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Research paper

Formulation of intravenous Carbamazepine emulsions by SolEmuls® technology

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Abstract

Oil in water (O/W) emulsions for parenteral nutrition can be employed as intravenous (i.v.) carriers for drugs that are poorly soluble in water and in oil by localising the drug in the interfacial lecithin layer, e.g. Amphotericin B emulsions. By now, the emulsion production required organic solvents. SolEmuls technology localises the drug in the interfacial layer by a solvent-free high-pressure homogenisation process. SolEmuls was applied to produce Carbamazepine emulsions at increasing drug concentrations from 0.5 to 10 mg/ml. Drug powder and Lipofundin emulsion were mixed and homogenised at 1500 bar. Characterisation of emulsions and short-term stability were performed by photon correlation spectroscopy (PCS) and laser diffractometry. Drug incorporation (absence of non-dissolved drug crystals) was investigated by light microscopy and a centrifugation test. The emulsions were physically stable and complete drug dissolution is possible up to 3 mg/ml. Up to 10 mg/ml drug hybrid dispersions of emulsion droplets and ultrafine nanocrystals were obtained. Both, emulsions and hybrid dispersions are suitable as i.v. injectables regarding size and stability.

Keywords: Carbamazepine; Emulsions; Poorly soluble drugs; Stability; Particle size

1. Introduction

Parenteral oil in water (O/W) emulsions are used as intravenous (i.v.) drug carriers since about 40 years. They are used as carriers for drugs, which are poorly water-soluble but can be dissolved in the oil phase of the emulsions, typically being LCT oils (soy oil) or mixtures of long chain trigylcerides (LCT) and middle chain triglycerides (MCT) oils. This allows 'solubilisation' of these drugs without the use of organic solvents and avoids as well the use of solubilisers potentially having side effects (e.g. Cremophor EL). These emulsions are not a delivery system for targeting; they reduce side effects of drugs occurring during or after injection (e.g. diazepam, inflammation at injection site). Compared to other particulate carriers such as liposomes and polymeric nanoparticles, they possess a number of advantages. The O/W emulsions are composed of accepted excipients; they can be produced on large scale using existing production lines for emulsions for parenteral nutrition. They can be terminally sterilised by autoclaving and are physically long-term stable. In contrast to liposomes, they are a low-cost product and are ready-to-use.

However, despite these manifold advantages, there is only a small number of drugs on the market formulated as i.v. emulsions, that means basically we have just three drugs: diazepam, etomidate and propofol. Commercial products are, for example, Diazepam-Lipuro, Etomidat-Lipuro and Propofol-Lipuro. What are the reasons for this?

There are two reasons:

1. poor solubility of drugs in regulatorily accepted oils and
2. poor solubility of drugs in water and simultaneously in oils in general.

To justify the development and registration of a new drug formulation, the drug needs to promise sufficiently high annual sales. The problem is that all drugs, being of commercial interest to be formulated as i.v. emulsion, do not show a sufficiently high solubility in the regulatorily accepted LCT and MCT oils. The low solubility would lead to a too large injection volume being not acceptable. The

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costs for the necessary toxicity study to register a non-accepted oil are very high, thus the companies are too reluctant to develop new emulsions based on new oils excipients.

Secondly, many drugs of commercial interest such as Amphotericin B show generally a too low solubility in oils. They can only be formulated as i.v. emulsions by incorporating the drug molecules into the interfacial lecithin layer of the emulsion droplets [1]. To achieve this, the drug needs to be dissolved together with the lecithin in an organic solvent, the solvent evaporated and the obtained lecithin/drug mixtures being used for the de novo production of the emulsions [2]. This is no production-friendly process for large-scale industrial production; in addition, it is very costly. Therefore, no emulsions are on the market using this technology – despite the fact that for such emulsions also a reduction of side effects such as nephrotoxicity of drugs could be seen [3,4].

The SolEmuls technology is a novel approach to localise drugs in the interfacial area of emulsions without the use of any solvents. The drug powder is mixed with the emulsion and subjected to a high-pressure homogenisation process [5–7]. This paper describes the use of SolEmuls technology for the formulation of i.v. Carbamazepine emulsions. Carbamazepine is available as e.g. tablets, but there is still a lack of an i.v. formulation for cases in which a parenteral administration would be desirable.

2. Materials and methods

Lipofundin MCT was used as basic emulsion, it was purchased from B. Braun Melsungen AG (Melsungen/Germany). Carbamazepine was obtained from Sigma Chemicals (Steinheim/Germany).

High-pressure homogenisation was performed using a Micron LAB 40 (APV Systems GmbH, Unna/Germany). Homogenisation was performed at 45°C, typical production parameters were 1500 bar and 1–20 homogenisation cycles. To prepare a pre-dispersion (drug powder dispersed in surfactant solution) for homogenisation, an Ultra-Turrax was used (Jahnke and Kunkel, Staufen/Germany). Stirring velocity was 8000 rpm for 1 min. For quantitative determination of non-dissolved drug crystals, the drug-loaded emulsions were centrifuged at 17.000 × *g* for 30 min. using a Biofuge 22R centrifuge (Hereaus, Osterode/Germany).

Particle sizing was performed by photon correlation spectroscopy (PCS) using a Zetasizer 4 (Malvern Instruments, Malvern/UK). PCS yields the mean diameter of the bulk population and a polydispersity index (PI) for the width of the distribution. To analyse the content of micrometer droplets, laser diffractometry (LD) was employed. Analysis was performed using a Coulter LS 230 (Coulter Electroncis, Krefeld/Germany). Size distribution and diameters were calculated using the Mie theory in connection with PIDS. For performing the Mie calculation, a real refractive index of 1.46 and an imaginary refractive index of 0.01 were used being suitable for Lipofundin emulsions [8].

Zeta potential determination was performed using also the Zetasizer 4. Measurements were conducted in distilled water having the conductivity adjusted to 50 μS/cm by addition of sodium chloride as recommended by Müller [9]. The pH of the water was between 7.7 and 6.2. Calculation of the zeta potential was performed using the Helmholtz–Smoluchowski equation.

The content of remaining drug crystals in the emulsions was analysed by light microscopy using a Leitz microscope (Leitz, Wetzlar/Germany). The employed magnification was 630-fold, for each sample 20 microscoping fields of the undiluted emulsion were screened. The method was previously described by Müller and Heinemann [10]. It is a method recognised by regulatory authorities to assess the content of micrometer droplets in emulsions for parenteral nutrition.

In addition, a centrifugation test was developed and employed to screen for remaining undissolved drug microcrystals and also drug nanocrystals. The drug-containing emulsions were given into a 2 ml Eppendorf vial and centrifuged for 30 min at 17.000 × *g*. It was calculated that a spherical 1 μm Carbamazepine crystal would take 0.4 s to reach the bottom of the vial under these centrifugation conditions. The calculated centrifugation time for a 200 nm drug crystal is 8.9 s. From this it could be assumed that any remaining drug crystals in the emulsion should be detected in the pellet after the 30 min centrifugation time. Obtained pellets were washed three times with 2 ml water applying the same centrifugation conditions. The pellet was analysed by UV spectrophotometry after dissolution in methanol, detection wave length was 283 nm.

The theoretical sedimentation times of spherical drug crystals of different size were calculated, to validate the centrifugation test, a known amount of drug powder (e.g. 1 mg/ml) was added to Lipofundin and this non-homogenised mixture was subjected to the centrifugation test, applying even longer centrifugation times than calculated. It should be assessed if the full amount of micrometer particles could be recovered. In addition, to assess if drug nanocrystals can also be separated from the emulsion droplets, a Carbamazepine nanosuspension with a mean diameter of 484 nm was added to Lipofundin and processed. Even for the drug nanoparticles, about 80% of the theoretical amount could be recovered that means the assay should be able to detect non-dissolved Carbamazepine crystals in the homogenised mixture. The amount of the non-dissolved drug to be recovered was calculated on the known solubilities of the drug in oil and water of the emulsion, ignoring the solubility in the lecithin. The amount dissolved in the lecithin layer is not known, therefore, the recovery 80%, which is below 100%, is attributed to some particles dissolved in the lecithin.

3. Results and discussion

Amphotericin was one of the first drugs being formulated as liposomal dispersion for i.v. injection, the commercial product is Ambisome®. Disadvantages of the product are the need to reconstitute it prior to administration and the relatively high price (US$ 1300/daily treatment compared to US$ 24 with the solvent mixture Fungizone®) [11]. During the introduction of Ambisome®, it was already known that Amphotericin-loaded emulsions showed a comparable reduction in nephrotoxicity. Based on this knowledge and considering the very high price of Ambisome®, hospital pharmacists tried to generate a 'cheaper solution'. They injected the Amphotericin solution Fungizone® into bottles of parenteral emulsions (Intralipid, Lipofundin), shook the bottle to partition the Amphotericin into the lecithin layer of the emulsion. However, there was no dissolution of the Amphotericin in the lecithin layer. In fact, they performed a classical precipitation by adding a solvent (Fungizone®) to a non-solvent (water phase of emulsion) leading to the precipitation of Amphotericin crystals. Due to the white colour of the emulsion, this was hard to detect. Shaking of the bottle did not lead to the dissolution of the crystals. A paper reports that shaking over 18 h at a frequency of 2800 rpm is required to dissolve at least the majority of the crystals [12]. What are the reasons for this?

Amphotericin is a drug with very low saturation solubility in water (<0.01 mg/ml), typically an extremely low dissolution velocity dc/dt is associated with drugs of low solubility. Therefore, even shaking for a few days at low frequency does not lead to the complete dissolution of the Amphotericin crystals [13].

Precipitation as performed above can lead to relatively large crystals, that means the surface area is relatively small. However, in order to achieve the dissolution a much more efficient 'shaking' or 'stirring' is necessary, favourably in combination with a large surface area. These two principles are exploited in the SolEmuls technology. The drug powder is added to a pre-formed emulsion (e.g. Intralipid, Lipofundin) in a finely dispersed form, that means as jet-milled product or in the form of drug nanocrystals. It results a hybrid dispersion being simultaneously composed of liquid oil droplets dispersed in water and drug micro/-nanoparticles dispersed in the water phase. This dispersion is subjected to a high-pressure homogenisation. In the homogenisation gap, high streaming velocities occur, i.e. it is a kind of 'supersonic' stirring which leads to the fast dissolution of the drug crystals and molecules partitioning into the lecithin layer (Fig. 1).

This technology was successfully employed to formulate Amphotericin B emulsions [5–7], a molecule with a certain amphiphilicity already known to be able to localise in lecithin layers. In the paper, we studied the possibility to apply this technology also to Carbamazepine and to assess to which extent this technology can be applied in a more general way.

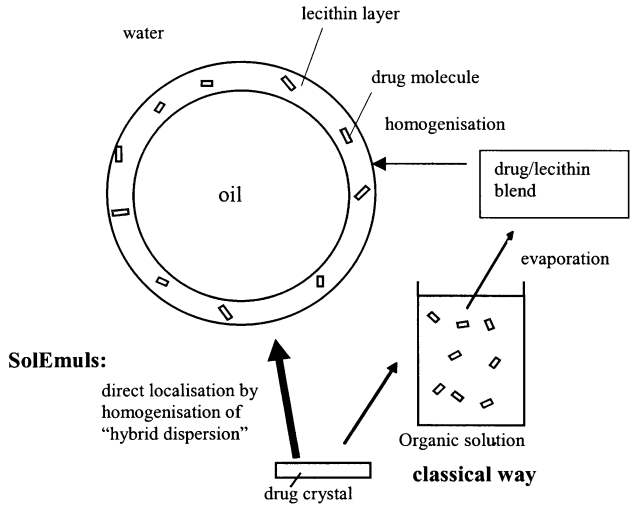

Fig. 1. Drug incorporation into the lecithin layer of the emulsions: conventional method via organic solvents (right) and SolEmuls technology via accelerated dissolution of drug crystals under high-pressure streaming conditions (left).

3.1. Production of Carbamazepine emulsion: 0.5 mg/ml

Calculating the maximum solubility of Carbamazepine in an emulsion based on its solubilities in water and the LCT/MCT mixture would result in a maximum Carbamazepine concentration of 0.64 mg/ml emulsion. To avoid overloading the emulsion system, the first emulsions were produced with a moderate loading capacity of 0.5 mg/ml drug. This preparation should also give evidence if dissolved drug impairs basically the physical stability. The drug powder with a mean diameter of 17.7 μm was added to Lipofundin MCT 20% emulsion by stirring. In this case, a relatively large size of powder was employed, the size distribution is given in Fig. 2 (curve A).

The mixture was homogenised at 1500 bar, samples were drawn at 1, 5, 10, 15 and 20 cycles for analysis. Fig. 2 shows the size distribution of the original Lipofundin emulsion. Size analysis of the homogenised mixture (Fig. 2C) revealed that the size of the drug-loaded emulsion was further slightly reduced and no drug crystals were detectable anymore (i.e. to be precise, no crystals larger than the bulk population of the emulsion).

The mean PCS bulk diameter decreased slightly from the 300 nm in the original Lipofundin to 249 nm at cycle 5, then it stayed practically constant (250–255 nm). The PI is slightly increased at cycle 20 which is attributed to the decrease in the mean size and simultaneously having some larger droplets being non-diminuted, thus broadening slightly the size distribution (Fig. 3, upper). To quantify the larger sized droplets being present in the emulsion, the diameters 90, 95 and 99% were calculated (D 90%, D 95%, D 99%). The LD data are based on the volume distribution and thus – in contrast to the number distribution – very sensitive towards the presence of a few larger sized particles. The mean PCS diameter of the bulk population

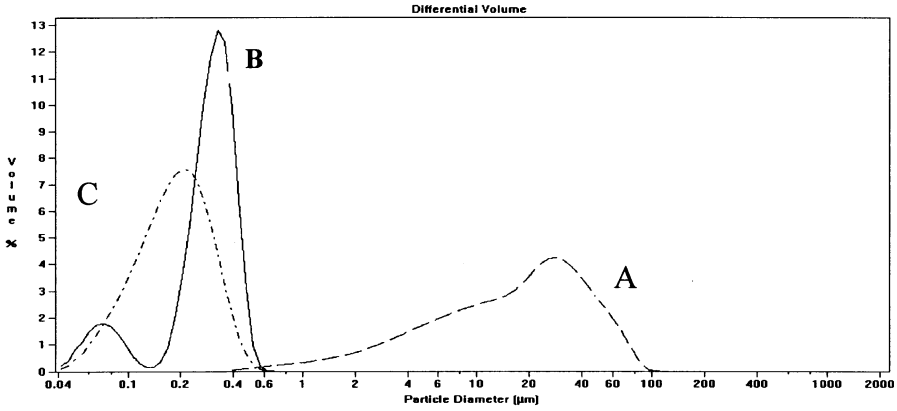

Fig. 2. Size distribution of Carbamazepine drug powder before addition to the emulsion (A), size distribution of the original Lipofundin MCT emulsion (B) and size distribution of the homogenised mixture with incorporated Carbamazepine (C) (*y*-axis: volume %, *x*-axis: size [µm], standard deviation <0.1%)

showed no change after cycle 5, the diameter D 99% showed a slight increase (Fig. 3, lower). That means additional cycles and the related energy input created some limited droplet coalescence. This is in agreement with the slight increase of the PCS PIs, the content of micrometer emulsion droplets. However, the content is so low that a cycle number of 20 can be applied when necessary for complete dissolution of a drug; the emulsion is still an i.v. injectible product.

3.2. Carbamazepine emulsions with increasing drug load

No remaining drug crystals could be detected in the low concentrated 0.5 mg/ml emulsion, neither by light microscopy nor by the centrifugation method. Therefore, in the next step, emulsions with increasing drug load were produced having the concentrations 1.0, 5.0 and 10 mg/ml. Size analysis by PCS revealed that increasing the drug load had a distinct effect on the obtained mean diameter of the bulk droplet population. The PCS diameters decreased with increasing drug load, e.g. 250 nm at 0.5 mg/ml to below 200 nm at 10 mg/ml (cycle 20). The PCS diameters at different cycle numbers were very similar or even identical with each drug concentration (Fig. 4, upper) indicating that the highest dispersitivity was reached even at just five homogenisation cycles. The remaining cycles up to 20 were

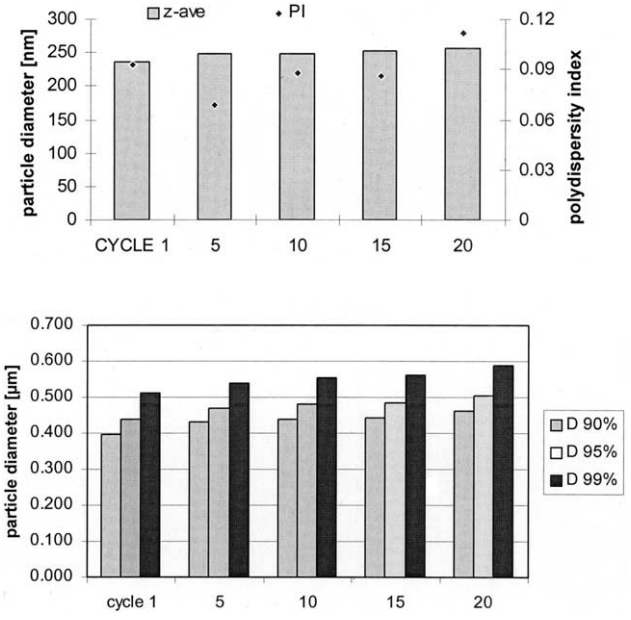

Fig. 3. PCS diameter (Z-ave) and polydispersity index (PI) (upper) and LD diameters D 90, 95 and 99% (lower) of the homogenised emulsion as a function of cycle numbers (drug concentration 0.5 mg/ml, standard deviations <0.1%).

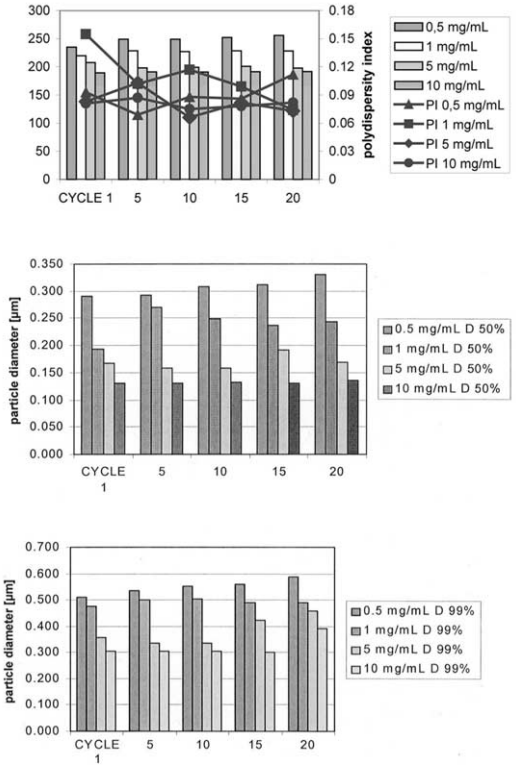

Fig. 4. PCS diameters and polydispersity index (PI) (upper) and LD diameters D 50% (middle) and D 99% (lower) as a function of cycle number of emulsions loaded with increasing amounts of Carbamazepine ($n = 3$).

to ensure complete disintegration and dissolution of any drug crystals, or at least to dissolve which was dissoluble in the lecithin layer.

The LD diameters showed a similar behaviour. There was a distinct decrease in diameters 50 and 90% with increasing drug concentration (Fig. 4, middle and lower). The diameter 99% is a very sensitive diameter towards the presence of even a few larger particles. For increasing the drug concentration a much higher amount of large drug micrometer particles had to be added. Consequently the energy input per homogenisation cycle has to be distributed on a larger crystal mass, that means per unit drug less energy is available which should result in a slower decrease of the large drug crystals (i.e. higher D 99% values). Surprisingly, a decrease was even found for the D 99% values, even at high drug concentrations. This suggests a very fast dissolution of the crystals under the high-pressure conditions, i.e. the high streaming velocities of the water going up to approximately 700 m/s. Of course, the resolution of LD towards the detection of a few large particles in the presence of a huge bulk population of small particles has to be considered [8]. Therefore, these measurements were complemented by light microscopy and centrifugation studies (cf.3.4).

It is noteworthy, that at same energy input (1500 bar, 20 cycles), the droplet size of the emulsion decreased with increasing drug load. The only explanation is that the drug incorporation in the lecithin film changed its emulsifying properties, the oil is easier to disperse resulting in smaller droplets.

3.3. Assay of free, non-incorporated drug

Light microscopy was performed by analysing undiluted emulsions. The emulsions are not diluted to increase the probability of detecting even only a few large particles being present, a standard method applied in emulsion technology [10]. The microscopic fields were analysed at different magnifications that means, 630-fold to detect crystals with a size of a few micrometer and at 1250 magnification (oil immersion), to go for drug crystals in the range of a few 100 nm. To validate the light microscopy, drug nanocrystals of a nanosuspension were added to the emulsion in a concentration of 10 mg/ml and a 100-fold lower concentration, i.e. 0.1 mg/ml. Even at the lower concentration, drug crystals could be detected directly after addition, i.e. the method is sensitive enough to detect even such low amounts of 0.1 mg/ml undissolved drug (Fig. 5). Of course at the low concentration of 0.1 mg/ml, the crystals started dissolving (0.1 mg/ml is below saturation solubility!) and disappeared after approximately 10 min. No drug crystals even at large magnification could be detected in emulsions with 5 mg/ml, also none were found in 10 mg/ml when applying light microscopy (Fig. 5). These results were cross-checked by the centrifugation test.

Emulsions produced with increasing amount of Carbamazepine were analysed. At 5 mg/ml, drug could be detected, drug crystals were found also in the 10 mg/ml emulsion. This non-dissolved drug represents about 41% (Table 1) of the drug added to the emulsion system. Based on this, it should be possible to produce Carbamazepine emulsions with a drug load up to 3 mg/ml without any problems. It is not recommended to approach too much the maximum loading capacity to ensure complete dissolution of the drug. Changes in temperature during storage might lead to a supersaturation and uncontrolled crystal formation, crystals, which do not dissolve again. From this, a maximum concentration of 3 mg/ml appears more than sensible.

Applying light microscopy, in contrast to the centrifugation assay, no crystals were detectable in the 5 and 10 mg/ml emulsion. This is attributed to the facts that (a) according to PCS and LD, the crystals are ultrafine (around 200 nm) and (b) their number in relation to the emulsion droplets is extremely low (20% oil in emulsion, only 0.1% drug (= 1 mg/ml)). The size of the drug nanocrystals added prior to homogenisation (and also used for validation of the light microscopy) was still above 500 nm.

An increasing drug load was studied to assess the maximum concentration to be incorporated without having free drug crystals. It is important to incorporate the maximum drug concentration to minimise the injection volume. Knowing the maximum concentration to be incorporated without any crystals (mg/ml) the dose required for i.v. injection can be estimated on the basis of the single oral dose, its bioavailability and the shape of the blood profile to stay above the minimum therapeutic concentration.

The oral single dose is 200 mg, the oral bioavailability is about 70–80% [14]. Considering the shape of the blood profile, the dose range for i.v. injection might be somewhere in the range of 20–50 mg. Assuming an emulsion concentration of 3 mg/ml, this would lead to a total injection volume of 7–18 ml which is in an acceptable range.

3.4. Short-term stability of Carbamazepine emulsions

It is well known that incorporation of drugs into the interfacial layer of emulsions can impair there physical stability. Incorporation can lead to a reduction in the zeta potential and consequently in reduced electrostatic repulsion, it is also possible that the microviscosity of the interfacial film changes. A reduction in the microviscosity leads to more fluid films and promotes coalescence of emulsion droplets. Lab experience shows that in many, such phenomena occur relatively fast and can be easily detected when applying highly sensitive sizing methods such as PCS. Due to the high sensitivity of the PCS, the standard deviation of typically about 1%, even slight increase in size at the beginning of the stabilisation can be detected. Therefore, as a first step a short-term stability over 4 weeks was performed.

Fig. 6 shows the PCS (upper) and LD data (lower)

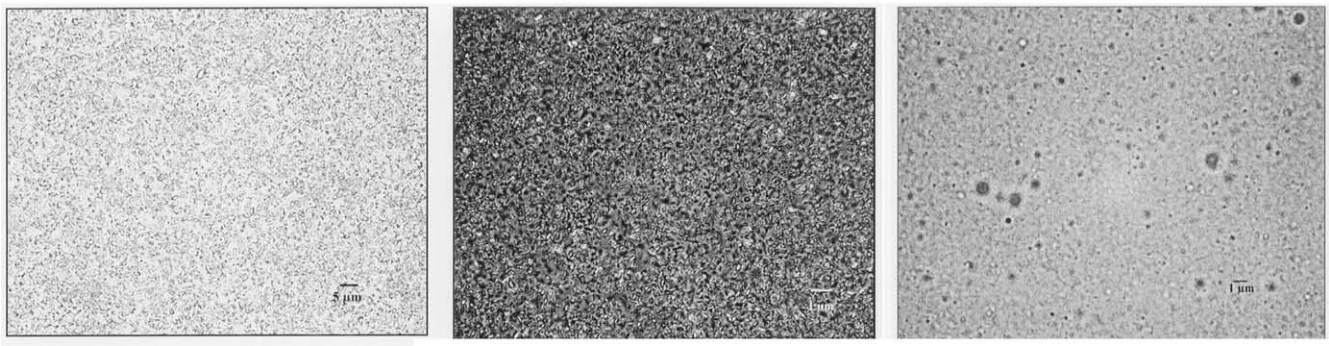

Fig. 5. Light microscopy analysis (polarised light, magnification 1000-fold) of Lipofundin emulsion spiked with 10 mg/ml Carbamazepine nanosuspension (left), 0.1 mg/ml (middle) – both non-homogenised and homogenised emulsion with 10 mg/ml (right, no crystals detectable).

obtained for the different concentrated emulsion systems. The variations observed in PCS and LD data are in the range of normal fluctuations (Fig. 6). A slight increase was observed for the emulsion system loaded with 10 mg/ml Carbamazepine, the zeta potentials for all emulsions with 0.5–10 mg/ml are in a similar range of about −42 mV, increasing the drug concentration leads to an increase of the potential to above −50 mV. From this, it can only be concluded that a too high drug incorporation does not affect the interfacial properties of the stabilising lecithin layer leading to no increase in fluidity, at least from the data controlled by now.

3.5. Long-term stability of Carbamazepine emulsions

Of course the zeta potential measurements is only one parameter to predict the long-term stability of emulsions. Physical instabilities can be caused by localisation of the incorporated drug in the interfacial layer. This is exactly the case when applying the SolEmuls® technology. Incorporation of the drug into the interfacial layer can lead to a reduction in zeta potential below the critical value of 30 mV. However, this is not the case with Carbamazepine emulsions. A zeta potential above 30 mV is considered providing a good physical stability [9], however, it assumes for emulsions that one has a sufficient rigidity of the emulsifier layer. Incorporation of drugs can reduce the rigidity, that means increase the fluidity thus leading to fusion of the emulsifier layers and formation of larger droplets. Therefore, the long-term stability was monitored by particle size measurements.

From the technical point, there are two interesting drug formulations:

1. O/W emulsions with copied dissolution of the drug, because ideally, a high drug concentration;
2. hybrid dispersion being composed of drug-loaded droplets and additionally, simultaneously added drug crystals, allowing i.v. administration in distinctly lower volumes compared to 1.

Therefore, stability was monitored for the 3 (emulsion) and 10.0 mg/ml (hybrid emulsion). Fig. 7 shows the PCS and LD data of all formulations. There was practically no change in the PCS values, only very little increase in the LD diameters. The droplets are still far below 5 μm, the critical value for capillary blockade and, therefore, still injectable via the i.v. route.

It should be pointed out that these emulsions were prepared just by using the standard emulsion formulation for parenteral nutrition, i.e. the standard concentration of lecithin without any additional stabilising surfactants. Of course, it is possible to further improve the stability to yield systems to yield up to 3 years by optimising further the lecithin concentration or adding a co-surfactant e.g. a steric stabiliser such as Tween 80. Tween 80 is accepted for i.v. administration, therefore, it is no problem for the regulatory authorities. To achieve maximum stabilisation effect, combination of electrostatic repulsion and steric stabilising an appropriate surfactant mixture makes sense. In another study, ketoconazole was incorporated. It proved to be a classical example for destabilisation of the lecithin layer by

Table 1
Results of centrifugation test – total amount of Carbamazepine added to 100 ml emulsion, recovered amount of non-dissolved drug crystals in the centrifugation test and calculation as percentage of non-dissolved drug

Total amount of Carbamazepine added to 100 ml emulsion (mg)	Drug concentration (mg/ml)	Recovered amount of non-dissolved drug crystals (mg/ml)	% Non-dissolved drug	SD
50	0.5	0	0	–
100	1.0	0	0	–
500	5.0	2.07	41.3	±0.6
1000	10.0	2.98	29.8	±0.5

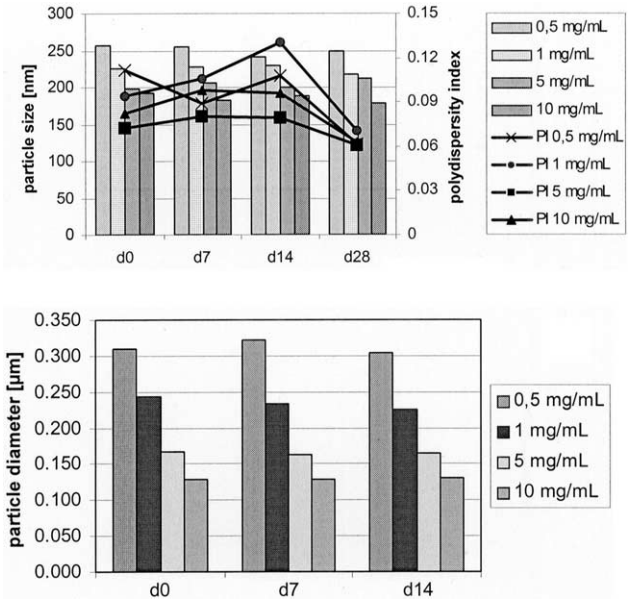

Fig. 6. PCS (upper) and LD diameters D 50% (lower) for Carbamazepine emulsions of different concentrations as a function of storage time.(d, days).

an incorporated drug, droplet coalescence occurred within the first few hours after the emulsion production. However, by adding Tween 80 as a sterically stabilising surfactant this problem was overcome [15].

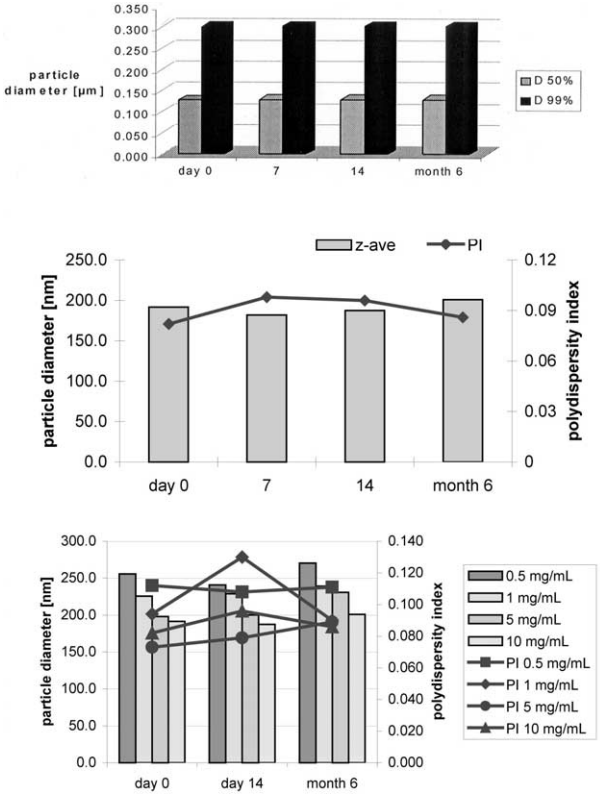

Fig. 7. LD diameters D 50%, D 99% (upper) and PCS values and polydispersity index (PI) (middle) for Carbamazepine emulsions (10 mg/ml) and PCS diameters and the polydispersity index (PI) for all concentrations (lower) as a function of a longer period of storage time.

4. Conclusions

The SolEmuls technology is able to incorporate Carbamazepine into i.v. emulsions at least up to 3 mg/ml drug concentration in dissolved form. The emulsion itself is overloaded at 10 mg/ml as indicated by free drug crystals in the dispersion. However, even the hybrid emulsions containing additionally ultrafine nanocrystals in a stable dispersed form are i.v injectable. Studies being presently performed are the emulsion/hybrid dispersion stability during autoclaving and the long-term stability after sterilisation. However, even if autoclaving would not be possible, production of Carbamazepine emulsions could be performed aseptically because the production equipment used is suitable for aseptic production. To summarise, SolEmuls appears as a promising technology for the production of emulsions with drugs, which have to be localised in the interfacial layer due to their simultaneously poor solubility in water and oils. The striking feature of the technology is its simplicity.

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