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European Journal of Pharmaceutics and Biopharmaceutics 62 (2006) 227–234
European Journal of Pharmaceutics and Biopharmaceutics
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Research paper

# Development of an in vitro/in vivo correlation for lipid formulations of EMD 50733, a poorly soluble, lipophilic drug substance

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Received 3 September 2004; accepted in revised form 20 August 2005
Available online 24 October 2005

**Abstract**

**Purpose**: To develop lipid semisolid formulations of EMD 50733, a poorly soluble, neutral drug candidate and to develop an in vitro–in vivo correlation for these formulations using the dog as the in vivo model. **Methods**: The model drug, EMD 50733, (with BCS Class II properties) was dissolved in molten lipid/surfactant mixtures and the melt was filled into hard capsules and allowed to re-solidify at room temperature. The dissolution profiles in bio-relevant dissolution media and the bioavailability in dogs were measured and compared to that of a standard formulation consisting of a lactose/drug mixture. **Results**: The best results with respect to dissolution, stability upon storage and bioavailability were obtained with a formulation that contained a commercially available lipid mixture (Gélucire 44/14) and a solubilizing agent (2-vinylpyrrolidone). With this formulation it was possible to dissolve a typical drug dose in a fill volume suitable for a #0 capsule. Additionally, surface tension measurements showed that the formulation formed micelles during dissolution in aqueous media: the molecular dispersion of the drug in this self-micelle forming system is postulated to protect the drug from precipitation in vivo as well as in vitro. For other formulations tested, neither the in vitro nor the in vivo performance indicated sufficient drug solubilizing properties. **Conclusion**: To achieve adequate and reliable dissolution of poorly soluble drugs in vivo, lipid excipients should not only have appropriate solubilizing properties for the drug in the formulation, but should also assist in maintaining drug in solution during release in the GI tract.


*Keywords:* Poorly soluble drugs; Gélucire 44/14; Vitamin E TPGS; Lipid excipients; BCS class II; Dissolution; Bioavailability; In vitro–in vivo correlations

## 1. Introduction

Until the late 1980s new drugs were discovered mostly by derivation and optimization of the chemical structure of 'lead compounds' that were traditionally identified from the structures of neurotransmitters, hormones and other endogenous substances, or which were extracted from plants and other sources [1]. The situation changed dramatically during the 1990s with the establishment of combinatorial chemistry and high throughput screening (HTS) methods [2,3]. The spectrum of structures expanded and as a result a large number of new pharmacologically active substances were identified. Unfortunately the pharmacological activity was often accompanied by problematic physicochemical and biological properties such as poor solubility and permeability. All too often, the poor bioavailability resulting from solubility and/or permeability problems were identified at a rather late stage of the development process, making it difficult to modify the chemical structure of the compound and forcing pharmaceutical companies to invest resources in formulation development of new chemical entities (NCEs) to a virtually unprecedented extent.

The model drug of the present work, EMD 57033, has properties fairly typical of the 'new breed' of drugs: poor solubility in water (just under 5 μg/ml at 37 °C) but moderately high lipophilicity (log $P = 2.7$) indicating good passive permeability through the gastrointestinal (GI) membrane. The maximum absorbable dose (MAD) of a drug depends on the factors such as solubility, permeability, intestinal water volume and intestinal transit time [4]. In the case of poorly soluble, lipophilic drugs (typically belonging to Class II of the BCS) [5],

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doi:10.1016/j.ejpb.2005.08.009

a major limiting factor to oral bioavailability is the solubility of the drug. In the case of EMD 57033, the MAD was calculated to be much lower than the dose required to achieve the intended pharmacological effect.

One strategy to improve the oral absorption of such drugs is to administer them with food. The observation that the bioavailability of poorly soluble drugs often increases when taken with food can often be associated with two factors, direct interactions of the drug with food components and their digestive products and the physiological changes in conditions in the GI tract associated with the change from fasted to fed state [6–8]. The former often arise in conjunction with the emulsification process of the fatty food components as oils and fats are degraded into mono- and diglycerides. These interactions led to an interest in the development of formulations containing ingredients similar to fatty food components [9,10]. An innovation in the field of emulsions was the self-emulsifying drug delivery systems (SEDDS), which consist mainly of an oil component and a surfactant [11–15]. As the name suggests, emulsions are spontaneously formed when a SEDDS formulation comes in contact with aqueous media.

The purpose of the present work was first to investigate formulation of the model drug with excipients according to the SEDDS principle. The most promising excipients tested in terms of their ability to completely dissolve a dose of EMD 50733 in a small enough volume to permit fill into an easy to swallow #0 capsule, were Gélucire 44/14 and Vitamin E TPGS. These formulations were then investigated further with respect to their dissolution profiles, ability to lower the surface tension of dissolution media and hence prevent precipitation, stability after storage at room temperature, and, their bioavailability in dogs. In the Bioavailability studies, the lipid formulations were compared to a standard formulation consisting of a simple drug–lactose mixture and to intravenous (i.v.) administration.

## 2. Materials and methods

### 2.1. Materials

A commercially available mixture of mono-, di- and triglycerides and esterified PEG (Gélucire 44/14™, HLB = 14) and a structurally similar surfactant with a lower HLB (Labrafil M 2130 CS™, HLB = 4) were generously donated by Gattefossé s.a., France. 2-pyrrolidone (Soluphor P) was obtained from BASF (Ludwigshafen, Germany). Vitamin E TPGS (an alpha-tocopheryl-derivate) was purchased from Eastman (Kingsport, USA) and PEG 1000 was obtained from Merck KGaA (Darmstadt, Germany). EMD 57033 (log *P*: 2.7, neutral compound, aqueous solubility (37 °C): 5 μg/ml, MW: 425, MP: 167 °C) was synthesized at Merck KGaA. Sodium glycocholate was purchased from Fluka Chemie AG (Steinheim) and the egg-lecithin was kindly donated by Lipoid GmbH (Ludwigshafen).

Table 1
Overview of the formulations tested

| Formulation | Ingredients | Amount per capsule (mg) |
|---|---|---|
| Gélucire | EMD 57033 | 30 |
| | Soluphor P | 110 |
| | Gélucire 44/14 | 780 |
| Vitamin E TPGS | EMD 57033 | 30 |
| | Vitamin E TPGS | 420 |
| | PEG 1000 | 140 |
| | Labrafil M 2130 CS | 140 |
| Drug/lactose mixture (10%) | EMD 57033 | 30 |
| | Lactose | 270 |
| i.v.-Formulation | EMD 57033 | 30 |
| | PEG 200 | 2220 |

### 2.2. Preparation of the formulations

The formulations are summarized in Table 1.

After melting the lipid excipients at 65–80 °C, the drug was added under continuous stirring. After completely dissolving the drug, the drug-melt dispersion was then filled into hard gelatine capsules by means of a dispenser and allowed to cool in the capsule to room temperature to re-solidify. In one formulation, an appropriate quantity (12%) of a solubilizing agent (2-vinylpyrrolidone) was added to the drug-Gélucire 44/14 dispersion in order to completely dissolve the drug. The resulting capsules contained 30 mg EMD 57033 (0.07 mmol). In a second formulation, Labrafil M 2130 CS and PEG 1000 were used in addition to Vitamin E TPGS to achieve complete drug dissolution. The control formulation was a simple drug–lactose triturate prepared in a Turbula-Mixer and containing 10% w/w EMD 57033. The i.v. solution was prepared by dissolving 30 mg of EMD 57033 in 2.22 g PEG 200 at room temperature.

### 2.3. Analysis of in vitro samples by HPLC

For analysis of samples from content uniformity and dissolution studies, a HPLC system consisting of a Merck Hitachi pump L-6200 A, a Merck Hitachi Autosampler AS-4000 and a Merck Hitachi UV–vis Detector L-4250 was used. The peak areas were calculated using Merck Hitachi D-7000 Chromatography Data Station software. For EMD 57033, the analysis were performed on a Licrospher 60, RP select B 125-3 (5 μm) column, using a mixture of 70% water and 30% acetonitrile as mobile phase with a flow rate of 1 ml/min. The drug was detected at a wavelength of 204 nm and eluted at approximately 9 min. Standard curves, constructed over the concentration range of interest, were used to determine concentrations. The limit of detection for EMD 57033 was determined to be 0.02 μg/ml. Stress testing regarding light (at dry and dissolved status), pH and heat were performed and it was shown that EMD57033 is stable to these factors.

### 2.4. Solubility studies

The solubility of the drug was determined in Simulated Gastric Fluid USP 25 (sine pepsin) containing 0.1% Triton X 100 ('SGF+'), Fasted State Simulated Intestinal Fluid ('FaSSIF') and Fed State Simulated Intestinal Fluid ('FeSSIF') [16–19] and also in the aforementioned media with the addition of either the excipients of the Gélucire 44/14 or the Vitamin E TPGS formulation in amounts corresponding to those used in the preparation of the respective formulation. Approximately 30–50 mg EMD 57033 were weighed into a vial and about 15 ml of one of the above-mentioned dissolution media were added. The vials were shaken at 37 °C at 150 rpm and samples drawn after 3, 24, 48 and 72 h, filtered immediately through a 0.45 μm filter and analyzed per HPLC as described above.

### 2.5. Preparation of the dissolution media

The simulated gastric fluid is based on the Test Solution of the same name described in the United States Pharmacopeia [20], with the modifications that SGF+ contains no pepsin and 0.1% Triton X 100 (surfactant) is used to reduce the surface tension to that typically observed in gastric aspirates [21].

FaSSIF, containing 3 mM sodium taurocholate and 0.75 mM lecithin, having a pH of 6.5, was prepared according the following method: 138.5 ml 0.1 N NaOH, 3.9 g €KH2PO4 and 7.7 KCl were brought to a final volume of 1 l with de-ionized water to produce 'blank' FaSSIF. Then 1.65 g of sodium taurocholate was dissolved in 450 ml of the 'blank' FaSSIF and 5.9 ml of a 10% solution of egg-lecithin in chloroform was added to this solution to produce an emulsion. The chloroform was then driven off on a rotavapor and the resulting clear solution was adjusted to 1 l with 'blank' FaSSIF.

FeSSIF, containing 15 mM sodium taurocholate and 3.75 mM lecithin was prepared according to the method for FaSSIF solution, with the following adjustments: first, the 'blank' FeSSIF buffer consists of 101 ml 1 N NaOH, 144 ml 1 M acetic acid and 15.2 KCl in total volume of 1 l and second, the FeSSIF is prepared with 8.25 g of sodium taurocholate and 29.54 ml of a 10% solution of egg-lecithin in chloroform.

### 2.6. Dissolution experiments

The dissolution characteristics of the various formulations were examined by the paddle method (USP XXV method 2) using a Pharma Test (Type PTWS) dissolution tester. The release profiles were examined in 900 ml SGF+, FaSSIF and FeSSIF using a paddle speed of 50 rpm and all tests were performed in triplicate. Samples (5 ml) were periodically withdrawn using a glass syringe fitted with a stainless steel sampling device. The drawn volume of media was replaced with the same volume of blank media, which was kept in a separate vessel at 37 °C. The sample was immediately filtered through a 0.45 μm filter (Spartan® 13/0,45 RC, PP; Merck Eurolab GmbH) and appropriately diluted prior to analysis of dissolved drug concentration by HPLC.

### 2.7. Surface tension measurements

Surface tension of solutions of the excipients of the lipid formulations in de-ionized water in concentrations from 0.01 g/l up to 100 g/l were measured to investigate whether the formulation contained enough surface active behaviour to produce micelles under standard dissolution conditions (37 °C, 900 ml). Surface tension was measured at 37 °C by the plate method (Krüss digital tensiometer K12, Krüss GmbH, Hamburg) ($n = 10$ per concentration).

### 2.8. Bioavailability studies with EMD 57033

A cross-over study of the three formulations, i.e. the drug–lactose mixture, the Gélucire 44/14 formulation, the Vitamin E TPGS formulation, and an i.v. bolus dose (drug dissolved in PEG 200) was conducted in four male beagles. After an overnight fast of 16 h the dogs were administered one of the formulations; venous blood samples were collected at 30 min, 1, 2, 4, 6 and 24 h and analyzed by HPLC. The dogs had access to water ad libitum, but no food until 4 h after the dose was administered.

The plasma samples were stored at −20 °C until they were analyzed. After the samples were defrosted, they were mixed (Vibrofix), a portion was discarded and the internal standard (EMD54616) was added. EMD 57033 and the internal standard were extracted with 1-Chlorobutan and the extract evaporated under nitrogen. The dry residual was re-dissolved with solvent and analyzed by HPLC. The limit of quantification for EMD 57033 was determined to be 10 ng/ml when 0.2 ml plasma was used.

Ethical approval for the study was obtained from the Merck KGaA Ethics Approval Committee (approval number DA 4/174).

### 2.9. Data analysis and statistical presentation

Results for in vitro studies are reported as means with standard deviations.

For the animal studies the pharmacokinetic parameters were determined as follows. $C_{max}$ and $t_{max}$ were identified from each individual concentration data set. AUC was calculated for each profile according to the trapezoidal rule, truncating results at 24 h (last sampling time). Absolute bioavailability was calculated on the basis of the $AUC_{0-24\ h}$ values. Results are reported as mean and coefficient of variation for $C_{max}$ and AUC, for $t_{max}$ the median value is reported.

Correlations were established on a rank order (modified USP Level C) basis. Rather than correlating %dissolved at a given time point with a descriptive pharmacokinetic parameter, e.g. AUC or Cmax, the dissolution rate was used as the in vitro correlating parameter. This was necessary because of the incomplete dissolution of the lactose triturate.

## 3. Results

### 3.1. Solubility and dissolution of EMD 57033 and its formulations

The solubilities of EMD 57033 in various dissolution media are compared in Fig. 1. In addition, the solubility enhancement of the drug due to the presence of the lipid excipients in the media (in amounts corresponding to the content of one capsule in the standard volume of dissolution medium) is shown. EMD 57033 has a solubility ranging from 4.7 μg/ml in pure water through 7.8 μg/ml in SGF+ and 6.4 μg/ml in FaSSIF to 12.6 μg/ml in FeSSIF. The influence of the excipients in the Gélucire 44/14 and Vitamin E TPGS formulations resulted in only a slight solubility enhancement in all media.

The dissolution behaviour of the lactose (control) formulation, which contains the micronized drug in a crystalline form, is shown in Fig. 2. The rank order of results in the three media reflects the solubility of the drug in these media. This is affirmed by results in Table 2, which compares the solubilities with the maximum concentrations reached during dissolution.

The dissolution behaviour of EMD 57033 from the Gélucire formulation is depicted in Fig. 3. In contrast to the results with the lactose formulation, the semisolid formulation containing Gélucire 44/14 shows a nearly 100% release of the drug. In addition to data obtained with the freshly prepared formulation, the dissolution behaviour after 2 years storage, performed in SGF+, is also shown. Even after 2 years of storage the profile did not change. The maximum concentration resulting from dissolution of a capsule containing the Gélucire formulation is much higher in all media than from the drug/lactose mixture, and considerably exceeds the solubility of the drug—even when the effect of the excipients on the equilibrium solubility in the dissolution media are taken into account (Table 2). Therefore dissolution from the Gelucire formulation results in supersaturation. The plateau in the curves indicates that the drug does not precipitate even during an extended period of dissolution (3 h).

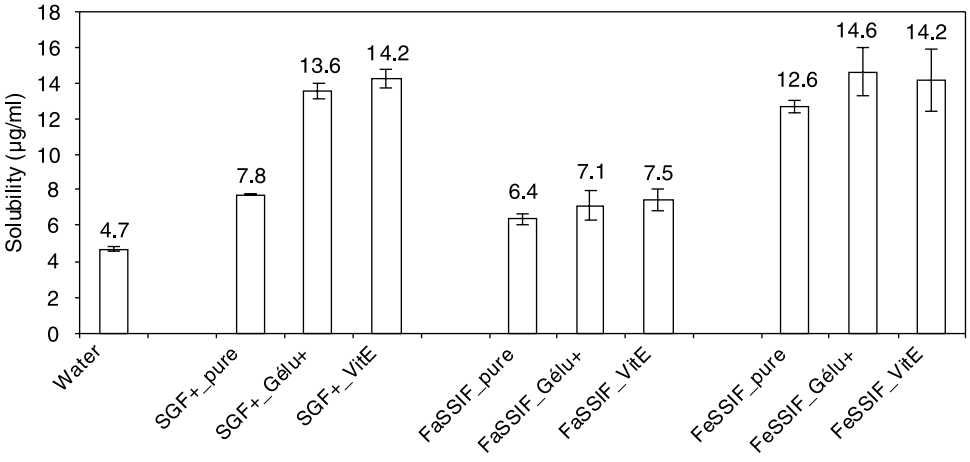


Fig. 1. Solubility of EMD 57033 in various media with and without the addition of lipid excipients.

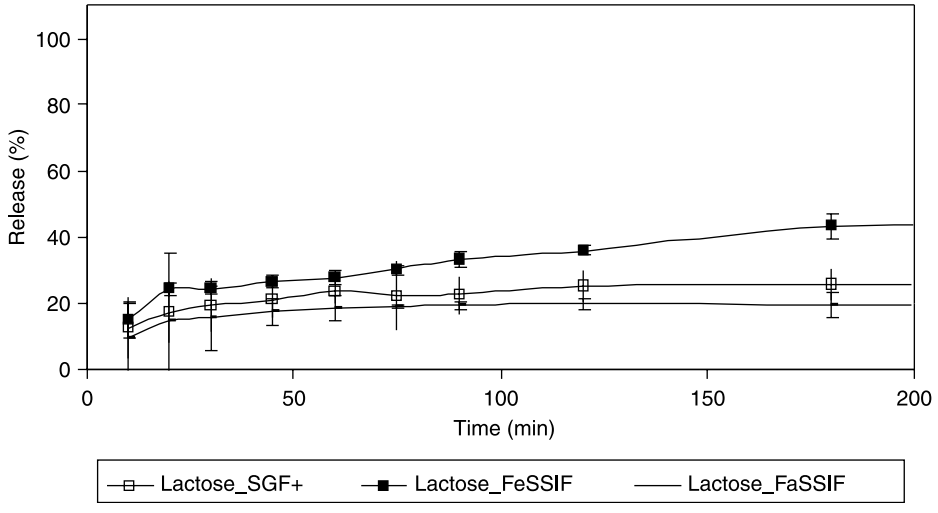


Fig. 2. Dissolution of the EMD 57033/lactose formulation in various media.

Table 2
Solubilities of EMD 57033 in different dissolution media and maximum concentrations resulting from dissolution of different formulations

| Media | Solubility of EMD 57033 at 37 °C (μg/ml) | Maximum concentration upon dissolution from lactose-standard (μg/ml) | Maximum concentration upon dissolution from Gélucire (μg/ml) | Maximum concentration upon dissolution from Vitamin E TPGS (μg/ml) |
|---|---|---|---|---|
| SGF+ | 7.8 | 9.2 | 26.1 | 30.9 |
| FaSSIF | 6.4 | 5.7 | 29.3 | Not tested |
| FeSSIF | 12.6 | 12.2 | 29.3 | Not tested |

The dissolution results with the formulation containing Vitamin E TPGS as the main excipient are shown in Fig. 4. The curve resulting from the freshly prepared formulation is flatter compared to the Gélucire-formulation, but also provides release of over 90%. With a maximum concentration of 30.9 μg/ml compared to the solubility of 7.8 μg/ml of EMD 57033 in SGF+, the dissolution is highly supersaturated in this case, too. Unfortunately after 1 month of storage at room temperature, the dissolution decreased to a maximum of less than 40% release.

### 3.2. Surface properties of the lipid formulations

The results from the measurements of the surface tensions with the two semisolid formulations are shown in Figs. 5 and 6. The components of the Gélucire-formulation have a critical micelle concentration (CMC) of about 0.01 g/l. As one capsule contains about 900 mg of formulation, the concentration of the lipid excipients is about 1 g/l after complete dissolution in a volume of 900 ml. Because this concentration is well above the

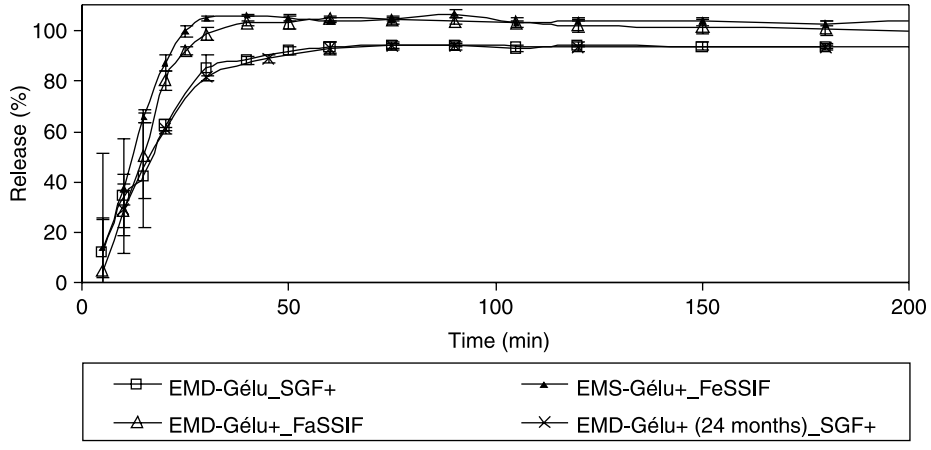


Fig. 3. Dissolution of the EMD 57033 Gélucire formulation in various media and in SGF+ after 2 years' storage at room temperature.

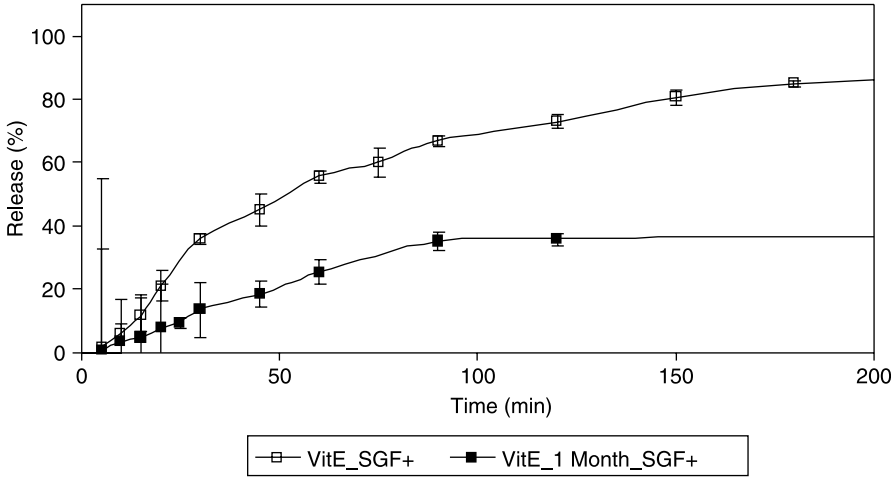


Fig. 4. Dissolution of the EMD 57033-Vitamin E TPGS formulation in SGF+ (freshly prepared and after 1 month's storage at room temperature).

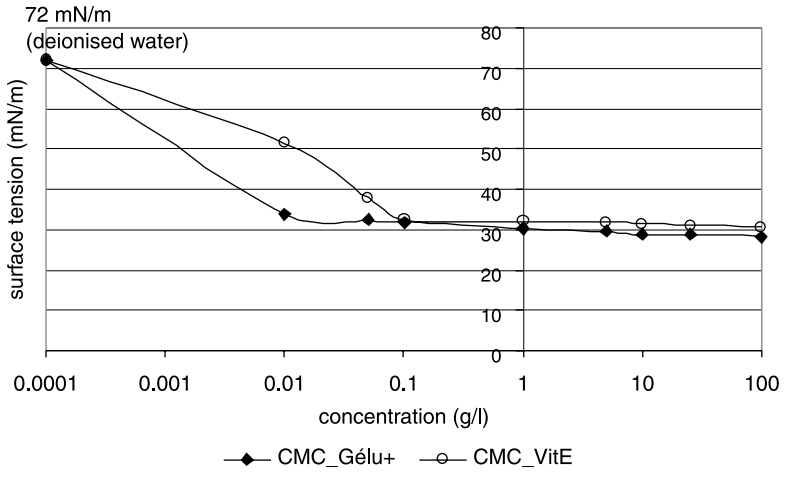


Fig. 5. CMC measurement of the ingredients of the Gélucire formulation and of the Vitamin E TPGS formulation, respectively.

measured CMC, it can be concluded that micelles are formed during release in the dissolution medium. Although the CMC of the Vitamin E TPGS formulation is slightly higher than that of the Gélucire formulation, the results indicate that, in this case, also a solution containing micelles is formed during dissolution.

### *3.3. Bioavailability studies with the lipid formulations*

The bioavailability studies with the three oral formulations and the i.v. control, which were performed in beagles, are illustrated in Fig. 7. The bioavailability of EMD 57033 from the drug/lactose mixture was 4.7%, calculated as absolute bioavailability compared to i.v. application of a pure solution of EMD 57033 in PEG 200. The bioavailability of the drug from the Vitamin E TPGS formulation was fourfold better than the standard, whereas the highest bioavailability, resulting from the Gélucire-formulation, was 10 times that of the standard, i.e. 47.8% (see also Table 3).

## 4. Discussion

### *4.1. Solubilities and dissolution*

The solubility of EMD 57033 was similar in the various dissolution media tested. These results indicate that the influence of bile salts and lecithin on the solubility is rather modest. It was previously shown by Mithani et al. [22] that bile component solubilization first becomes significant when the lipophilicity of the compound exceeds

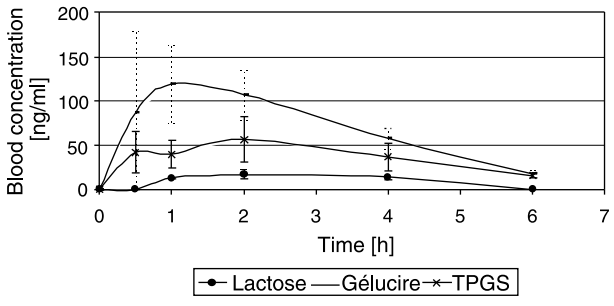


Fig. 6. Blood concentration against time after administration.

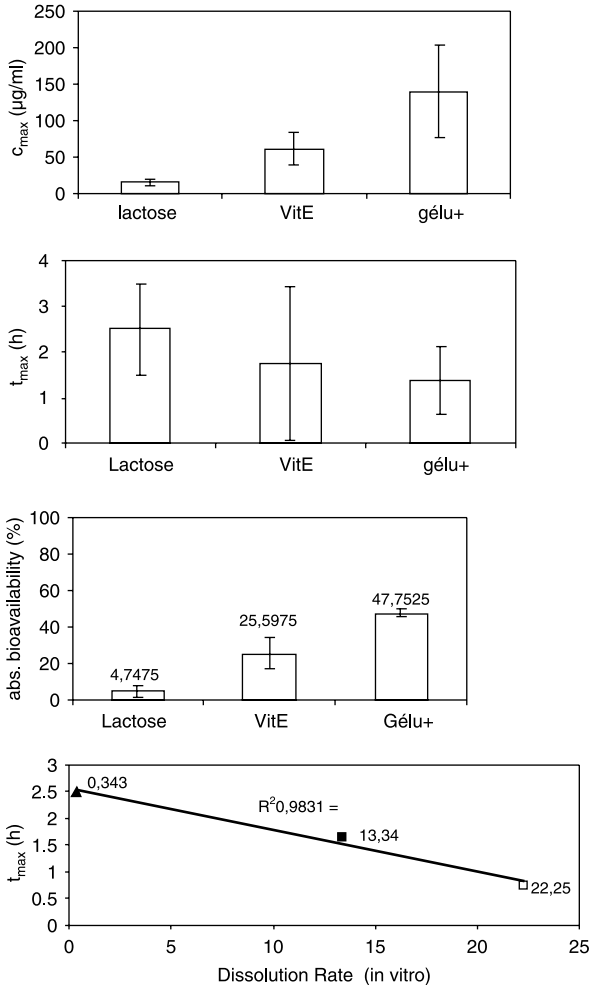


Fig. 7. Bioavailability of EMD 57033 in beagles from various formulations and Level C correlation ($t_{max}$ against dissolution rate in vitro).

Table 3
Overview over the pharmacokinetic data of the in vivo study in beagles

| Formulation | | Beagle 1 | Beagle 2 | Beagle 3 | Beagle 4 | Mean* | CV (%) |
|---|---|---|---|---|---|---|---|
| Lactose | $C_{max}$ (ng/ml) | 18.0 | 11.0 | 22.0 | 12.0 | 15.8 | 32.9 |
| | $T_{max}$ (h) | 2.00 | 2.00 | 2.00 | 4.00 | 2.00* | – |
| | AUC (ng/ml×h) | 37.75 | 16.95 | 75.80 | 25.60 | 39.03 | 66.5 |
| VitE | $C_{max}$ (ng/ml) | 60.0 | 50.0 | 94.0 | 43.0 | 61.8 | 36.6 |
| | $T_{max}$ (h) | 0.50 | 0.50 | 2.00 | 4.00 | 1.25* | – |
| | AUC (ng/ml×h) | 216 | 164 | 290 | 181 | 213 | 26.3 |
| Gélu$^{+}$ | $C_{max}$ (ng/ml) | 149 | 225 | 91.0 | 93.0 | 140 | 45.2 |
| | $T_{max}$ (h) | 2.00 | 0.50 | 1.00 | 2.00 | 1.5* | – |
| | AUC (ng/ml×h) | 454 | 504 | 364 | 322 | 411 | 20.2 |
| PEG 200 (i.v.) | $C_{max}$ (ng/ml) | 471 | 537 | 604 | 533 | 536 | 10.1 |
| | $T_{max}$ (h) | 0.125 | 0.125 | 0.125 | 0.125 | 0.125* | – |
| | AUC (ng/ml×h) | 912 | 1060 | 807 | 663 | 861 | 19.5 |
| | $T_{1/2}$ (h)$_{0.125–6}$ | 1.25 | 1.69 | 1.07 | 0.984 | 1.25 | 25.2 |

Data with asterisks indicate that the median value is reported rather than the mean.

about log $P=2$. Thus, the modest increase observed for EMD 50733 is consistent with its log $P$ value. Further, the excipients used in the two lipid formulations had barely any effect on the solubility of EMD 50733, at concentrations equivalent to the contents of one capsule in the standard volume of medium used for dissolution testing.

Much higher concentrations of EMD 50733 in solution were achieved during dissolution testing of the two lipid formulations than would be indicated by the corresponding solubility experiments or which could be achieved with the drug/lactose mixture. These results indicated that, on the one hand, the drug was present as a solid solution in the formulation and on the other hand, that the presence of the excipients was able to prevent precipitation, even during an extended dissolution period of 3 h. Reproducibility of results after 2 years' storage of the Gélucire formulation at room temperature indicated that the drug candidate remained in solution in the formulation over this period. In contrast, the promising release characteristics of the Vitamin E TPGS formulation could not be sustained during storage, indicating that in this case crystallization of EMD 50733 occurred with time.

The plateau in the dissolution profiles, indicating lack of precipitation, is postulated to be due to the formation of micelles by the dissolving excipients. As the formulation dissolves, the drug candidate would be automatically incorporated in these micelles, thus protecting it from nucleation and subsequent precipitation. A diagram depicting this hypothesis is shown in Fig. 8. Further experiments, in which the pure drug was dissolved into dissolution media containing pre-dissolved excipients, indicated that dissolution only reached the % released commensurate with the drug solubility (results not shown, see [23]). The disparity in dissolution results with excipients in the formulation vs. in the dissolution medium at the beginning of the experiment underscore the importance of concomitant formation of the micelles in the hydrodynamic boundary layer during the dissolution of the drug.

### 4.2. Comparison of in vitro and in vivo performance

The bioavailability studies showed that there was a very strong rank order correlation between the dissolution characteristics of the solid formulations of EMD 50733 in various bio-relevant media and the extent of absorption of these formulations in beagles. Formulations that release the drug only slowly or incompletely in vitro were shown to behave in a commensurate manner in vivo. These results suggest that selection of a suitable lipid formulation of a poorly soluble, neutral drug candidate such as EMD 50733, can be performed at least partly on an in vitro basis.

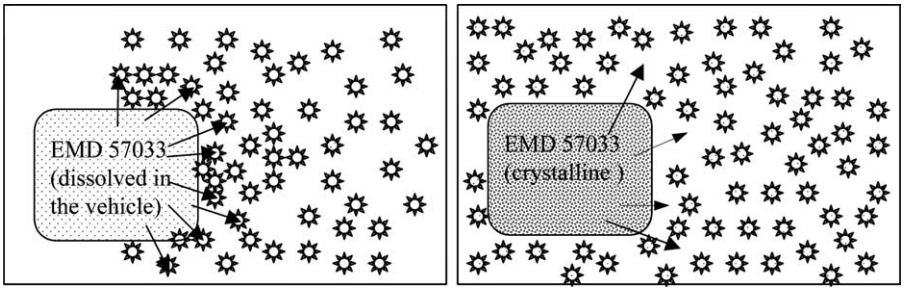


Fig. 8. Left: The drug candidate is directly incorporated in the micelles. Drug dissolution and formation of the micelles occurs simultaneously. Right: The micelles are already formed before the drug dissolves. The drug candidate does not penetrate into the micelles efficiently.

## Acknowledgements

The financial support of Karen Schamp during this project by Merck KGaA is gratefully acknowledged.

These studies were reported in part at CRS-Meeting (in 2000, Paris) and AAPS-Meeting (in 2001, Denver) as posters.

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