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SolEmuls®—novel technology for the formulation of i.v. emulsions with poorly soluble drugs

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Abstract

Intravenously injectable o/w emulsions of drugs being poorly soluble in water and simultaneously in oils need to be produced by locating the drug in the interfacial lecithin layer, e.g. amphotericin B. For achieving this, up to now organic solvents were required. The objective was to develop a solvent-free production method for such emulsions. Drug and the pre-formed parenteral emulsion Lipofundin® were mixed and subjected to high pressure homogenisation. Drug powder and emulsions were characterised regarding size and physical stability by photon correlation spectroscopy (PCS), laser diffractometry (LD) and zeta potential measurements. Drug incorporation was studied using light microscopy, electron microscopy (EM) and a centrifugation test to separate non-dissolved drug. Amphotericin B and carbamazepine were used as model drugs. The high streaming velocities lead to accelerated drug dissolution and partitioning into the interfacial layer (so-called "solubilisation by emulsification", SolEmuls® Technology). The interfacial layer could incorporate (solubilise) a certain amount of drug, revealed by EM pictures. Exceeding this concentration, hybrid dispersions were formed consisting of drug-loaded oil droplets and drug nanocrystals of similar size (approximately 200 nm).

Both dispersion types are i.v. injectable opening the opportunity to deliver the drug in a concentrated form at desired low injection volume, e.g. 10 mg/ml.

Keywords: Amphotericin B; Carbamazepine; Emulsion; High pressure homogenisation; SolEmuls®

1. Introduction

The issue of poorly soluble drugs and their formulation attracted increasing attention during the last 5 years and is one of the "hot topics" in pharmaceutical formulation development. By now, about 10% of the drugs on the market have solubility problems and consequently bioavailability problems after oral administration. An alternative to oral administration is parenteral injection. However, due to their poor solubility they cannot be injected straight forward as a solution. Special formulation approaches need to be taken such as e.g. solvent mixtures, solubilisation or complex formation (e.g. cyclodextrins). The problem is increasing, at present about 40% of drugs being in the pipeline of the pharmaceutical companies are poorly soluble (Speiser, 1998), looking at the drugs coming directly from new synthesis even about 60% have a solubility below 0.1 mg/l (Merisko-Liversidge, 2002). This emphasizes the need for smart technological

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formulations to overcome these bioavailability problems and make the new drugs available to the patients.

Oral administration is the route of first choice for the patient. Therefore, improved formulation attempts focused first on development of oral formulations. One approach used for many years is micronization of the drug powder to overcome bioavailability problems caused by a too slow dissolution velocity. However, for drugs with very low solubility micronization is not sufficient. Therefore, during the last 5 years increasing attentions focused on nanonization that means transforming the drug powder to drug nanocrystals. Most promising approaches are the production of drug nanocrystals by jet milling using pearl/ball mills leading to the so called NanoCrystals™ (Liversidge and Cundy, 1995), high pressure homogenisation in water (DissoCubes®) (Müller et al., 1988, 1999) and in water-reduced or water-free media (NanoPure®) (Müller et al., 2000; Müller, 2002). However, for some drugs even nanonization does not lead to a sufficient bioavailability, in addition, it can not overcome oral bioavailability problems of poorly soluble drugs which are caused by other factors, e.g. metabolisation in the gut wall or *p*-glycoprotein transport (Ayrton and Morgan, 2001). There are also cases requiring a parenteral formulation, mostly for intravenous injection or infusion (e.g. intensive care patients, emergency cases). Therefore, even when an oral formulation of a poorly soluble drug is available—there is also a need for parenteral/intravenous formulations of poorly soluble drugs.

There are a number of principles to formulate poorly water soluble drugs as intravenous formulations. Examples are solvent mixtures, solubilisation and liposomes. The applicability of these approaches is very limited as clearly proven by the low number of products on the market being based on these technologies. Liposomes have the additional disadvantages of being relatively expensive and still exhibiting physical stability problems thus often requiring lyophilization. Of course, a lyophilized product has to be reconstituted and is therefore not ready-to-use. The reconstitution procedure might be tedious, e.g. AmBisome® liposomes. In contrast to this parenteral o/w emulsions used as drug carriers have been established since the 50 s of the last century, are of low cost and ready-to-use. Examples are emulsions with Diazepam (Diazepam-®Lipuro, Diazemuls®) or etomidate (Etomidat®-Lipuro). However, also the number of drug-loaded emulsions on the market is very limited, basically only three major drugs are formulated as emulsions, i.e. diazepam, etomidate and propofol. There are two main reasons for this:

1. Poorly water soluble drugs of commercial interest do not show a sufficiently high solubility in the registered oils (e.g. soya oil, MCT and its mixtures), companies are not prepared to use new oil excipients and pay for the costly toxicity studies.
2. Drugs of interest (e.g. amphotericin B) are simultaneously poorly soluble in the water and the oil phase thus requiring being located in the interfacial lecithin layer, a process being not economical by now and therefore not performed by industry.

The principle method to localize a drug in the interfacial lecithin layer of emulsions is dissolution of lecithin and the drug in an organic solvent, removal of the solvent by evaporation and using the remaining lecithin–drug mixture for emulsion production (Davis and Washington, 1988; Lance et al., 1995). This process is not production-friendly, especially not for a sterile production and simultaneously costly. For drugs such as amphotericin B it could be shown that amphotericin B emulsions also reduce drug side effects such as nephrotoxicity (Kirsh et al., 1988; Caillot et al., 1993). However, despite these positive effects in vivo, due to the costs the solvent method is not used for emulsion production.

Amphotericin B and carbamazepine are both poorly soluble in oil and in water. Amphotericin B is especially of commercial interest. Often the patients have to make a choice between the expensive AmBisome®, being US$ 1300 per day and the nephrotoxic effects of Fungizone® (being US$ 24 per day). Therefore, a cheap formulation alternative with reduced nephrotoxicity is needed for amphotericin B. Carbamazepine has a sufficient oral bioavailability in its market products but does not have a parenteral formulation alternative for patients, who are not able to administer an oral formulation, e.g. patients in coma.

This paper describes the production of emulsions without the use of any organic solvent. It is a principal technology to formulate drugs being poorly soluble in water and simultaneously in oils, thus requiring interfacial location.

2. Materials and methods

Lipofundin® N 20 and 10% and Lipofundin® MCT 20 and 10% were obtained from B. Braun Melsungen AG (Melsungen/Germany), Intralipid® from Baxter (Erlangen/Germany). Amphotericin B was obtained from Allpharma (Copenhagen/Denmark). Tween 80 was obtained from Sigma (Munich/Germany) and lecithin was a kind gift provided by B. Braun Melsungen AG (Melsungen/Germany).

2.1. Emulsion preparation

Drug-loaded emulsions were produced either by adding the powdered drug to the emulsion by stirring (Ultra-Turrax, Jahnke & Kunkel, Staufen, Germany) or alternatively by preparing a finely wet-milled drug suspension which was mixed with the emulsions by gentle stirring. The obtained dispersions containing oil droplets and drug crystals were then subjected to a high pressure homogenization process using a Micron LAB 40 (APV Systems GmbH, Unna/Germany). Production was performed typically at 45 °C applying 1500 bar and 1–20 homogenization cycles.

2.2. Particle sizing

Particle sizing was performed by laser diffractometry (LD) using a Coulter LS 230 (Coulter Electronics, Krefeld, Germany). The obtained distribution is a volume distribution, as characterization parameters the LD diameters 50, 90, 95 and 99% were calculated. For example a diameter 90% means that 90% of the volume of the particles is below the given size in μm. The mean diameters of the bulk population of the emulsion and of the drug suspension were determined by photon correlation spectroscopy (PCS) using a Malvern Zetasizer 4 (Malvern Instruments, Malvern/UK). The mean PCS diameter is the so-called intensity-weighted "z-average". The polydispersity index (PI) is a measure for the width of the distribution ranging from 0.000 (monodisperse) to 0.500 (relatively broad distribution). Basically for parenteral emulsions PI values up to 0.250 are acceptable. The LD values are higher than the PCS diameter, because LD yields a volume distribution and PCS is a light intensity based measurement.

2.3. Zeta potential measurement

The ZetaSizer 4 was also used to measure the zeta potential by electrophoresis. The zeta potentials were measured using the large bore capillary cell and applying an effective voltage of 20 V/cm. The electrophoretic mobility (μm/s) was converted into the zeta potential (mV) by applying the Helmholtz-Smoluchowski equation. Measurements were performed in distilled water having its conductivity adjusted to 50 μS/cm by addition of 0.9% concentrated sodium chloride solution. This avoids fluctuations in the height of the zeta potential due to differences in electrolyte concentration (Müller, 1996). The pH of the water was in the range of 5.5–6.0.

2.4. Light microscopy studies

Light microscopy was performed using a Leitz microscope (Wetzlar/Germany). The magnification selected was 1000-fold, oil immersion applied. Emulsions were analyzed undiluted; typically 20 microscopic fields were analyzed under polarized light for the detection of remaining drug crystals.

2.5. Centrifugation test to separate non-dissolved drug

For quantitative determination of non-dissolved drug crystals, the drug-loaded emulsions were centrifuged at 22,938 × *g* for 30 min. using a Biofuge 22R centrifuge (Heraeus, Osterode/Germany). After centrifugation, the supernatant was discarded and the remaining pellet—if any—washed three times with 2 ml of water. Centrifugation was performed in 2 ml Eppendorf tubes. The washed drug crystals were analyzed by dissolving them in an organic solvent (methanol for amphotericin B and carbamazepine) and performing UV spectrophotometry (406, 283 nm, respectively). The drug concentration was calculated using calibration curves.

2.6. Electron microscopy studies

Electron microscopy was performed using a Zeiss microscope (Wetzlar/Germany). The emulsions were placed on a copper grid, after evaporation they were stained with phosphotungstic acid. After water

evaporation they were analyzed at voltage of 10–60 kV. Drug suspensions were processed in the same way, but without additional staining.

3. Theory

The introduction of the liposomal formulation AmBisome® led to a distinct improvement in therapy, the nephrotoxicity was drastically reduced (Hann and Prentice, 2001). However, the product has a very high price. This led to the fact that hospital pharmacists tried to incorporate amphotericin B into parenteral emulsions (e.g. Intralipid®) (Nucci et al., 1999) for which was known that they were able to achieve also a reduction in nephrotoxicity. The common approach taken in the hospitals was the injection of amphotericin B solution (Fungizone®) into bottles of emulsions for parenteral nutrition. Fungizone® is composed of 50 mg amphotericin B and 41 mg sodiumdeoxycholat. Injecting this solubilizing solution into the water phase of an emulsion led to the precipitation of amphotericin B crystals. This is a classical precipitation step adding the solvent to a miscible non-solvent. The emulsions were shaken and it was assumed that the amphotericin B was localized in the interface. This assumption was based on the successful incorporation of amphotericin B into lecithin layers, but it was ignored that a previous incorporation step of the drug in the lecithin was performed (dissolution of both components in an organic solvent followed by solvent removal and de novo production of the emulsion). Studies in our laboratory showed that normal shaking of the emulsion did not completely dissolve the amphotericin B crystals. It is reported that shaking for 18 h at a high frequency of 2800 rpm could only dissolve about 90% of the drug (Shadkhan et al., 1997).

Theoretically the amphotericin B will diffuse from the aqueous phase into the lecithin layer according to its partitioning coefficient. However, the rate-limiting step is the dissolution of amphotericin B from the crystals. It is a well-known phenomenon that drugs with very poor solubility show simultaneously a very low dissolution velocity. Based on this, localization of the amphotericin B in the lecithin layer appeared feasible to achieve when accelerating the dissolution velocity from the amphotericin B crystals.

Firstly, precipitation of the amphotericin B by injecting Fungizone® into the water phase of a parenteral emulsion can lead to relatively large crystals. To enhance the dissolution rate it is required to provide a surface area as large as possible that means using drug crystals as small as possible. Secondly, dissolution is accelerated by stirring, shaking, etc. that means increased velocity of the dissolution medium. Dissolution medium streaming across the crystal surface will remove dissolved drug in the vicinity of the crystal, thus leading to a reduction in the diffusional distance h that means leading to a thinner layer in which the concentration gradient $c_s - c_x$ occurs. Consequently, the diffusion gradient increases leading to a faster dissolution velocity according to Noyes–Whitney equation:

$$\frac{dc}{dt} = \frac{DA(c_s - c_x)}{h}$$

where dc/dt is the dissolution velocity, A is the surface area, D is the diffusion coefficient, c_s is the saturation solubility (on particle surface), c_x is the bulk concentration, h is diffusional distance, and $(c_s - c_x)/h$ is concentration gradient.

The higher the streaming velocity of the dissolution medium across the crystal surface is, the smaller will be h, which means the larger is the dissolution velocity. In an ideal situation, h should go towards zero, simultaneously dc/dt going towards indefinite (Fig. 1).

The stirring velocities and related streaming velocity of the fluid is relatively limited when shaking an

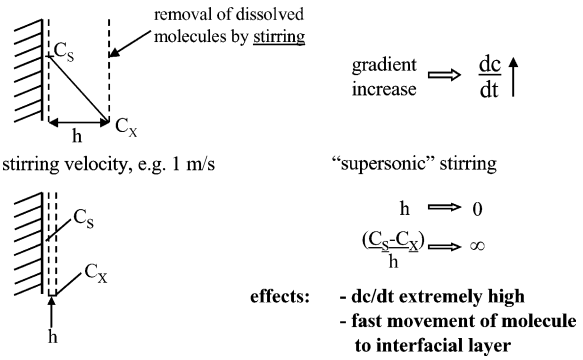

Fig. 1. Increase of solubilization velocity by "supersonic stirring": situation at crystal surface during the dissolution process, reduction of h during stirring of the dissolution medium (upper: normal stirring) and h approaching zero at ultra high speed stirring e.g. in high pressure homogenizer (fluid velocity across the crystal, lower).

emulsion with crystals. A simple process creating very high fluid velocities (500–700 m/s) is high pressure homogenization. Homogenizers to be employed can be based on the jet stream principle (Microfluidizer) or on the piston-gap principle (e.g. APV Gaulin machines).

Based on this, drug powder was added to parenteral emulsions (e.g. Intralipid®, Lipofundin®) and subjected to a high pressure process (1500 bar, 1–20 cycles) leading to the complete dissolution of amphotericin B. Alternatively, instead of adding the drug to a preformulated emulsion, the drug can be admixed during the novo production of emulsions. A drug suspension is prepared in which the oil phase is subsequently dispersed. The obtained pre-dispersion consisting of oil droplets and simultaneously drug crystals in water is then subjected to a normal production process of a parenteral emulsion. During the homogenization, the oil is finely dispersed at simultaneous dissolution of the drug crystals and localization of the drug molecules in the lecithin layer. This is a universal principle for all drugs being poorly soluble in the water phase of emulsions and simultaneously in the oil phase but possessing a suitable lipophilicity to interact with the lecithin molecules in the interfacial layer. The principle is demonstrated using amphotericin B and carbamazepine as model drugs.

Of course, the incorporation capacity of an o/w emulsion is not unlimited. At a certain stage the interfacial layer is saturated with drug, thus leading to non-dissolved small drug crystals being present in the dispersion. The drug concentration should be chosen this way that it stays below the saturation level of the interfacial layer. Of course, also hybrid dispersion is injectable having oil droplets and small drug nanocrystals present simultaneously. The two model drugs were investigated with respect to the concentrations at which drug crystals are detectable in the dispersion.

4. Results and discussion

4.1. Emulsion production

Finely milled amphotericin B powder was added under stirring to Lipofundin® N 20% emulsion (1 mg/ml). Stirring was performed by an Ultra-Turrax at 9000 rpm for five minutes. The obtained dispersion was then homogenised at 1500 bar for 20 cycles. Fig. 2 shows the particle size distribution of the amphotericin B powder (measured after dispersion in surfactant solution) (A), the size distribution of the emulsion prior to homogenisation (B) and the size distribution of the emulsion after dissolution of the amphotericin B (C). The size distribution of the amphotericin B emulsion was determined by laser diffractometry, the LD diameter 50% being 0.21 μm. Laser diffraction analysis could not detect remaining drug crystals apart from the bulk population of the emulsion droplets. The size distribution of the homogenised emulsion shifted slightly to smaller values (Fig. 2, left).

To accelerate the dissolution velocity of the amphotericin B crystals, finely milled amphotericin B was used. The amphotericin B powder was dispersed in a surfactant solution containing 1.2% Tween 80 and then wet-milled by high pressure homogenisation. A suspension with the mean PCS diameter of 990 nm and a polydispersity index of 0.263 resulted. The drug concentration of the suspension was 10%. In the next step 400 μl concentrated drug suspension were added to 40 ml Lipofundin® N 20%, mixing was performed by gentle stirring and the mixture processed as described above (1500 bar, 1–20 cycles). The homogenised emulsions were analyzed by light microscopy with respect to detectable drug crystals. After 10 cycles no drug crystals could be detected anymore. The PCS diameters were 242 and 236 nm and the polydispersity indices 0.163 and 0.144, respectively for the mixtures homogenized with 10 cycles and with 20 cycles. The small differences in the mean bulk diameter and polydispersity are not relevant for i.v. administration. It is important that complete dissolution of the drug crystals were observed after 10 cycles which eases production on industrial scale.

As second drug, carbamazepine was incorporated into Lipofundin® MCT 20%. A wet-milled stock suspension of 2.5% carbamzepine in 0.5% Tween 80 surfactant solution was prepared by high pressure homogenization applying 1500 bar and up to 20 cycles. The mean PCS diameter was 484 nm and the polydispersity index 0.230, the zeta potential in conductivity water was −7 mV. The suspension was added to Lipofundin® MCT 20% emulsion. Eight milliliters of drug suspension was taken and Lipofundin® added to a total of 40.0 g leading to a drug concentration of

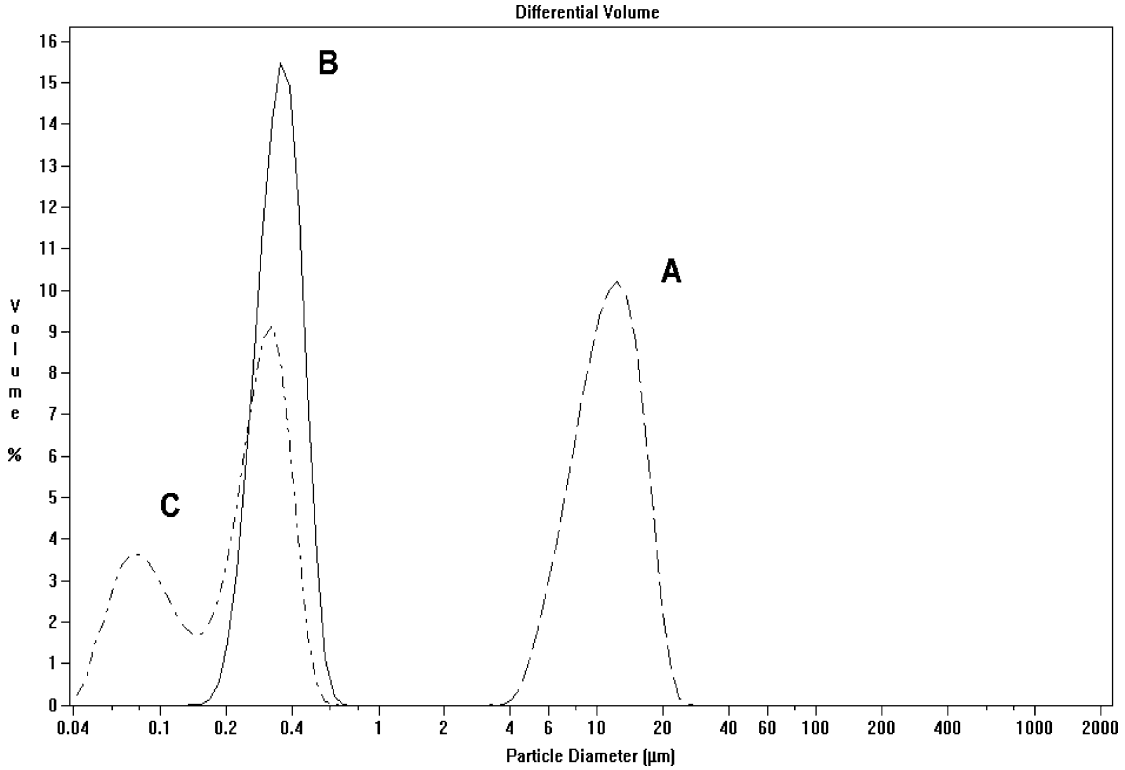

Fig. 2. Size distribution of drug powder before incorporation (A), size distribution of Lipofundin N 20% (B) and size distribution of the homogenized mixture (C) (*Y*-axis: vol.%, *X*-axis: size (μm)).

5.0 mg/ml. A second formulation was produced taking 16 ml carbamazepine drug suspension, adding Lipofundin MCT 20% again to a total of 40.0 g resulting in a drug concentration of 10 mg/ml. Both dispersions were homogenized at 1500 bar applying different production cycles. Table 1 shows the PCS and LD diameters as a function of homogenisation cycles.

The difference in drug load obviously had little effect on the bulk population of the emulsion droplets. However, very tiny remaining drug crystals could be detected in the higher concentrated emulsion (cf. 4.2) indicating that the system was overloaded.

A comparable experiment was performed producing an amphotericin B emulsion with 5 mg/ml. At this concentration a few, very small remaining drug crystals could be detected (cf. 4.2) indicating that the system has reached its maximum incorporation capacity. This shows—as expected—that there are different maximum loading capacities depending on the structure of the drug and its ability to interact with

Table 1
PCS diameter (nm), polydispersity index (PI) and LD diameters 50, 90 and 95% (μm) for the two carbamazepine emulsions (5.0, 10.0 mg/ml) as a function of homogenization cycles

Homogenisation cycles	PCS ∅	PI	Laser diffractometry d50%, d90%, d95%
5 mg/ml			
Cycle 1	206	0.083	0.165, 0.273, 0.302
Cycle 5	199	0.092	0.157, 0.250, 0.270
Cycle 10	198	0.066	0.160, 0.254, 0.279
Cycle 15	201	0.082	0.160, 0.265, 0.300
Cycle 20	197	0.076	0.167, 0.290, 0.330
10 mg/ml			
Cycle 1	189	0.081	0.130, 0.227, 0.255
Cycle 5	191	0.087	0.133, 0.227, 0.254
Cycle 10	190	0.075	0.132, 0.227, 0.254
Cycle 15	191	0.078	0.130, 0.225, 0.252
Cycle 20	191	0.082	0.128, 0.224, 0.252

the lecithin molecules and to be incorporated in the interfacial layer.

4.2. Crystal detection

There is a limited sensitivity by laser diffractometry to detect a low number of larger particles being present besides large bulk population of small particles (Müller and Schuhmann, 1997). In addition, drug crystals might dissolve to a large extent, reaching a size as small as the emulsion droplets themselves. Laser diffraction is not able to differentiate between similarly sized droplets and crystals. Therefore additional analytical methods for crystal detection are essential, applied were light microscopy and a centrifugation method.

The amphotericin B emulsions with 2 mg/ml were analyzed microscopically applying a magnification of 1000-fold (oil immersion), analysis was performed using undiluted emulsions to increase the probability to detect a few remaining crystals. Fig. 3 (upper) shows the polarized microscopy image of the overloaded amphotericin B emulsion with a few, tiny crystals.

Microscopical analysis of undiluted emulsion is an established method to characterize emulsions for parenteral nutrition, especially mixtures for total parenteral nutrition (TPN) regarding the content of larger, coalesced droplets (Müller and Heinemann, 1992; Müller and Heinemann, 1993). The method is semi-quantitative, that means normally the particles per microscopic field are counted exceeding certain sizes, e.g. 1, 2, 5 and 10 μm. In general 20 microscope fields are analyzed. In the amphotericin B emulsion crystals were very few and small in size (typically < 1 μm) which makes the counting very difficult. In addition, it would be desirable to quantify the undissolved drug in percent of the drug added to the emulsion system. Therefore a centrifugation method was established for quantitative analysis.

The homogenized emulsion was subjected to a 30 min centrifugation at 22,938 × g. This leads to the flotation of the oil layer and sedimentation of potential drug crystals as a pellet. Based on Stoke's law and assuming a particle density of 2.5 g/cm^3, a viscosity of 1 mPa s (water), a sedimentation distance of 2 cm (Eppendorf tube) a centrifugation time of 4.3 s was calculated for a 500 nm spherical particle and 7 min and 7 s for a 50 nm particle. Prior to analysis the sediment was washed three times with distilled water, analysis was performed by UV photometry. The system was validated by adding a defined amount of drug suspension to an emulsion and separating the particles again by centrifugation. Recovery was 1.02 μg/ml (being 85%), considering the fraction of the drug being soluble in the oil and water phase of the emulsion. Of course, as the solubility in the lecithin layer is unknown, consider this the amount found should correspond to >90% of the insoluble fraction of drug added.

No non-dissolved carbamazepine could be detected when analyzing the 1 mg/ml carbamazepine emulsion, in the 10 mg/ml the non-dissolved fraction detected was 29.8%. These results are in agreement with light microscopy data (Akkar and Müller, 2003).

4.3. Physical stability during long-time storage

Non-sterilized drug-loaded emulsions were stored at room temperature and investigated regarding their stability in size. By now only amphotericin B data were available which showed very good physical stability of the emulsions during storage (Table 2).

The physical stability of the non-autoclaved emulsion shows in principle that it is possible to produce the emulsions aseptically. Aseptic production might be an alternative if it is not possible to maintain a sufficiently high chemical stability during a thermal sterilization by autoclaving (121 °C, 15 min).

4.4. Electron microscopy characterization

EM graphs of the emulsions were taken by placing them on a copper grid, letting the water evaporate and staining them with phosphotungstic acid. In comparison to the drug-free emulsions (Fig. 4, upper), the amphotericin B loaded emulsions showed

Table 2
PCS diameters (μm), polydispersity indices and LD diameters d99% (μm) as function of storage time for amphotericin B emulsions loaded for 1 mg/ml

	PCS	PI	d99%
Day 1	0.201	0.059	0.430
Month 1	0.204	0.117	0.486
Month 3	0.207	0.132	0.536

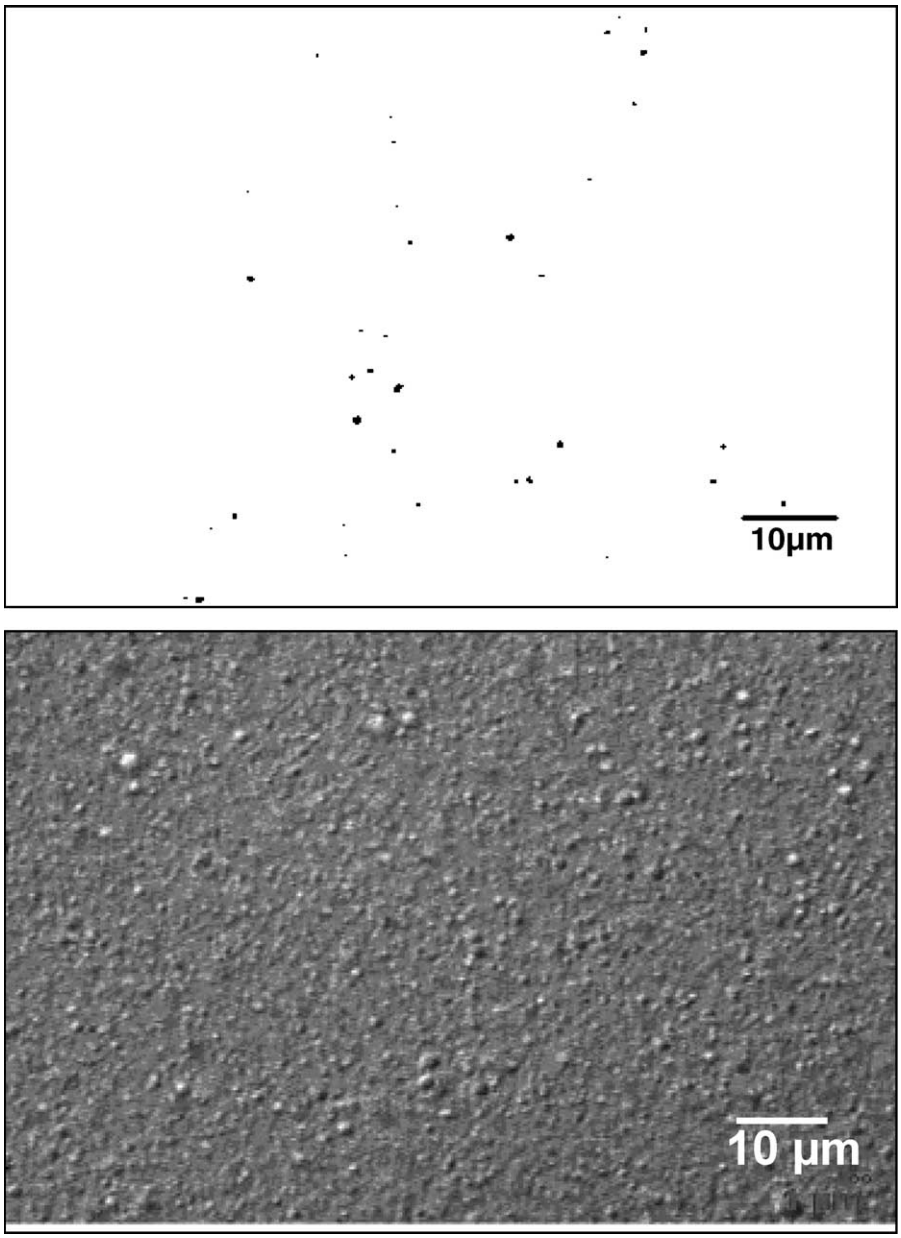

Fig. 3. Polarized light microscopy of undiluted amphotericin B emulsion 2 mg/ml, magnification 1000-fold (upper) and normal light microscopy (lower).

a different appearance at the droplet surface (Fig. 4, lower).

The change in the interfacial appearance was localized to certain regions. Firstly, the change in appearance was attributed to incorporation of amphotericin B into the lecithin. Secondly, the patchwise appearance supports the hypothesis that amphotericin B is not evenly distributed in the lecithin layer but seems to form special arrangements within the lecithin layer, a certain ordered structure. Such a certain ordered, localized structure is explainable by a specific interaction between certain numbers of lecithin and drug

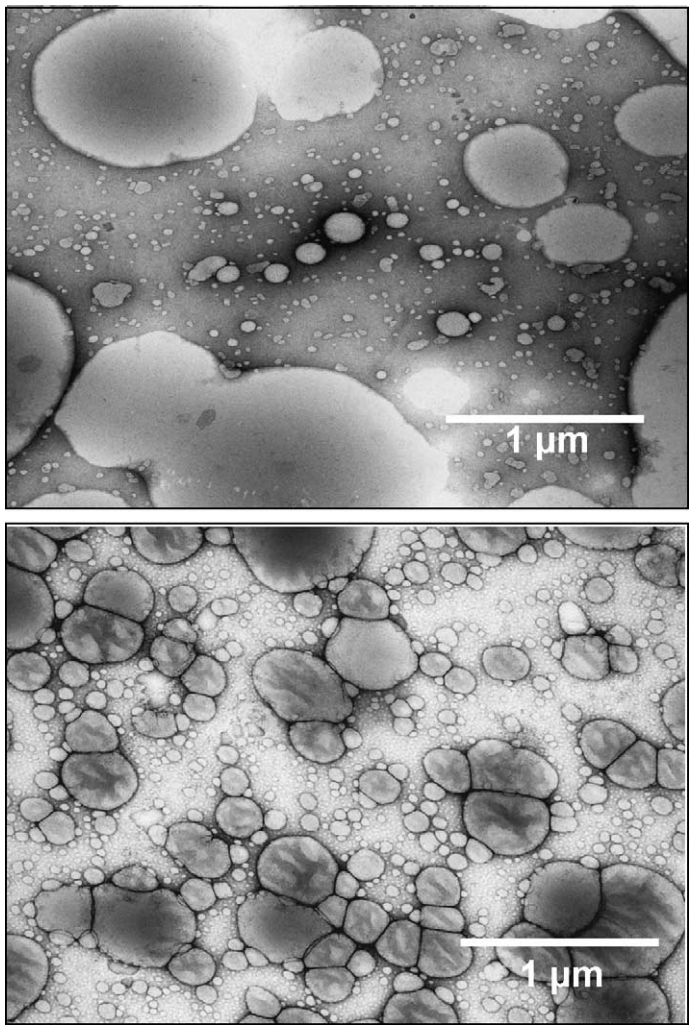

Fig. 4. EM graphs of drug-free emulsions (upper) and amphotericin B-loaded emulsion (lower).

molecules, comparable to a complex formation. The observed structures are being presently under further investigation; however the EM graphs clearly indicate the successful incorporation of the drug into the lecithin layer.

Drugs being poorly soluble in water and simultaneously in the oil phases of o/w emulsions can be successfully incorporated into the lecithin layer by accelerating the drug crystal dissolution process using high pressure homogenization. Very conveniently, the drug dissolution can also be performed during the emulsion production. The approach of solubilisation by emulsification (SolEmuls®) appears as a general formulation principle for poorly soluble drugs. Major advantages are that no additional excipients are needed in the formulation; the established production process of high pressure homogenization can be used without any changes leading to a product of high acceptance by the regulatory authorities.

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