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Development and characterization of lipid microparticles as a drug carrier for somatostatin

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Abstract

Somatostatin, a therapeutic peptide with a high therapeutical potential but a very short biological half-live was encapsulated within microparticles by a modified solvent evaporation method and a melt dispersion method without the use of organic solvent. As the use of synthetic polymer matrix materials often goes along with detrimental effects on incorporated peptides, we investigated the potential of physiological lipids such as glyceryl tripalmitate (Dynasan 116®) as an alternative matrix material. The two preparation methods were evaluated with respect to surface topography, particle size distribution, encapsulation efficiency, in-vitro release behavior and modification of the resulting microparticles. Microparticles with a suitable particle size distribution for i.m. or s.c. injection could be prepared with both methods. The encapsulation efficiency of the peptide into glyceryl tripalmitate microparticles was substantially influenced by the preparation method and the physical state of the peptide to be incorporated. The melt dispersion technique and the incorporation of the drug as an aqueous solution gave the best results with actual drug loadings up to 9% and an encapsulation efficiency of approximately 90%. Microparticles prepared by the melt dispersion technique crystallized in the unstable α-modification. The peptide was released almost continuously over 10 days with no burst effect, 20–30% of the incorporated somatostatin was not released in the monitored time period.

Keywords: Microencapsulation; Somatostatin; Triglycerides; Melt dispersion; Solvent evaporation

1. Introduction

Somatostatin (SST) is a cyclic tetradecapeptide and gastrointestinal hormone with a high therapeutical potential and diverse indications like the treatment of diseases associated with an excess hormone secretion such as acromegaly, gastrointestinal disorders, peptic ulcers, enterocutaneous and pancreatheocutaneous fistula, acute pancreatitis, gastroenteropathic encocrine tumors and severe bleedings in the gastrointestinal tract (Dutta, 1993). Furthermore it has been shown,

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that the coadministration of SST with insulin can control hyperglycemia in the insulin-dependent diabetic patient more effectively than insulin alone, as the peptide inhibits the secretion of many endogenous hormones including gluconeogenic compounds, such as growth hormone and glucagon, insulin and corticosteroids and catecholamines (Edelman et al., 1996). As many other therapeutic peptides, SST is not effective after peroral administration and has a very short biological half-live of 2–3 min caused by enzymatic degradation (Peters and McMartin, 1983). Therefore, analogues of SST such as octreotide (sandostatin®) and vapreotide with a longer biological half-live have been synthesized. However, especially for the long-term treatment of diseases such as acromegaly and diabetes mellitus, long-acting injectable dosage forms would be clinically desirable to avoid frequent injections or continuous intravenous infusions. The long term delivery of SST or its analogues for up to 2 months has been achieved by the formulation of injectable microparticles consisting of poly(DL-lactide-co-glycolide-D-glucose) or poly(DL-lactide-co-glycolide) (Bodmer et al., 1992, 1997). By using peptide-loaded implants consisting of polylactic acid (PLA) manufactured by extrusion or injection molding, a satisfactory blood level of the SST analogue vapreotide in rats was measured over approximately 250 days (Rothen et al., 1998, 1999). However, especially for the treatment of severe gastrointestinal bleedings, dosage forms that ensure therapeutic blood levels of SST over approximately 1 week are desirable to avoid frequent injections or continuous infusions.

Furthermore, the use of synthetic polymer matrix materials often goes along with detrimental effects on incorporated peptides during manufacturing of the formulations or during the erosion of the polymers after application (Schwendeman et al., 1996). Therefore, alternatives for polymer matrix materials are needed.

Lipid materials, e.g. triglycerides and cholesterol, may have the potential as biocompatible and biodegradable carriers for peptides and proteins. Solid lipid nanoparticles (SLN) represent a carrier system with a great potential as a parenteral controlled release device for a large variety of drugs (Müller et al., 2000), including peptides (Morel et al., 1996). In the form of implants (Wang, 1992) or microparticles (Cady et al., 1989), lipid matrix materials might provide a less detrimental environment for peptides and proteins during the application of the dosage form. Sustained release devices based on lipids can be produced without the use of organic solvents, as standard tableting equipment can be used to prepare lipid compacts and lipid microparticles can be manufactured by spray congealing (Cady et al., 1989) or melt dispersion techniques (Bodmeier et al., 1992a).

In our study, we investigated the potential of physiological lipids such as triglycerides as an alternative to polymers as a matrix material for controlled release devices for the peptide SST. We focused on lipid microparticles which allow for subcutaneous or intramuscular administration into tissue via injection through a syringe. The aim of this study was to investigate various methods of preparing lipid microparticles with respect to their suitability to encapsulate SST and to characterize the resulting systems with respect to particle size, modification of the lipid matrix and the in-vitro release behavior.

2. Experimental

2.1. Materials

The following materials were used as received: somatostatin acetate (SST, M.W. of the free base 1638 D. Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) as a sterile, freeze-dried solid, sealed in ampoules (acetate salt, purity $>97\%$, HPLC) or as bulk material, Dynasan® 116 (glyceryl tripalmitate, Hüls AG, Germany), poly(vinyl alcohol) (PVA, 88 mol.% hydrolyzed, M.W. 88 000, Acros Organics, NJ, USA), methylene chloride, acetonitrile, phosphoric acid 85% (all in p.a. grade from Merck, Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation methods of lipid microparticles

Two methods of preparing SST-loaded lipid microparticles were evaluated: a modified solvent evaporation method, widely used for the preparation of polymeric microparticles and a melt dispersion technique without the use of organic solvents (also referred to as 'hot melt microencapsulation') (Mathiowitz and Langer, 1987; Bodmeier et al., 1992b). The drug was incorporated as a solid or as a solution in 100 μl isotonic pH 7.4 phosphate buffered saline. In a typical preparation (solvent evaporation method), the lipid (glyceryl tripalmitate, 300 mg) was dissolved in 1.0 ml of methylene chloride. The peptide was incorporated as a solid (S/O/W) by vigorous vortex-mixing (Vortex Genie 2, Scientific Industries, USA) or ultrasonication (Sonifier S-250A, Branson, Danbury, USA) for 10 s (output 40 W), after grinding the lyophilizate in a mortar with the addition of liquid nitrogen to a particle size of approximately 5 μm (assessed by light microscopy). Alternatively, the peptide was incorporated as a solution (W/O/W). No surfactant was added to stabilize the primary W/O-emulsion, as somatostatin itself is known to be an emulsion stabilizer due to its surface activity (Herrmann and Bodmeier, 1995b). In both cases (S/O/W or W/O/W), the resulting preparation was further emulsified into a small volume (3.0 ml) of a stabilizer-containing aqueous phase (PVA 1% (w/v), 40°C) by vortex-mixing. The emulsion was poured into a larger volume (150 ml) of an ice-cooled (5°C) aqueous phase (PVA 0.1% (w/v)) and stirred with a propeller stirrer (4×4 cm) to allow evaporation of the organic solvent. The hardened microparticles were separated from the aqueous phase by filtration, rinsed with 40 ml of water and vacuum dried over night at room temperature.

With the melt dispersion technique, a lipid melt (glyceryl tripalmitate, 300 mg) was used instead of the solution of the lipid matrix material in an organic solvent. After incorporating the peptide into the lipid melt as a solid or a solution by vigorous vortex-mixing, the preparation was emulsified into a small volume of aqueous phase (3.0 ml, PVA 1% w/v) heated above the melting point of the lipid (65°C). The following steps were similar to the solvent evaporation method. The stirring time in the ice-cooled aqueous phase (5°C, 150 ml) was reduced from 30 to 5 min, because no organic solvent had to be evaporated.

2.2.2. Scanning electron microscopy

The surface topography of microparticles prepared by different methods was analyzed by scanning electron microscopy on a JSM-840 scanning electron microscope (Jeol, Peabody, MA, USA) after coating of the particles with gold using a Polaron E 5200 sputter-coater (Polaron Equipment Ltd., Watford, UK).

2.2.3. Particle size distribution

The size of the microparticles was determined using a Coulter®-Counter Multisizer IIe (Coulter Electronics Lmt., Luton, UK) with a capillary diameter of 280 μm.

2.2.4. Differential scanning calorimetry (DSC)

Thermal analysis of the bulk lipid and the microparticles was performed with a TA-instruments 2920 CE DSC calorimeter (TA-instruments, New Castle, DE, USA) using accurately weighed samples of 2 mg bulk material or microparticles. Thermoscans were recorded after equilibration at 20°C with a scan rate of 5°C/minute from 20 to 90°C. The cooling rate was also 5°C/min from 90 to 20°C. The obtained data were evaluated with the DSC-software Universal Analysis for Windows 95/98/NT, version 2.5 H (TA instruments).

2.2.5. Wide angle X-ray diffraction (WAXD)

WAXD spectra were recorded with a PV 1729 X-Ray generator, a PW 1050 X-Ray spectrometer and a PW 1710 diffractometer control device (all from Philipps, Netherlands). Measurements were performed with an anode voltage of 40 kV, a current of 40 mA and a scan rate of 0.5° per minute.

2.2.6. Determination of the drug content

The drug content of the microparticles was determined by dissolving the microparticles (approximately 10 mg, accurately weighed) in 2.0 ml hexane followed by the addition 2.0 ml of an appropriate aqueous phase. The two phase system was agitated gently for 2 h on a horizontal shaker, the aqueous phase was removed and the drug concentration of the extraction solution was determined with a stability sensitive HPLC procedure: ERC-64 A HPLC-pump, ERC-3312 Degasser, ERC-7210 (ERC, Alteglofsheim, Germany), Marathon Basic autosampler (Spark Holland, AJ Emmen, The Netherlands) and an Autochrom M300 gradient controller (Autochrom Inc., Mildford, MA, USA), Apex 3.2 Chromatography Software. The concentration of SST was determined with a gradient elution HPLC-method: Nucleosil ET 250/8/4 300-5 C_{18} column 25×4 mm (Macherey und Nagel, Düren, Germany); mobile Phase A: 94.5% H_2O (V/V), 5% acetonitril (V/V), 0.5% phosphoric acid (V/V); mobile Phase B: 49.5% H_2O (V/V), 50% acetonitril (V/V), 0.5% phosphoric acid (V/V); the linear gradient was increased from 20% Phase B to 62% within the first 40 min and the decreased to the start conditions within 15 min. The flow rate was 1 ml/min and the analysis was conducted at ambient temperature. The UV-detection was performed at 210 nm. SST solutions of known concentrations (0.001–0.1 mg/ml) were used to generate calibration curves. This method was checked with respect to linearity ($r^2 > 0.98$), sensitivity (5×10^{-3} mg/ml), precision ($\pm 4\%$ RSD) and accuracy ($\pm 11\%$ RSD) (Debesis et al., 1982).

2.2.7. In-vitro release behavior

Microparticles (approximately 10 mg, accurately weighed, $n = 2$) were suspended in 1.0 ml of the release medium [PBS-buffer pH 7.4, 0.05% w/v Pluronic F 68, 0.05% (w/v) NaN_3] and incubated at 37°C in a horizontal shaker water bath. In addition to somatostatin in the release medium, the residual peptide in the microparticles was determined periodically by the extraction method described above.

3. Results and discussion

The most popular method for the preparation of preparation peptide-loaded biodegradable microparticles is the solvent evaporation technique (Ogawa et al., 1988), where the drug is dissolved, dispersed or emulsified into an organic polymer solution, which is then emulsified into an external aqueous or oil phase. The microparticles are formed after solvent diffusion and evaporation and polymer precipitation. When compared to the numerous papers published on the preparation of microparticles using polymers as carriers, only few authors have described the use of lipids or waxes in the field of microencapsulation (Steber et al., 1988; Cady et al., 1989; Bodmeier et al., 1992b; Domb, 1993).

In our study, we investigated whether SST-containing lipid microparticles can be produced in the desired size range as an alternative to polymeric microparticles.

A major advantage of waxes and lipids compared to polymers is the favorable processability of low-viscosity melts thus obviating the need for organic solvents. Therefore we investigated the suitability of a melt dispersion method as an alternative to the solvent evaporation technique.

When water soluble substances such as peptides are to be encapsulated, it is often favourable to choose an external oil phase to prevent loss of drug during the encapsulation process. However, to eliminate possible unwanted interactions between the oil and the emulsified wax such as swelling or dissolution, we chose an external aqueous phase.

3.1. Physico-chemical characterization of lipid microparticles without a drug prepared by solvent evaporation and melt dispersion

Irrespective of the matrix material, particle size of microparticles intended for intramuscular or subcutaneous injection has to be below 150 μm to ensure their injectability. Microparticles prepared by the solvent evaporation method using methylene chloride as an organic solvent (medium diameter: 56.9 μm) as well as microparticles prepared by the melt dispersion technique

(medium diameter: 92.8 μm) would be suitable for i.m or s.c. injection (Fig. 1). In case of the solvent evaporation method the yield was 65–75% while it was 85–90% when the melt dispersion technique was employed.

With lipid drug delivery systems, polymorphic transformations may occur during the preparation of the dosage form and during subsequent storage

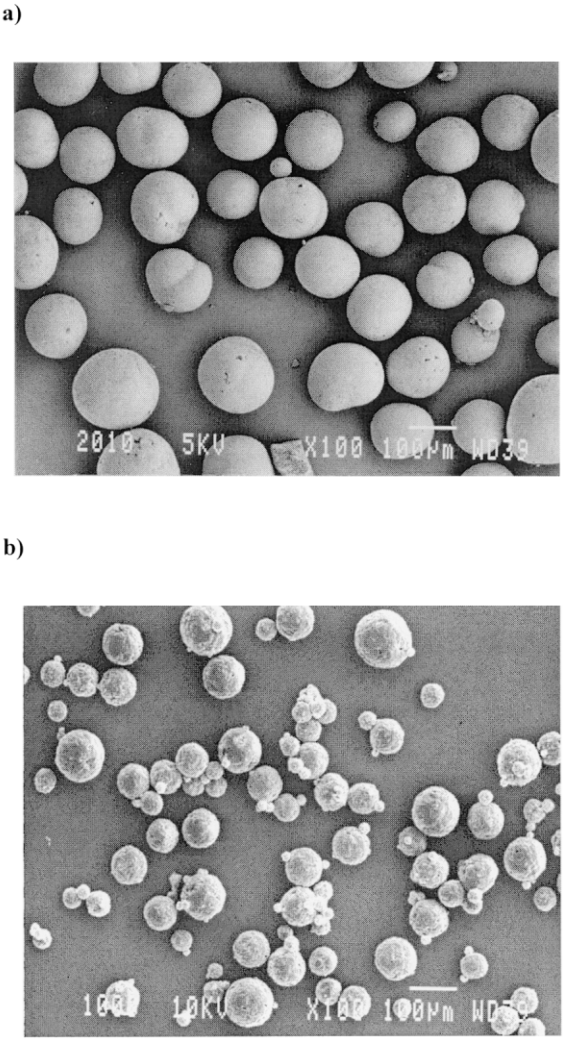

Fig. 1. Scanning electron micrographs of glyceryl tripalmitate microparticles without SST prepared by various methods (magnification 100 ×): (a) microparticles prepared by the melt dispersion technique; and (b) microparticles prepared by the solvent evaporation technique (solvent: methylene chloride). The bars represent 100 μm.

(Eldem et al., 1991a,b; Westesen et al., 1997). During solidification of the melt or the solution, the triglyceride can crystallize in different polymorphic forms depending on the composition of the lipid and the cooling rate. This phenomenon may cause differences in solubility and melting point of active and auxillary substances, and especially the conversion of one polymorph to another may change the physical properties of the substances (Eldem et al., 1991a). Therefore, we investigated the microparticles produced by both methods as well as the bulk lipid (glyceryl tripalmitate) with respect to the modification by DSC and WAXD.

The thermal behavior of microparticles prepared by solvent evaporation and melt dispersion as well as the behavior of the bulk lipid is illustrated in Fig. 2. The DSC-thermogram of the bulk lipid (first heating scan, 5°C/min) shows one single endothermic peak that stems from the melting of the stable crystalline form (β-modification). Microparticles prepared by solvent evaporation showed the same thermal behavior, giving rise to again a single endothermic DSC peak. This can be explained by the slow diffusion of the organic solvent methylene chloride into the outer aqueous phase, causing a slow solidification of the microparticles. Because of this slow process, the lipid molecules can arrange in the thermodynamically most stable β-modification (Garti, 1988). The thermograms of the microparticles produced by melt dispersion in contrast differed significantly. Three endothermic peaks were visible in the DSC-thermogram. The first peak represents the melting of the α-modification, followed by an exothermic peak representing the recrystallization of the α-form. The second endothermic peak represents the melting of the β′-modification and the third peak corresponds to the melting of the stable β-modification. Due to the fast congealing during the preparation of the microparticles by the melt dispersion technique, the instable α-modification of the triglyceride was formed.

These results were confirmed with the WAXD-experiments (Fig. 3). The bulk matrix material as well as the microsphere preparation produced by solvent evaporation showed the typical signals of the β-modification of triglycerides (Thoma et al.,

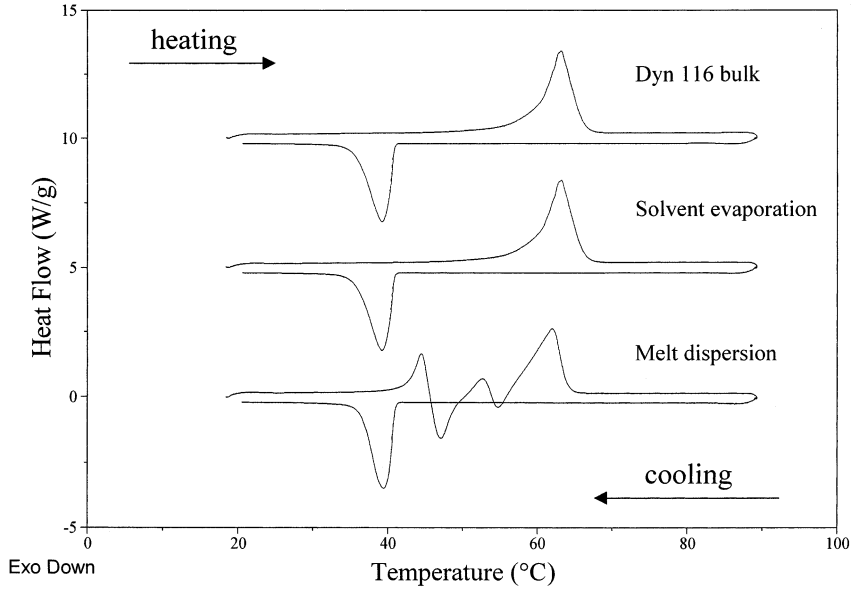

Fig. 2. DSC heating and cooling curves of glyceryl tripalmitate (Dyn 116) bulk material, microparticles prepared by solvent evaporation and microparticles prepared by melt dispersion 1 day after the preparation. (The plots are displaced vertically for better visualization).

1983; Garti, 1988) , whereas the microparticles prepared by melt dispersion crystallized in the unstable α-modification.

As the α-modification of triglycerides is known to undergo polymorphic transformation into the stable β-modification (Eldem et al., 1991b), these findings have to be taken into account with respect to possible changes in the in-vitro release behavior of the microparticles upon storage (Akiyama et al., 1993).

3.2. Evaluation of the extraction method to determine to SST-content of the microparticles

In order to develop a reliable extraction method, lipid matrices, containing known amounts of SST (0.3, 1.5 and 3.0% w/w) were prepared by dispersing the peptide in a solution of the lipid in methylene chloride by sonication and evaporation of the organic solvent under vacuum for 24 h. A known amount of this preparation (approximately 20 mg, exactly weighed) was dissolved in hexane, and SST recovery was measured under various extraction conditions (Table 1). When PBS-buffer pH 7.4 was chosen as an aqueous phase, the recovery of the peptide was incomplete, probably because at pH 7.4, a certain amount of the peptide was in its non-ionic form (isoelectric point of SST: 9.5) und was not extracted into the aqueous phase. At pH 3.0 (citrate-buffer), the peptide recovery was almost complete und the system hexane/citrate-buffer was chosen for further determinations of the microsphere drug content. The low pH had no detrimental effect on the peptide stability (Herrmann and Bodmeier, 1995a).

3.3. Evaluation of various methods of SST microencapsulation into lipid microparticles

Due to the large number of factors influencing the outcome of the microencapsulation processes, we investigated various parameters such as preparation method, physical state of the drug to be incorporated and the dispersion method employed with respect to the influence on the encapsulation efficiency to find the most effective method to incorporate SST into triglyceride microparticles (theoretical loading: 2% w/w) (Fig. 4). In all experiments the melt dispersion technique gave

higher encapulation efficiencies than the solvent evaporation technique (solvent: methylene chloride). In case of the incorporation of the peptide as a solution (W/O/W), this can be explained with the higher stability of the primary W/O-emulsion, which is a key factor in the encapsulation process (Schugens et al., 1994). When the lipid solution in methylene chloride was used, the aqueous phase coalesced rapidly, especially when the emulsion was prepared by vortex-mixing. May be the use of additional stabilizers could improve the emulsion stability and the encapsulation efficiency in case of the W/O/W-solvent evaporation method. Using the lipid melt, the primary emulsion was much more stable due to the higher viscosity of the lipid phase, which acted as an efficient barrier between the inner and the outer aqueous phase, preventing the diffusion of the peptide solution into the outer phase (Bodmeier et al., 1992b). The incorporation of the peptide as a solution was more effective than the incorporation as a solid. This may have been caused by an insufficient wetting of the dispersed solid peptide particles by the lipid solution or the lipid melt, resulting in an expulsion of the drug from the microparticles during solidifica-

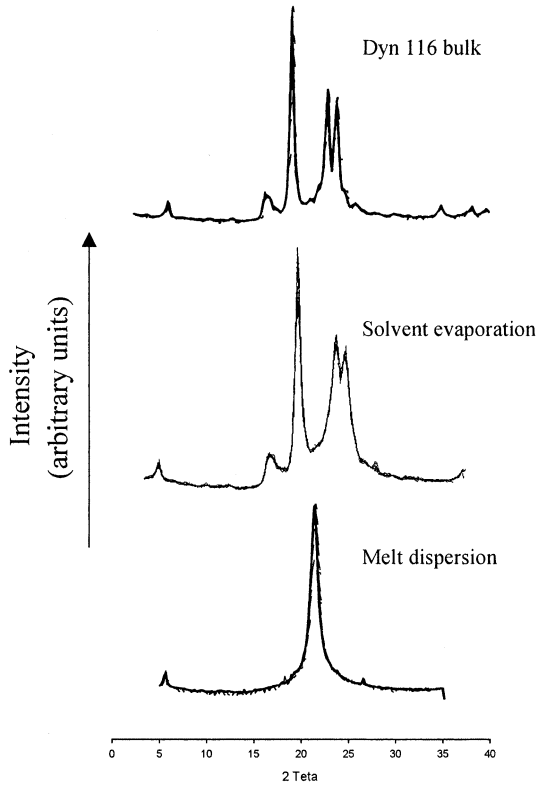

Fig. 3. WAXD-curves of glyceryl tripalmitate (Dyn 116) bulk material, microparticles prepared by solvent evaporation and microparticles prepared by melt dispersion 1 day after the preparation. (The plots are displaced vertically for better visualization).

Table 1
Effect of the pH of the aqueous phase on the SST recovery from glyceryl tripalmitate matrices[a]

Peptide concentration (%, m/m)	Peptide recovery (%)	
	Hexane/PBS-buffer pH 7.4	Hexane/citrate-buffer pH 3.0
0.3	68 ± 2.7	98 ± 2.2
1.5	74 ± 2.1	99 ± 2.1
3	67 ± 4.6	89 ± 2.3

[a] Extraction conditions: hexane 2.0 ml, aqueous phase 2.0 ml, extraction time: 2 h, gentle agitation; the peptide content was determined by HPLC, $n = 3$.

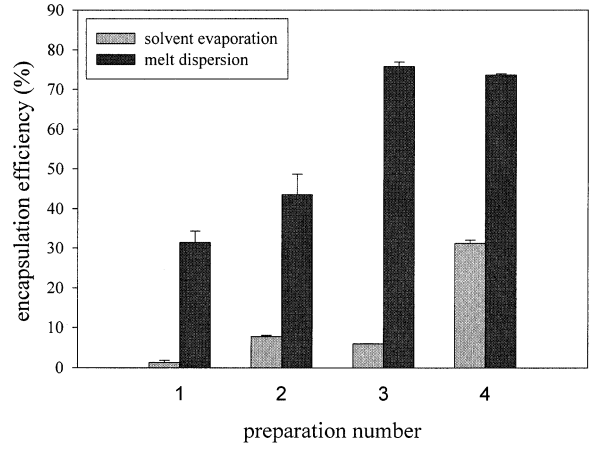

Fig. 4. Effect of various preparation methods on the encapsulation efficiency. (Theoretical SST loading: 2% w/w, matrix material: glyceryl tripalmitate, organic solvent: methylene chloride). Preparation Nr. 1: peptide incorporated as a solid, vortex mixing. Preparation Nr. 2: peptide incorporated as a solid, ultrasonication. Preparation Nr. 3: peptide incorporated as a solution in 100 μl PBS-buffer pH 7.4, vortex mixing. Preparation Nr. 4: peptide incorporated as a solution in 100 μl PBS-buffer pH 7.4, ultrasonication.

Table 2
Effect of the SST type on the encapsulation efficiency[a]

Theoretical loading (%)	Encapsulation efficiency (%)	
	SST in ampoules	SST bulk material
2	79 ± 1.5	97 ± 7.0
5	72 ± 2.0	n.d.
10	64 ± 9.0	91 ± 4.0

[a] Melt dispersion technique, SST incorporated as a solution in 100 μl PBS-buffer pH 7.4 by vortex-mixing, $n = 3$, n.d. = not determined).

tion. May be the use of a surfactant could enhance the wetting of the solid peptide by the lipid solution or the lipid melt. In the case of the lipid solution, water may have diffused into the droplets of the inner phase and dissolved the solid peptide, leading to a leaching of the drug into the outer aqueous phase.

In general, dispersion of the peptide solution or the solid in the lipid solution or the melt by sonication resulted in higher encapsulation efficiencies than dispersion by vortex mixing, due to a smaller droplet size of the primary emulsion and a more homogenous distribution of the solid peptide, respectively. Surprisingly, in case of the lipid melt and the incorporation of the peptide as a solution, dispersion of the peptide solution by vortex mixing gave approximately the same encapsulation efficiency than the dispersion by ultrasonication. This may be explained by the surface activity of SST, leading to a sufficiently stable primary emulsion after the dispersion by vortex mixing.

The melt dispersion technique with the peptide being incorporated as a solution by vortex mixing was the most effective method of producing SST containing lipid microparticles. Consequently, the following experiments were conducted with this technique.

As it is desirable to produce microparticles with a high drug content to reduce the amount of microsphere preparation that has to be injected in-vivo as a single dose, we investigated the influence of the theoretical loading on the encapsulation efficiency (Table 2). With increasing theoretical loading, the encapsulation efficiency decreased significantly and the encapsulation process was less reproducible when SST in ampoules was used. This was caused by the tendency of the peptide to form a gel at high concentrations at room temperature (Herrmann and Bodmeier, 1995a), probably due to excipients present in the lyophilizate. The highly viscous preparation could not be emulsified into the lipid melt homogenously, resulting in decreasing encapsulation efficiencies. When the bulk SST was used, no gelation occured and a stable primary emulsion could be produced. Thus, even at a high theoretical loading (10% w/w) the encapsulation efficiency was very good, and microparticles with an actual drug content of approximately 9% could be manufactured without the use of sonication, which often causes peptide degradation due to cavitational forces and the large amount of energy applied to the system.

The high viscosity of the internal aqueous phase may also be responsible for the high encapsulation efficiency at high drug loadings. Normally, the efficiency decreases at higher theoretical loadings.

3.4. In-vitro release behavior

As SST is not stable in the release medium (PBS-buffer pH 7.4) at 37°C (Herrmann and Bodmeier, 1995a), the amount of drug remaining in the microparticles rather than the amount of drug released was determined in order to characterize the drug release (Fig. 5). The peptide extracted from the microparticles was intact, no degradation products were detected in the extraction solution with the stability indicating HPLC-method.

Microparticles with actual drug loadings of 2.0, 4.5 and 9.3% were analyzed with respect to their in-vitro release behavior. In all batches, no burst effect was detectable. Drug release was relatively fast during the first 7–10 days, followed by a phase of slow release. Approximately 20–30% of the incorporated SST was not released in the monitored time period (14 days). As the residual drug content was determined, it is theoretically possible that the peptide was released and then readsorbed to the lipid microparticles.

The morphology of the microparticles incubated in the release medium at 37°C for 14 days changed significantly compared to the morphology of the microparticles shortly after the preparation (Fig. 6). Microparticles prepared by the melt dispersion technique showed a very smooth surface, whereas the batches incubated in the release medium for 14 days were partly degraded and showed an eroded surface, which possibly influences the release behavior of the peptide from the microparticles. In vivo, enzymes such as lipases present at the injection site (s.c. or i.m.) may degrade the particles, which has been shown in the case of solid lipid nanoparticles (lipid matrix: cetylpalmitate, glyceryltripalmitate or glyceryltristearate) incubated with the lipolytic enzyme pancreatic lipase in combination with pancreatic colipase (Olbrich and Müller, 1999). However, triglyceride implants (lipid matrix: glyceryltrilaurin, glycerlytrimyristin, glyceryltripalmitin, glyceryltristearin) produced by compression showed no apparent changes after subcutaneous implantation into rats after 1 month (Wang, 1989). The in-vivo fate of the microparticles prepared in this study after subcutaneous injection is currently under investigation.

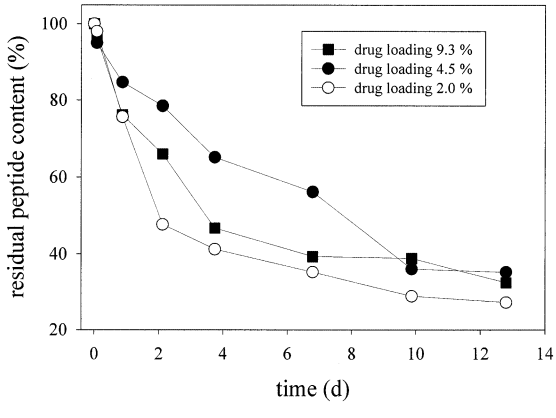

Fig. 5. In-vitro SST release from glyceryl tripalmitate microparticles with various drug loadings prepared by the melt dispersion technique (release medium: PBS-buffer pH 7.4, 37°C, $n = 3$).

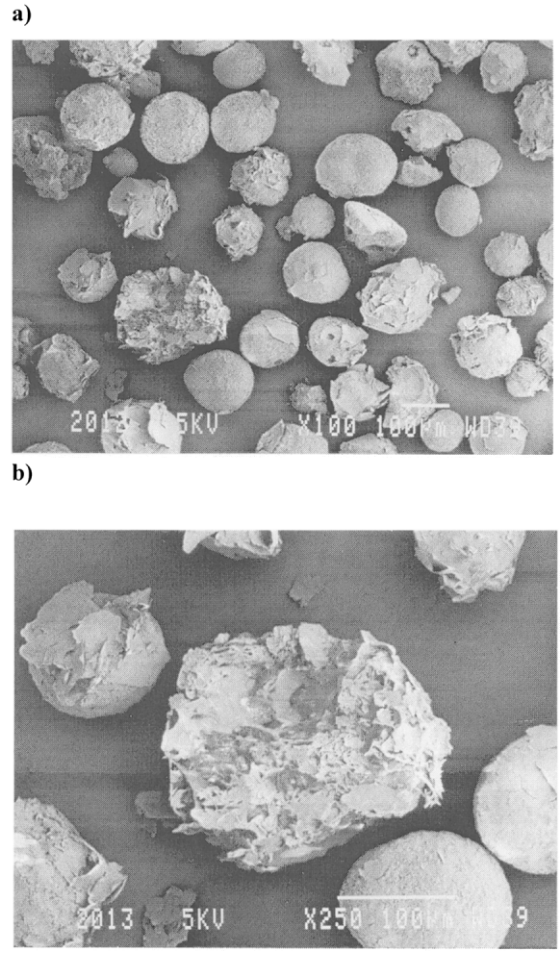

Fig. 6. Scanning electron micrographs of glyceryl tripalmitate microparticles after incubation in PBS-buffer pH 7.4 (37°C) for 14 days: (a) magnification 100 ×; and (b) magnification 250 ×. The bars represent 100 μm.

4. Conclusions

In our study, we prepared lipid microparticles in the size range suitable for intramuscular or subcutaneous injection by a solvent evaporation technique and a melt dispersion technique without the use of organic solvents. Microparticles prepared by the melt dispersion technique crystallized in the unstable α-modification, which has to be taken into account during the storage of the preparations. The encapsulation efficiency of the peptide into glyceryl tripalmitate microparticles was substantially influenced by the preparation

method and the physical state of the drug to be incorporated. The melt dispersion technique and the incorporation of the drug as an aqueous solution gave the best results with actual drug loadings up to 9% and an encapsulation efficiency of approximately 90%. The peptide was released in-vitro almost continuously over approximately 10 days with no burst effect.

Lipid microparticles with characteristics described in this study are an attractive alternative to continuous infusions or polymeric carrier systems, especially when the release of SST over shorter time periods is intended, e.g. in the treatment of severe gastrointestinal bleedings.

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