated using the Mettler software.

3. Results and discussion

3.1. Crystallinity: Tetracaine- and etomidate-loaded Dynasan SLN

Dynasan 112 SLN, loaded with either tetracaine or etomidate stabilized with Lipoid S 75, were prepared as reported previously [5] (for composition: Table 1). They remained in the liquid state after production for more than 12 months (investigated period). No melting peak was observed in the DSC diagrams. A solid matrix is however a prerequisite to adjust the release profile of a drug. Release from liquid lipid droplets (e.g. oil in water emulsions) is very fast and takes place within seconds [11].

The liquid Dynasan SLN could be transferred to a solid state by lyophilisation or by simple drying of the dispersion at air exposure. The drug-free Dynasan SLN showed a depression of the melting point to 44.7°C, compared to 46.2°C of the lipid itself (Table 2). The melting enthalpy decreased compared to the lipid from 170.3 to 116.5 J/g. Taking the enthalpy of the lipid as being 100%, this corresponded to a crystallinity of 68.4%.

The melting points of the drug-loaded SLN were below the lipid, but similar to the drug-free SLN. The melting point of the lipid was close to the theoretical value of 46.4°C for the β modification [12], the β' being 12.5°C lower [13]. Apart from the SLN loaded with 10% drug, the melting enthalpies were similar to drug-free particles (Table 2). The enthalpies were calculated using the AUC of the melting peak at ≈44°C related to total weighted-in quantity.

It is conceivable that the delay in recrystallization can be attributed to the presence of Lipoid S 75 and to the small particle size. It is reported that lecithin, as well as the dispersed state of the lipid, led to distortions of the crystalline structures [7,12,14]. This induced a depression of the melting point [16] and the recrystallization point of the SLN, which can prevent recrystallization at room temperature [7]. The effect of the surfactant on recrystallization was previously proven by producing Dynasan 112 SLN surfactant-free. The lipid was dispersed in a Tylose H300 solution leading to SLN in the solid state [15]. However, these SLN possessed a distinctly larger mean diameter of 696 nm, were very polydisperse and therefore, not considered to be suitable for i.v. injection (capillary blockade due to contamination by microparticles).

With regard to the DSC data (Table 2), it is not possible to quantify the contribution of the incorporated drug in the lipid matrix incorporated surfactant to the observed effects because the amounts of lecithin inside the particles are not known. From the SLN produced to-date, it can be concluded that in general, the delay in recrystallization increases with increasing surfactant and decreasing lipid concentration.

3.2. Crystallinity: Tetracaine- and etomidate-loaded Compritol SLN

Due to the recrystallization problems of Dynasan SLN, Compritol was chosen as lipid matrix. Compritol is composed of ~64–72% mono- and diglycerides and possesses a melting point of ~71.1°C. It is reported, that SLN, which are composed of glycerides with a heterogeneous composition,

Table 2

Melting peaks and enthalpies of air-dried Dynasan SLN, air-dried Compritol SLN and of Compritol-SLN aqueous dispersion, respectively

	Lipid	R	T 1%	T 5%	T 10%	E 1%	E 5%	E 10%
Dynasan-SLN (air-dried)								
Melting peak (°C)	46.2	44.7	46	44.8	44.3	44.9	45.2	44.1
Enthalpy (J/g)	170.3	116.5	113.9	109.2	101.9	111.8	110.1	104.4
Compritol-SLN (air-dried)								
Melting peak (°C)	71.1	71.1	71.4	71.5	70.9	70.7	70.9	69.2
Enthalpy (J/g)	114.8	80.2	86	87.2	92.3	81.8	92.3	80.3
Compritol-SLN (aqueous dispersion)								
Melting peak (°C)	71.1	69.6	69.7	68.8	67.8	69.5	69	68.8
Enthalpy (J/g)	114.8	9.6	9.1	9.8	5	9.9	9.7	10.6
Crystallinity (%)	100	83.6	79.3	85.4	43.6	86.2	84.5	92.3

Incorporated drugs are tetracaine (T) and etomidate (E) in concentrations of 1, 5 and 10% (in the lipid matrix). R: drug-free SLN. The melting enthalpies were calculated on the basis of the total weighted-in quantity (dried SLN dispersion: drug-free or drug-loaded lipid particles and surfactant; aqueous SLN dispersion: drug-free or drug-loaded lipid particles, surfactant and water). The melting enthalpy of pure Compritol (lipid) is used as reference (100%) to calculate a theoretical percentage of crystallinity of the Compritol SLN in aqueous dispersion (data 3 months after production).

possess a less pronounced melting point depression [16]. Therefore, it was supposed that recrystallinity problems can be avoided by using Compritol as the SLN matrix.

In fact, drug-free and drug-loaded Compritol SLN show a high degree of crystallinity in the form of the aqueous dispersion (Table 2, lower part). In case of drug-free SLN, the melting enthalpy decreased compared to the lipid from 114.8 to 9.6 J/g. Taking the enthalpy of the lipid as being 100% and considering the lipid content of the Compritol SLN being 10%, this results in a theoretical crystallinity of the drug-free Compritol SLN of 83.6% (Table 2, lower part). Drug-free Compritol SLN showed a melting peak at 69.6 °C compared to 71.1 °C of the lipid before homogenization. It can be assumed that the lipid and the lipid nanoparticles are present in the β' or β_i form [8].

In Compritol SLN, maximum loading capacities of ~10% tetracaine and etomidate could be reached. Higher amounts of both drugs could be incorporated, but led to immediate gelation of the SLN dispersion after production. The incorporation of tetracain up to 5% (in the lipid phase) and etomidate up to 10% had no influence on the melting enthalpy and melting point compared to drug free SLN. In contrast, 10% tetracaine reduced the crystallinity to ~40%. Apart from SLN loaded with 10% tetracaine, all Compritol SLN were regarded to be in the solid state (Table 2).

The melting points of the dried Compritol SLN were slightly higher than the ones obtained in the aqueous SLN dispersion, the melting enthalpies are in a similar order of magnitude when considering the removal of the water (10% particle dispersion in Table 2, middle part). This suggests that the SLN in the aqueous dispersion are in a solid state.

3.3. Crystallinity: prednisolone-loaded SLN

Production of drug-free Compritol SLN using 2.5% poloxamer 188 led to a melting point depression from 71.1 (lipid) to 69.5°C, incorporation of 0.83% prednisolone reduced it further to 67.6°C (Fig. 1). The shape of the DSC curves was different, a relatively sharp peak was obtained from the stored bulk lipid (curve A, Fig. 1). The peaks of the drug-free SLN stabilized with poloxamer were broader and shifted to the left, being attributed to surfactant incorporated in the particles and the dispersed state of the lipid (curve B, Fig. 1).

Incorporation of drug reduced the peak area (reduced melting enthalpy) (curve C, Fig. 1). The cooling curve showed one peak for the lipid, two peaks for the drug-free SLN. The second peak at 52.4°C was attributed to the formation of a second, less stable modification, as described by Eldem et al. [14]. Prednisolone loaded SLN yielded one peak. The presence of the drug prevents formation of this unstable modification or accelerates the transition to the stable form. An explanation could be that drug loaded SLN possess a higher amount of liquid lipids within the matrix. From suppositories it is known, that the content of liquid lipids accelerates the recrystallization to stable modifications [17]. Thus, drug incorporation can accelerate the transformation to the stable polymorph.

Interpretation of DSC diagrams of cholesterol SLN was not performed because some decomposition of the cholesterol, during the dissolution of the prednisolone at increased temperature, could not be excluded.

3.4. Drug release profiles of tetracaine- and etomidate-loaded SLN

The entrapment efficacy of both drugs was between 85 and 99%. As expected, a burst release of both drugs within a few minutes was observed for the Dynasan SLN in the liquid state. Transferring the SLN from the liquid into the

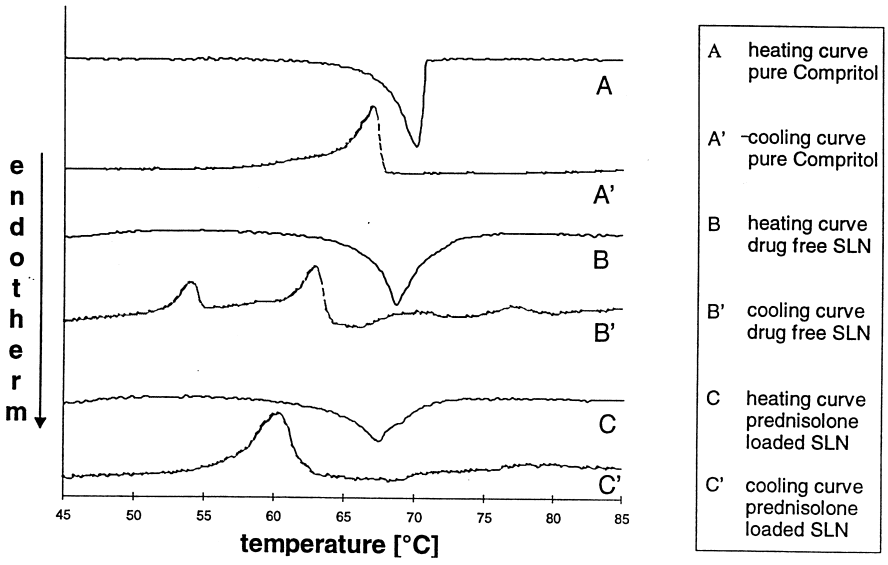

Fig. 1. DSC heating and cooling curves of stored, non-homogenized Compritol (A), drug-free Compritol SLN prepared with 2.5% poloxamer 188 (B) and Compritol SLN stabilized with 2.5% poloxamer 188 and loaded with prednisolone (C) (heating and cooling rate: 5°C/min).

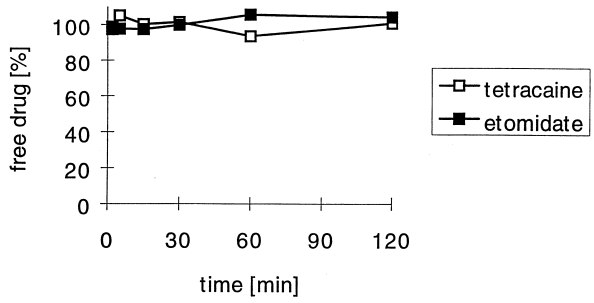

Fig. 2. Drug release profiles of Compritol SLN loaded with 5% drug, stabilized with 5% poloxamer 188.

solid state by freeze-drying could not avoid the burst release. Identical burst releases were obtained with tetracaine and etomidate incorporated in Compritol SLN (Fig. 2). Obviously, the solid state of the Dynasan and the Compritol matrix could not prolong the release of these drugs from the nanoparticles.

Factors contributing to a fast release are the large surface area, a high diffusion coefficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug (i.e. release from outer surface region of the nanoparticle). The increase in release velocity with decreasing particle size was described for drugs incorporated in polyester nanoparticles [18].

To assess the effect of surface area, lipid particles differing in size were prepared by a grinding process, fractionated by sieving and the drug release studied. A prolonged release of tetracaine for at least 6 h was only achieved with particles >125 μm. Particles below 40 μm exhibited a 100% release within 1 h (Fig. 3).

The particles were prepared by grinding, i.e. without the use of surfactant. The presence of surfactants was found to accelerate further drug release [19]. The small size of the tetracaine loaded SLN, in combination with the surfactant adsorbed and incorporated in the surface during the production process, will surely contribute to the observed burst release.

An identical dependency of the release on the size was obtained for differently sized etomidate loaded microparticles (Fig. 4). However, the fraction of particles <40 μm still led to a prolonged release over a period of 6 h. Considering that the molecular weights of tetracaine and etomidate are similar (264.4 and 244.3, respectively) this difference cannot be explained by faster diffusion due to molecular size differences. With respect to the identical composition of the matrices, a possible explanation is a difference in the matrix viscosity (i.e. different interactions of tetracaine and etomidate with Compritol).

It could be excluded that the formation of drug crystals is responsible for the fast release. The DSC measurements revealed no drug peak for all particles including the freeze- and air-dried ones. No drug crystals could be observed microscopically in the nanoparticle suspension. The concentration of free drug in the aqueous phase of the SLN

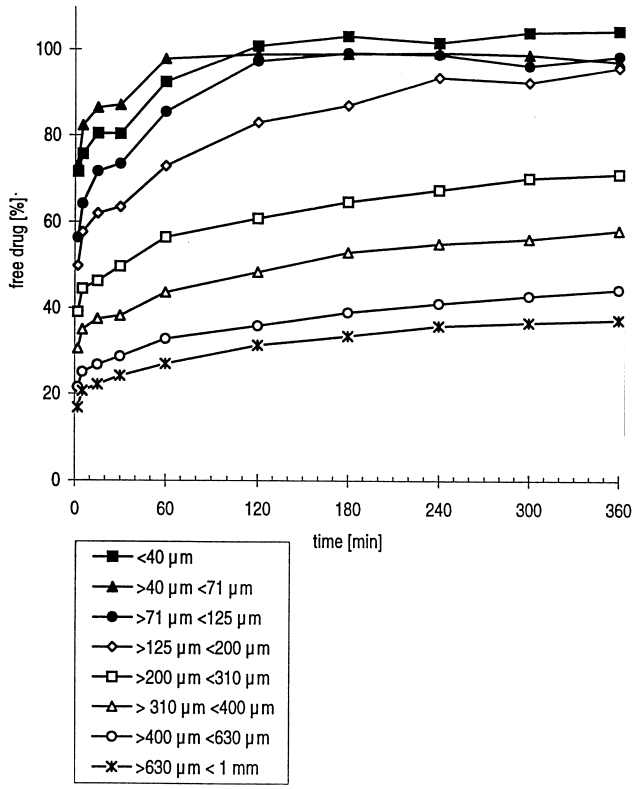

Fig. 3. Drug release profiles of tetracaine-loaded Compritol lipid microparticles as a function of particle size (8 particle fractions obtained by sieving, $n = 3$, drug load: 5%).

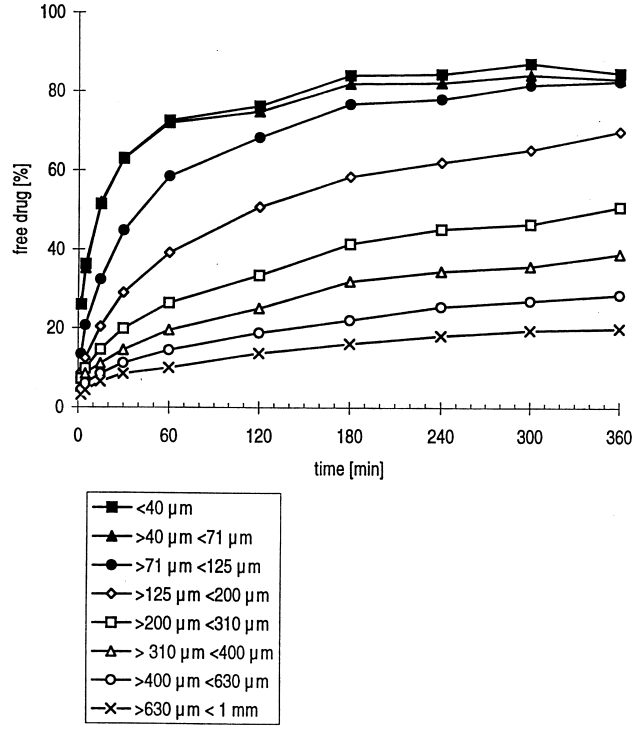

Fig. 4. Drug release profiles of etomidate loaded Compritol lipid microparticles as a function of particle size (8 particle fractions).

dispersion was clearly below the reported saturation solubility [15].

The observed differences, faster release from the lipid microparticles with tetracaine, cannot be explained by differences in the partition coefficients. The values for tetracaine are higher than those for etomidate for both lipids (Dynasan 112: 22.1 vs. 17.7; Compritol: 15.7 vs. 9.8, respectively). It should be noted that no differences in release could be measured for the two drugs when released from SLN.

A possible explanation is a short diffusion path due to an enrichment of drug in the outer region of the SLN or drug deposition on the particle surface. Such an enrichment might occur during the solidification of the SLN during the cooling period after homogenization at 70–90°C. In contrast to a fast precipitation (via humida paratum), the Ostwald–Mier region of a supersaturated solution (in case of lipids: supercooled mould) will be passed slowly, that means formation of large crystals is preferred. The lipid Compritol might start crystallizing first, forming an inner core of pure lipid. During the solidification process, a solid drug solution might be formed around this lipid core leading to an enrichment of drug in the outer particle region (Fig. 5, left). This could also happen when transferring the liquid Dynasan SLN to the solid state by freeze- or air-drying.

The existence of two phases, pure lipid core and an outer shell of a solid solution, could not be proven by DSC because the melting points are close together and the lipid nanoparticles showed a broad melting peak. However, recently atomic force microscopy (AFM) and small angle X-ray scattering (SAXS) measurements revealed a soft, deformable surface layer of 15–18 nm, which was identified as a drug-rich outer shell [20]. In addition, drug deposition on the surface of the SLN was found after incorporation of prednisolone. The fractal dimension decreased from 2.20 (drug-free SLN, rough surface) to 2.05 (prednisolone loaded SLN, surface smoothed by drug deposition). This is very close to 2.00 as value for a flat surface [20,21]. The same effect was reported for SLN loaded with coenzyme Q10 [20].

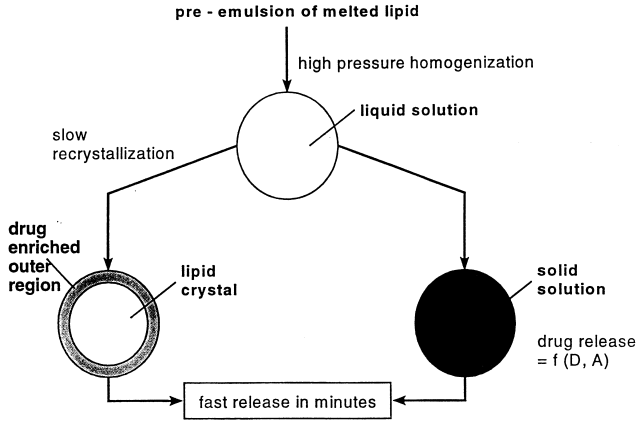

Fig. 5. Solidification process of tetracaine and etomidate SLN: after homogenization the particles are liquid, the drug is dissolved in the molten lipid (liquid solution). During solidification a lipid core is formed surrounded by a shell of a solid drug solution (left) or a nanoparticle consisting of a homogeneous solid solution matrix (right, Section 3.4).

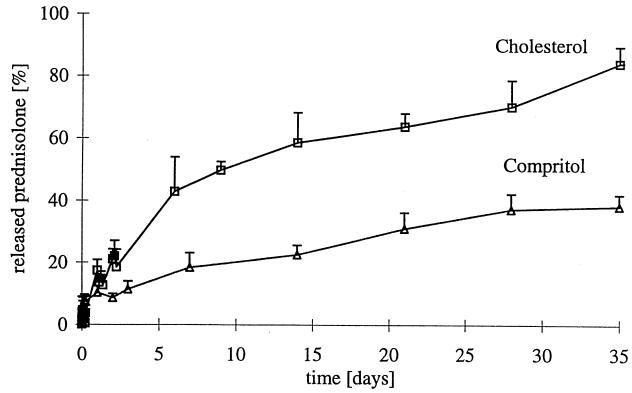

Fig. 6. In vitro release of prednisolone from cholesterol SLN and from Compritol SLN over a period of 5 weeks (stabilized with 2.5% poloxamer 188). The SLN systems were produced by using the cold homogenization method.

3.5. Drug release profiles of prednisolone loaded SLN

To avoid the heterogeneous crystallization of the drug loaded particles, a lipophilic drug was chosen with a distinctly higher melting point than the lipid matrix (prednisolone, mp 230°C under decomposition) and the SLN were produced by the cold homogenization technique. A solid solution of drug was ground and the suspension of the microparticles homogenized at room temperature. This should minimize melting effects during homogenization. Employing this method, cholesterol SLN could be loaded with 0.71% of drug (calculated in percent of lipid weight) and a prolonged drug release over 5 weeks was obtained (Fig. 6). No burst effect was observed. After 5 weeks, a total of 83.8% was released.

These data demonstrate that, in principle, a controlled release from SLN is possible. A prolonged release was also achieved when increasing the prednisolone load to 3.6%.

To assess whether a controlled release can also be obtained using lipids with lower melting points, prednisolone was incorporated in Compritol (0.80% drug load). As shown above, tetracaine and etomidate exhibited a burst release from Compritol SLN, whereas with prednisolone, a prolonged release for 5 weeks was observed (monitored period, Fig. 6). After 5 weeks a total of 37.1% was released. The differences in melting temperature of the lipid and the homogenization/room temperature were considered as important parameters determining the structure of the SLN matrix. Achieving prolonged release with lower melting lipids indicated that other factors, such as interactions between drug–lipid molecules [10], between surfactant-lipid molecules and solubility of the drug in the molten and solid lipid, play a major role [22].

A possible explanation is the presence of a solid solution

throughout the particle (Fig. 5, right) combined with a slow diffusion of prednisolone from the matrix. The partition coefficient of prednisolone for Compritol/water was 1.9 and below the values of tetracaine and etomidate. The slow release cannot be explained by the partition coefficient. Matrix viscosity might be higher in a solid solution of prednisolone than of etomidate in Compritol. The interactions between drug and lipid molecules will affect the viscosity of the solid lipid matrix. From the DSC diagrams, a more distinct melting point depression was observed after incorporation of 0.83% prednisolone compared to, e.g. 1% etomidate (67.6–69.5°C, respectively; lipid: 71.1°C). This supports the assumption of a molecular dispersed state or an interstitial inclusion of the drug which leads to more distinct drug–lipid interactions in the case of prednisolone incorporation.

Comparing the slope of the release profiles, very different release rates were observed for cholesterol and for Compritol matrices. The total amount released after 5 weeks differs distinctly (37.1 and 83.8%, respectively). This indicates the controlled adjustment of release can be achieved by modification of the chemical nature of the lipid matrix. In addition, surfactant, surfactant concentration and production temperature also affect the release profiles.

4. Conclusions

In the case of tetracaine and etomidate, high drug loadings into SLN could be achieved. Concerning the melting behavior, these drugs had little or no influence on the melting point and enthalpy of the lipid matrix. Only the entrapment of 10% tetracaine into the SLN led to a distinct reduction of the melting enthalpy. However, no controlled release could be achieved with these drugs. The release behavior was explained by the large surface area, a fast release from a drug-enriched outer layer of the particles and drug deposition on the particle surface being supported by AFM and SAXS data reported in the literature.

Prednisolone could be incorporated up to 3.6% in cholesterol SLN and 1.67% in Compritol SLN, respectively. Additionally, the drug present in the lipid matrix seems to accelerate the polymorphic transition to the stable modification in comparison to drug free particles. These results were attributed to a high degree of interactions between lipid and drug molecules and differences in the drug deposition within the particle. In previous studies only burst release from lipid nanoparticles was reported. The obtained prolonged release with prednisolone SLN demonstrates principally the suitability of SLN as prolonged release formulation for drugs.

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