Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 220–226
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Preparation and characterization of a self-emulsifying pellet formulation

Ahmed Abdalla, Karsten Mäder *

Department of Pharmacy, Martin Luther University, Halle/Saale, Germany

Received 28 June 2006; accepted in revised form 17 November 2006
Available online 29 November 2006

Abstract

The purpose of the current study is to investigate the feasibility of producing solid self-emulsifying pellets using the extrusion/spheronization technique. Pellets were made from a mixture of C18 partial glycerides, Solutol® HS15 and microcrystalline cellulose. Pellets with good physical properties (size, shape, friability) and self-emulsifying properties were produced. The pellets were, in contrast to pellets lacking Solutol, able to transfer a lipophilic dye and a spin probe into the aqueous media. The release kinetics and the microenvironment of the pellets during the release process were assessed using electron spin resonance (ESR) spectroscopy. The ESR results showed that the hydrophobic spin probe was localized mainly in the lipid environment all over the release time. Furthermore, the formulation was capable of accelerating the release of the drug diazepam and achieving a diazepam concentration above its saturation solubility.

In conclusion, spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. The pellets are capable of transfering lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs.

Keywords: Pellets; Extrusion/spheronization; Self-emulsifying drug delivery systems; Poorly water soluble drugs; Oral delivery system; ESR

1. Introduction

Nowadays, an increasing number of drugs are characterized by being poorly water soluble and highly lipophilic, resulting in a low and highly variable oral bioavailability. Due to this fact, many drug candidates fail to reach the market, although they exhibit potential pharmacodynamic activity. On the other hand, to achieve the desired plasma level, marketed poorly water soluble drugs are administered in higher doses than actually needed, leading to the rise of toxicity problems. Therefore, suitable formulation approaches need to be developed to improve solubility and bioavailability of poorly soluble drugs.

Strategies such as micronization, co-solubilisation, inclusion complexation [1], use of nanosuspensions [2], micellar solubilisation by surfactants, drug dispersion in carriers [3], and lipid-based formulations are presently employed to tackle the formulation challenges of poorly soluble drugs.

The use of lipid-based vehicles has generated considerable interest as a potential formulation approach to improve oral bioavailability of poorly water soluble drugs [4–6]. Lipid formulations are a diverse group of formulations with a wide variety of properties and usually consist of mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents [7]. Lipid-based formulations can decrease the intrinsic limitations of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilised phases from which absorption takes place. The achievement of such phases will not essentially take place from the formulation itself, but alternatively from taking

* Corresponding author. Department of Pharmacy, Institute of Pharmaceutics and Biopharmaceutics, Martin Luther University, Wolfgang-Langenbeck Str. 4, D-06120 Halle (Saale), Germany. Tel.: +49 345 55 25167; fax: +49 345 55 27029.
E-mail address: Karsten.Maeder@pharmazie.uni-halle.de (K. Mäder).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.11.015

the advantage of the intraluminal processing to which lipids are subjected [8]. The extent of drug absorption from lipid vehicles is significantly affected by the dispersability of the administered lipid and drug. On the other hand, because of the inherent physical instability, the large volume of the two phase emulsion, and the poor precision of dose, the use of conventional emulsions is problematic. A formulation approach for avoiding such restrictive problems is the use of microemulsions or self-emulsifying drug delivery systems (SEDDS). The most famous example of a microemulsion-based system is the Neoral® formulation of Cyclosporine, which replaced Sandimmune® [9]. SEDDS have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs [10,11]. SEDDS are composed of a mixture of oil and a surfactant and they are capable of forming an O/W emulsion upon gentle agitation condition provided by gastrointestinal motion [7]. In such system, the lipophilic drug is presented in solution, in small droplets of oil, leading to the elimination of the dissolution step which can be the rate-limiting step in absorption of poorly water soluble drugs. SEDDS are usually formulated in a liquid form which has some disadvantages, especially in the manufacturing process, leading to high production costs. Furthermore, incompatibility problems with the capsule shell are common. The incorporation of the self-emulsifying mixture into a solid dosage form is desirable, but challenging, because self-emulsifying properties are harder to achieve with solid materials. However, the potential advantages of solid self-emulsifying dosage forms have attracted several authors [12,13].

Pellets have many advantages, over conventional solid dosage forms, making them of great interest to pharmaceutical industry. Flexibility in designing and developing the dosage form, and improving the safety and efficacy of bioactive agents are among these advantages. Due to the fact that pellets disperse freely in the gastro-intestinal tract, drug absorption is maximized with a subsequent reduction in peak plasma fluctuations and hence minimizing potential side effects without lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit time and therefore a reduction of intra- and inter-subject variability of plasma profiles is achieved. In addition, pellets reduce the problem of high local concentration of drugs and thus avoiding irritation that may be caused by certain active constituents [14].

The most widely used techniques for pellet production in the pharmaceutical industry are extrusion/spheronization (ES), solution/suspension layering, and powder layering. The process of ES has become the method of choice in the preparation of pellet-based dosage forms since it offers many technological advantages over the other methods, including the spherical shape with a narrow monomodal size distribution, good flow properties, low friability and uniform packing characteristics.

It is therefore very attractive to combine the advantages of self-emulsifying delivery systems with pellets. However, the development of self-emulsifying pellets is challenging, because high lipid loads often impair pellet formation. Using extrusion/spheronization, we focused our investigation on mixtures of mono- and di-stearate, Solutol® HS15 and MCC. Pellets were characterized for their size, shape, friability and dissolution. In addition, nitroxide loaded pellets were produced and the microenvironment within the pellets during the release process was monitored in an online process by the use of electron spin resonance (ESR) spectroscopy, since ESR is considered a powerful spectroscopic technique to monitor drug release processes non-invasively and continuously [15].

2. Materials and methods

2.1. Materials

Avicel PH 101 (Microcrystalline cellulose (MCC)) was purchased from FMC BioPolymer (PA, USA), and was used as the pellet forming material. Solutol® HS 15 (Macrogol-15-Hydroxystearate) was kindly provided by BASF AG, Ludwigshafen, Germany. Cithrol GMS® (C18 mono-and di-glycerides) was kindly provided by Croda GmbH, Nettetal, Germany. Tempolbenzoate (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl-benzoate, TB) and Tempol (2,2,6,6-tetramethyl-4-hydroxy-piperidin-1-oxyl, TL), were purchased from Aldrich Chem. Co., USA. Sudan®-red 7B dye was purchased from Riedel-de Haën AG, Germany. Diazepam was purchased from Fagron GmbH, Barsbüttel, Germany.

2.2. Methods

2.2.1. Preparation of pellets

The details of the composition of the dry ingredients of the formulations prepared are given in Table 1. The reference pellets were prepared by the same method used for the preparation of the self-emulsifying pellets.

2.2.1.1. Preparation of the self-emulsifying mixture. The preparation of the self-emulsifying mixture involved the following steps:

- Melting of GMS and Solutol at 70 °C.
- Dissolving the model drug, the dye or the spin probe in the molten blend.
- Addition of water to the molten lipid blend until a creamy mass is produced.
- Cooling to room temperature.
- Addition of the dry MCC and mixing in a kneader for 15 min.
- Further addition of water until a mass suitable for extrusion is obtained.

2.2.1.2. Extrusion/spheronization. The wet mass was extruded at 40 rpm in a radial screen twin-screw extruder (Fuji-Paudal, Japan) equipped with a die of 1-mm diameter circular openings and 1-mm thickness. The extrudate was

Table 1
Composition of the investigated formulations

Ingredients	Diazepam pellets		Sudan Red pellets		Pellets for ESR	
	Self-emulsifying	Reference	Self-emulsifying	Reference	Self-emulsifying	Reference
MCC PH 101	49.5	49.5	49.9	49.9	50	50
C18 mono- and di-glycerides	25	50	25	50	25	50
Solutol® HS15	25	–	25	–	25	–
Diazepam	0.5	0.5	–	–	–	–
Sudan Red	–	–	0.1	0.1	–	–
Nitroxide (TL or TB)	–	–	–	–	2 mmol/kg	2 mmol/kg

then spheronized for 5 min in a 250-mm radial plate spheronizer (Fuji-Paudal, Japan) using a cross-hatch frictional plate of $3 \times 3\ mm^2$ pitch and 1.2 mm depth. The resulting pellets were dried in an oven at 50 °C until a constant weight had been reached.

2.2.2. Pellet size analysis

Size analysis was performed using a set of standard sieves (Retsch, Hann, Germany) of a $\sqrt{2}$ progression ranging from 500 to 2800, with 100 g of pellets, agitated on a sieve shaker (Retsch, Hann, Germany) for 20 min. The modal size fraction and the interquartile range (IQR) were determined from the cumulative percent undersize curve. The geometrical mean diameter (D_g) and the geometrical standard deviation (σ_g) were determined from the log-normal distribution curve [16].

2.2.3. Pellet shape analysis

Shape analysis was performed by the use of a stereomicroscope (SZX9, Olympus, Germany), a digital camera (DIG 1300C, Micromotion, Germany) connected to a personal computer with an Image analysis software Image C (Imtronic, Germany). One thousand pellets were used and for each pellet, 36 Feret diameters were measured and used to calculate the mean Feret diameter. The maximum Feret diameter and Feret diameter 90° to the maximum Feret diameter were obtained and the aspect ratio was calculated as the ratio between the maximum Feret diameter and the Feret diameter 90° [17].

2.2.4. Assessment of self-emulsification

For the preliminary assessment of the self-emulsifying properties of the formulation, 0.1% Sudan Red was incorporated. Pellets (1 g) were then gently agitated in 50 ml distilled water. Agitation was provided by gentle shaking on a shaking water bath at 50 oscillations per min and a temperature of 37 °C. Samples were taken after 30 min. For microscopic examination using a light microscope (Axiolab re, Carl Zeiss, Germany) with an optical zoom of $50 \times /0.70$ and an eye piece of $10 \times /20$.

2.2.5. Friability testing of pellets

Friability testing was conducted using a friability tester (Arzneimittelwerk, Dresden, Germany). A 10 g pellet sample was placed into the drum together with 10 g glass spheres of 5 mm diameter, and rotated for 10 min at 25 rpm [18]. Pellets were then weighed and friability was calculated according to:

$$\text{Friability}\% = \frac{m_b - m_a}{m_b} \times 100, \quad (1)$$

where m_b and m_a are the masses of pellets before and after testing and the result is the mean of three runs.

2.2.6. Disintegration testing of pellets

Disintegration time of pellets was measured by the use of a disintegration tester (Erweka ZT2, Heusenstamm, Germany), modified by the installation of 500 μm mesh at the bottom of tubes. Six pellets were tested in distilled water at 37 °C and the end point was taken at the point at which no particles were present on the sieve.

2.2.7. ESR measurements

2.2.7.1. Basic principles. Electron Spin Resonance (ESR) spectroscopy (also known as electron paramagnetic resonance (EPR) spectroscopy) is a magnetic resonance method principally related to the more popular nuclear magnetic resonance (NMR) spectroscopy. ESR is used to detect and characterize paramagnetic materials such as free radicals and transition metals (e.g., copper and manganese). Since the majority of drug delivery samples are diamagnetic and ESR silent, the incorporation of a paramagnetic molecule or groups (e.g., nitroxide spin probes) is therefore necessary. Nitroxide spin probes and labels are very sensitive to their environment, and information about their mobility, microviscosity and micropolarity, microacidity, and concentration of dissolved oxygen can be reported from their spectral line shape. As an example, the spectral line shape changes progressively when the mobility changes from a free rotation (tumbling) in a low viscous environment to that of a restricted motion in an extremely viscous environment or solid state (powder spectrum). Furthermore, the hyperfine splitting constant (a_N) is sensitive to the polarity of the environment. A very broad variety of low and high molecular weight nitroxides with different physicochemical properties are available. Further details about the principles and applications of ESR are described in a recent review [15]. In this study, we have used the water soluble Tempol (TL) and the lipophilic, poorly water soluble Tempolbenzoate (TB) (Fig. 1) as model drugs to assess the release kinetics and the microenvironment

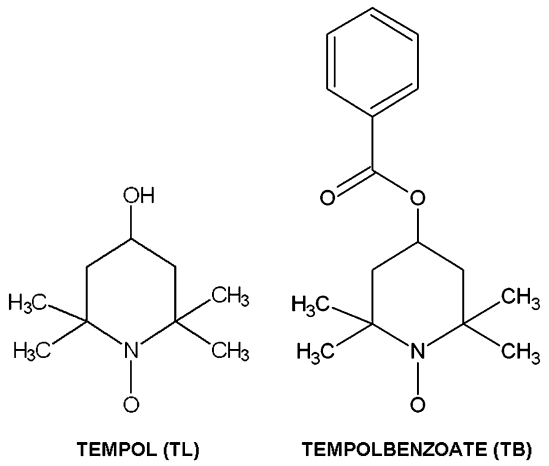

Fig. 1. Chemical structure of the ESR spin probes Tempol and Tempolbenzoate.

of the self-emulsifying pellets during the release process non-invasively and continuously by means of a flow through cell experiment [19].

2.2.7.2. ESR flow through cell experiment. Samples of 200 mg of Tempolbenzoate (TB), or Tempol (TL) loaded pellets (2 mmol/kg) were placed in a flow through cell [19]. Phosphate buffer (pH 6.8) was pumped into the cell, by means of peristaltic pump, at a rate of 4 ml/min and the ESR spectra were recorded continuously using a 1.3 GHz L-band spectrometer (Magnettech GmbH, Berlin, Germany) equipped with a reentrant resonator. The ESR parameters used were as follows: field center 49 mT, scan range 12 mT, scan time 60 s, and modulation amplitude of 0.14 mT.

2.2.8. Dissolution testing

The USP 24 rotating paddle apparatus (Pharma Test PTW II, Hainburg, Germany), rotating at a rate of 70 rpm and a temperature of 37 °C, was used to asses the release of diazepam from the pellets in two different conditions. In the first set of experiments, 900 ml phosphate buffer (pH 6.8) was used as the dissolution media and samples of pellets with a diazepam content

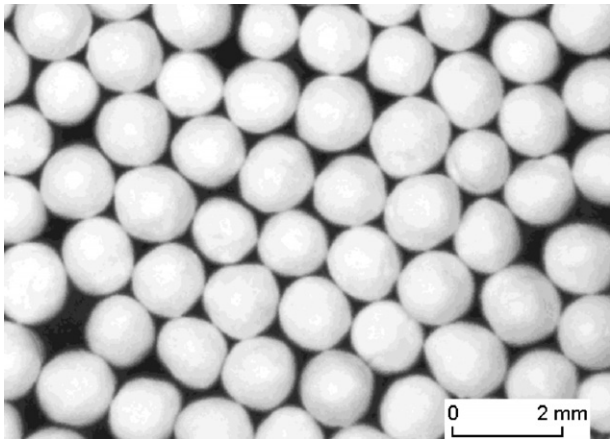

Fig. 2. Light microscopic picture of the produced pellets.

Table 2
Results of the size and shape analysis of the self-emulsifying pellets

Sieve analysis (100 g)	
D_g (μm)	1327
σ_g	1.26
IQR (μm)	355
Image analysis ($n = 1000$)	
$D_{Feret.Mean}$ (μm)	1307
SD	125.69
Aspect ratio	1.091
SD	0.0396

Table 3
Friability % and disintegration time for self-emulsifying pellets in the fraction 1000–1400 μm

Friability testing ($n = 3$)	
Friability (%)	1.2
SD	0.45
Disintegration testing ($n = 6$)	
Time (min)	22.32
SD	1.26

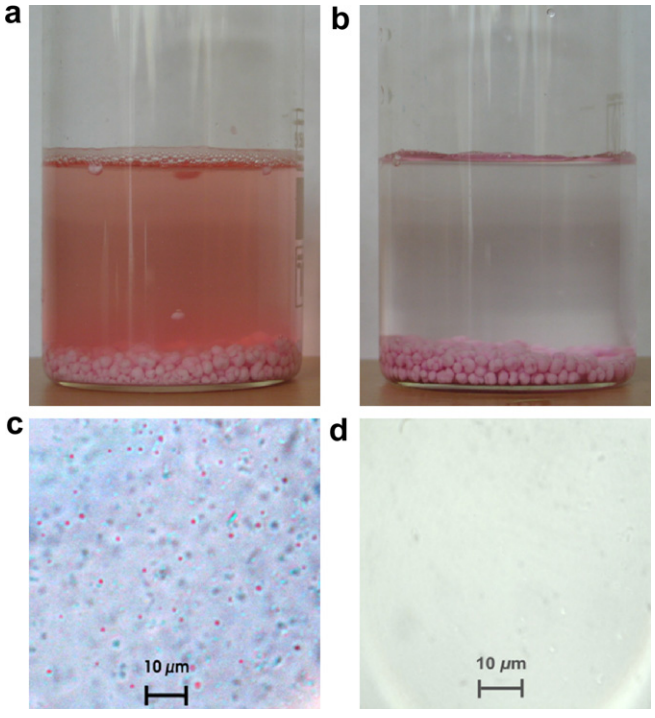

Fig. 3. Photograph showing the release media of (a) self-emulsifying pellet formulation. (b) Reference pellets, containing Sudan red dye, after 30 min of dissolution in distilled water at a temperature of 37 °C. And Microscopic picture of the release media of (c) self-emulsifying pellets. (d) Reference pellets.

of 2.5 mg were assessed. In the second set of experiments, the volume of the dissolution media was decreased to be 500 ml and pellets with diazepam content of 27.5 mg were used. Samples (5 ml) were withdrawn at regular time intervals, filtered and then assayed spectrophotometrically (Spectronic 60, Milton Ray, Ivyland, USA) at 241 nm.

3. Results and discussion

3.1. Physical characterization of the pellets

The amount of self-emulsifying mixture required to formulate pellets with good physical properties and without any apparent agglomeration was assessed, and the formula stated in this study was the best (Fig. 2). Aspect ratios were found to be 1.091 which conforms to the limit ($\leqslant$1.2) set by Chopra et al. [20] for optimum pellet shape and flow properties. The results of various physical measurements are shown in Tables 2 and 3.

The increase of Solutol content above 35% led to the production of pellets with poor physical characteristics. On the other hand, a loss of the self-emulsifying properties was observed when the content of Solutol was decreased below 25%. Furthermore, it was observed that the order of mixing is very critical for a successful extrusion/spheronization process. As an example, small rods rather than pellets were formed if the MCC was mixed with the molten glycerides prior to the addition of water.

3.2. Assessment of self-emulsification

The self-emulsifying formulation was able to introduce Sudan Red into water within the first few minutes following gentle agitation. While the reference pellets, composed of MCC and GMS, were not able to deliver the lipophilic dye into the media (Fig. 3a and b). Microscopic examination of the release media of the self-emulsifying pellets showed lipid droplets, incorporating the dye (Fig. 3c). On the contrary, microscopic examination of the release media of the reference pellets did not show any droplets (Fig. 3d).

3.3. ESR measurement

The release kinetics and the microenvironment of the formulation during the release process were assessed by low frequency ESR spectroscopy. The ESR spectra of the nitroxides in Solutol, GMS and GMS–Solutol mixtures were recorded (Fig. 4a and b). The mobility of the nitroxides is reflected in the line widths of the hyperfine splitting. Both spin probes are more mobile in Solutol compared to GMS. The mobility in 1:1 GMS–Solutol mixtures is

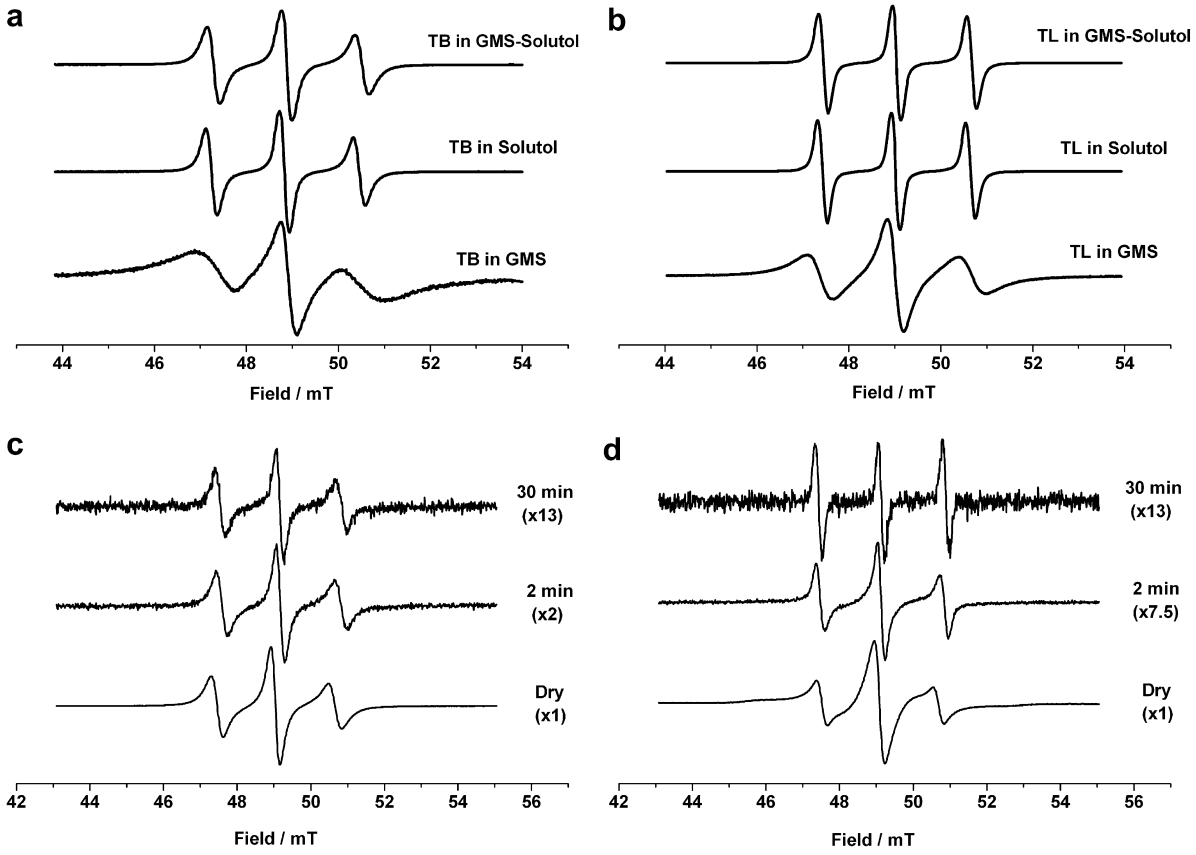

Fig. 4. ESR spectra of TB (a) and TL (b) loaded formulation ingredients and mixtures. ESR spectra of TB (c) and TL (d) loaded pellets before, 2 and 30 min after buffer exposure in the flow cell system.

comparable to that in pure Solutol and is higher compared to the mobility in dry pellets which contain MCC. This observation indicates that MCC causes a decreased mobility. However, the nitroxides still re-orientate quite fast in the solid material (within the nanosecond range).

After exposure to the dissolution medium, the ESR signal intensity decreased rapidly both for the hydrophilic TL and the lipophilic TB molecules due to the release of the nitroxides (Fig. 4c and d). Only small signals were detected after 30 min.

As the release media pass through the flow cell, the shape of the TL spectra changes significantly and rapidly into a sharp isotropic spectrum with a higher hyperfine splitting constant ($a_N = 1.72$ mT; Fig. 4d), indicating the presence of the spin probe in an aqueous environment. In contrast, the ESR spectra of the more lipophilic probe TB show no significant change of the spectral shape and the hyperfine splitting constant during the release process. This indicates the preferential localization of the TB spin probe in the lipid environment all over the study period (Fig. 4c).

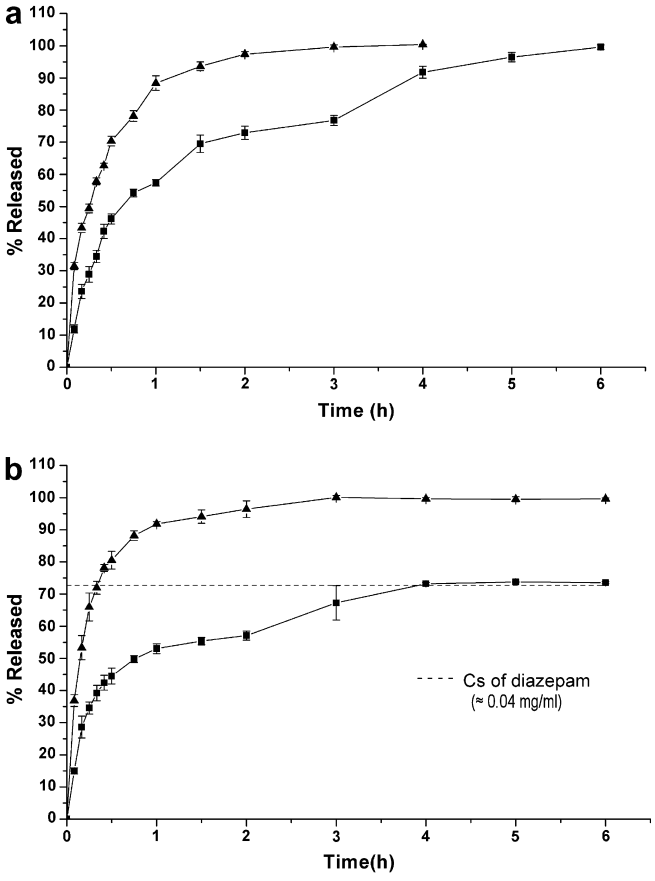

Fig. 5. Mean (±SEM, $n = 3$) percentage of (a) Diazepam released as a function of time (h) in 900 ml phosphate buffer, pH 6.8, and diazepam load of 2.5 mg from GMS/MCC pellets (■), and GMS–Solutol/MCC pellets (▲). (b) Diazepam release as a function of time (h) in 500 ml phosphate buffer, pH 6.8, and diazepam load of 27.5 mg from GMS/MCC pellets (■), and GMS–Solutol/MCC pellets (▲).

3.4. Dissolution testing

As shown in Fig. 5a, the complete release of diazepam from the non self-emulsifying GMS/MCC pellets has taken 3-fold the duration of that from the self-emulsifying pellets. Nearly 90% of the drug was released after 1 h, while only 55% was released from the GMS/MCC pellets after the same time. In the second experiment, with higher load of diazepam and lower volume of the dissolution media, the self-emulsifying pellets were capable of releasing diazepam into the media and a state of supersaturation was generated. Supersaturation was observed for several hours and there was no evidence of diazepam crystallization throughout the time of the experiment. On the other hand, pellets composed of MCC/GMS were only capable of releasing diazepam until the saturation solubility was reached (Fig. 5b).

4. Conclusion

The current results demonstrate that we were able to develop, by the use of extrusion/spheronization, a self-emulsifying pellet formulation with 50% of the self-emulsifying mixture. The pellets have a spherical shape, small size distribution, and low friability. In contrast to MCC–GMS pellets, they were able to transfer lipophilic dyes or drugs into the aqueous phase of the dissolution media. Therefore, a decreased food dependency (bile acid concentration, digestion rate) can be expected.

Pellet formation is strongly dependent on the pellet composition and the order of processing. MCC is essential as a spheronization aid in pellet production, therefore a compromise between the least amount of MCC that can produce pellets with good physical characteristics and the amount of lipid, drug containing phase, should be achieved. Since GMS alone is not self-emulsifying, Solutol was used to aid the self-emulsification process.

The ESR results indicate that the lipophilic spin probe (TB) mainly localizes in the lipid environment inside the pellets until it was completely released into the media. The release data showed a noticeable improvement in the in vitro dissolution of diazepam when compared to the release from the non-emulsifying formulation. Moreover, the results from the second release study, with higher load of diazepam and lower volume of the dissolution media, showed that the formulation was able to create and maintain a state of supersaturation for the poorly water soluble diazepam.

Acknowledgements

The authors are grateful to BASF AG for the generous gift of Solutol® HS 15 and to Croda GmbH for kindly providing Cithrol GMS®. The authors thank Ahmed Besheer for assistance in conducting the ESR measurements.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2006.11.015.

References

[1] J.W. Wong, K.H. Yuen, Improved oral bioavailability of artemisinin through inclusion complexation with β- and γ-cyclodextrins, Int. J. Pharm. 227 (2001) 177–185.
[2] V.B. Patravale, Abhijit A. Date, R.M. Kulkarni, Nanosuspensions: a promising drug delivery strategy, J. Pharm. Pharmacol. 56 (2004) 827–840.
[3] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[4] S. Chakrabarti, F.M. Belpaire, Bioavailability of phenytoin in lipid containing dosage forms in rates, J. Pharm. Pharmacol. 30 (1978) 330–331.
[5] T. Tokumura, Y. Tsushima, K. Tatsuuishi, M. Kayano, Y. Machida, T. Nagai, Enhancement of the oral bioavailability of cinnarizine in oleic acid in beagle dogs, J. Pharm. Sci. 76 (1987) 286–288.
[6] A.K. Trull, K.K.C. Tan, L. Tan, G.J.M. Alexander, N.V. Jamieson, Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion, Br. J. Clin. Pharmacol. 39 (1995) 627–631.
[7] C.W. Pouton, Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems, Eur. J. Pharm. Sci. 11 (2000) S93–S98.
[8] A.J. Humberstone, W.N. Charman, Lipid-based vehicles for the oral delivery of poorly water soluble drugs, Adv. Drug Del. Rev. 25 (1997) 103–128.
[9] J. Vonderscher, A. Meinzer, Rational for the development of Sandimmune, Neoral. Transplant Proc. 26 (1994) 2925–2927.
[10] C. Tuleu, M. Newton, J. Rose, D. Euler, R. Saklatvala, A. Clarke, S. Booth, Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone, J. Pharm. Sci. 93 (2004) 1495–1502.
[11] Shui-Mei Khoo, A.J. Humberstone, C.J.H. Porter, G.A. Edwards, W.N. Charman, Formulation and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, Int. J. Pharm. 167 (1998) 155–164.
[12] E. Franceschinis, D. Voinovich, M. Grassi, B. Perissutti, J. Filipovic-Grcic, A. Martinac, F. Meriani-Merlo, Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables and preliminary study on the in vitro absorption, Int. J. Pharm. 291 (2005) 87–97.
[13] M. Newton, J. Petersson, F. Podczeck, A. Clarke, S. Booth, The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture, J. Pharm. Sci. 90 (2000) 987–995.
[14] I. Ghebre-Sellassie, Pharmaceutical pelletization technology, Marcel Dekker, New York, 1989, pp. 1–7.
[15] D.J. Lurie, K. Mäder, Monitoring drug delivery process by EPR and related techniques- principles and applications, Adv. Drug del. Rev. 57 (2005) 1171–1190.
[16] A. Martin, Physical pharmacy, Lippincott Williams & Wilkins, Maryland, 1993, pp. 423–429.
[17] A.M. Bouwman, J.C. Bosma, P. Vonk, J.A. Wesselingh, H.W. Frijlink, Which shape factor(s) best describe granules? Powder Technol. 146 (2004) 66–72.
[18] R. Dreu, J. Širca, K. Pintye-Hodi, T. Burjan, O. Planinšek, S. Srčič, Physicochemical properties of granulating liquids and their influence on microcrystalline cellulose pellets obtained by extrusion-spheronisation technology, Int. J. Pharm. 291 (2005) 99–111.
[19] A. Besheer, K.M. Wood, N.A. Peppas, K. Mäder, Loading and mobility of spin-labeled insulin in physiologically responsive complexation hydrogels intended for oral administration, J. Control Release 111 (2006) 73–80.
[20] R. Chopra, F. Podczeck, J.M. Newton, G. Alderborn, The influence of pellet shape and film coating on the filling of pellets into hard shell capsules, Eur. J. Pharm. Biopharm. 53 (2002) 327–333.