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Research paper

In situ forming nimodipine depot system based on microparticles for the treatment of posthemorrhagic cerebral vasospasm

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ABSTRACT

The present study was conducted to examine the feasibility of nimodipine-loaded PLGA microparticles suspended in Tisseel™ fibrin sealant as an *in situ* forming depot system. This device locally placed can be used for the treatment of vasospasm after a subarachnoid hemorrhage. Microparticles were prepared via spray-drying by using the vibration mesh spray technology of Nano Spray Dryer B-90. Spherically shaped microparticles with different loadings and high encapsulation efficiencies of 93.3–97.8% were obtained. Depending on nimodipine loading (10–40%), the particle diameter ranged from 1.9 ± 1.2 μm to 2.4 ± 1.3 μm. Thermal analyses using DSC revealed that nimodipine is dissolved in the PLGA matrix. Also, fluorescent dye loaded microparticles were encapsulated in Tisseel™ to examine the homogeneity of particles. 3D-pictures of the *in situ* forming devices displayed uniform particle homogeneity in the sealant matrix. Drug release was examined by fluorescence spectrophotometry which demonstrated a drug release proportional to the square root of time. A prolonged drug release of 19.5 h was demonstrated under *in vitro* conditions. Overall, the nimodipine *in situ* forming device could be a promising candidate for the local treatment of vasospasm after a subarachnoid hemorrhage.

1. Introduction

Nimodipine is a dihydropyridine L-type Ca^{2+} channel antagonist. It regulates calcium channels to dilate arterioles especially in the brain, therefore increasing cerebral blood flow in animals and humans [1]. Cerebral vasospasm and delayed cerebral ischemia contribute substantially to secondary morbidity and mortality after severe subarachnoid hemorrhage (SAH). Some meta-analyses suggested that orally administered nimodipine is effective only as prophylactic therapy for cerebral vasospasm [2].

As a highly permeable drug with low solubility in gastrointestinal fluids (class 2 of biopharmaceutical classification system), nimodipine exhibits low bioavailability after oral administration [3]; therefore, for clinical applications, injections or infusions are widely used [4]. Despite clinical treatment with current infusion therapy [5,6] in 10–20% of SAH patients, permanent disability is observed [7].

A new approach in the treatment of cerebral vasospasm is the use of local subarachnoid depot implants. Kasuya et al. used implants consisting of nicardipine and poly(lactic-co-glycolic acid) (PLGA) [8]. Hänggi et al. used nimodipine pellets with a diameter of 1.5 mm, which led to significant intracranial arterial relaxation after SAH in rats [9].

Here, we present a novel *in situ* forming depot system consisting of nimodipine-loaded PLGA microparticles (NMPs) which were dispersed in Tisseel™ fibrin sealant. Due to its lipophilic character, nimodipine itself is not miscible with the sealer protein solution, consisting mainly of water for injection. PLGA was used as polymer matrix to encapsulate nimodipine. PLGA is the most extensively used material for biomedical applications owing to their well-established biocompatibility and biodegradability [10]. To prepare NMPs, a new Nano Spray Dryer B-90 was employed. Microparticles were dispersed in one component of Tisseel™ fibrin sealant. The fibrin glue is biocompatible, biodegradable [11], and stable in cerebrospinal fluid [12] and is therefore particularly attractive for the preparation of an intracisternal depot system. By using the Duploject system of Tisseel™, the two components of the sealant (with NMPs) can directly be mixed and placed into the brain forming a depot at the site of administration.

The intracisternal implantation of the *in situ* forming nimodipine device and the closure with fibrin sealant can be done in one step. The fibrin glue promotes wound healing as well which is an additional benefit of this procedure [13].

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This study was conducted to examine the feasibility of NMPs in Tisseel™ fibrin sealant as a novel depot system, which was designed to be used in the treatment of vasospasm after a subarachnoid hemorrhage.

2. Experimental part

2.1. Materials

Poly(D,L-lactide-*co*-glycolide) (PLGA, Resomers® RG502H) was obtained from Boehringer Ingelheim (Ingelheim, Germany). Nimodipine and coumarin 6 were purchased from Sigma–Aldrich (Steinheim, Germany). The fibrin sealant Tisseel™ (Duo S 0.5 mL Immuno) was acquired from Baxter (Unterschleissheim, Germany). All other chemicals and solvents used were of analytical grade.

2.2. Sample preparation

2.2.1. Preparation of micro-particulate powders

All formulations were spray-dried with the Nano Spray Dryer B-90 (Büchi, Flawil, Switzerland). The design of the instrument and the procedure of particle formation and collection have been described in literature [14,15]. Briefly, the spraying solutions are atomized by a vibrating-mesh actuated by a piezoelectric element. Thereafter, ejected droplets are dried in a flow of warmed gas and the dried particles are collected by an electrostatic particle collector. Depending on what drug, polymer, spaying solution, and spraying parameters are used either nano- or microparticles can be produced by using the Nano Spray Dryer B-90 [16,17].

To prepare nimodipine-loaded PLGA particles, 300 mg solid containing 0%, 10%, 20%, 30% or 40% (w/w) nimodipine and PLGA were dissolved in 50 mL dichloromethane. For the preparation of 0.5% fluorescent dye loaded particles, 1.5 mL coumarin-6 in dichloromethane (1 mg/mL) was added to 300 mg PLGA dissolved in 50 mL dichloromethane.

The cooled spray solutions were spray-dried using the following conditions, which were kept constant for each batch: 120 L/min drying gas flow rate, 45 °C inlet temperature, 50% relative spray rate, and 46 mbar pressure. The membrane (spray mesh) used in this study offers 7.0 µm sized holes. After 10 min of spraying (25 mL spraying solution residual), an additional 10 mL dichloromethane was added to replace evaporated dichloromethane and to avoid the formation of a high viscous spray solution. Finally, the resulting powder was collected using a rubber spatula. Using this method, three batches of unloaded (blanks, BMPs), nimodipine-loaded (10%, 20%, 30% and 40% w/w) (NMPs), and coumarin-6 loaded PLGA particles (CMPs) were prepared, respectively.

2.2.2. Preparation of depot systems

The microparticle formulations were suspended in Tisseel™ fibrin sealant to generate an *in situ* forming device. Therefore, 24 mg of particles was mixed in an Eppendorf cup with 0.5 mL of sealer protein solution via vortexing for 2 min. To remove air bubbles, the suspension was sonicated. After vortexing the Eppendorf cup a second time for 10 s, the suspension was drawn up into the empty sealer protein syringe. Afterward, the loaded sealer protein syringe and the unloaded thrombin solution syringe were placed in the Duploject system (Baxter Corp.). The nimodipine depot systems will be formed *in situ*. To mimic the formation of the device *in vitro*, the loaded Tisseel™ system was injected onto a glass slide as shown in Fig. 1 and immediately covered by a glass cover slip.

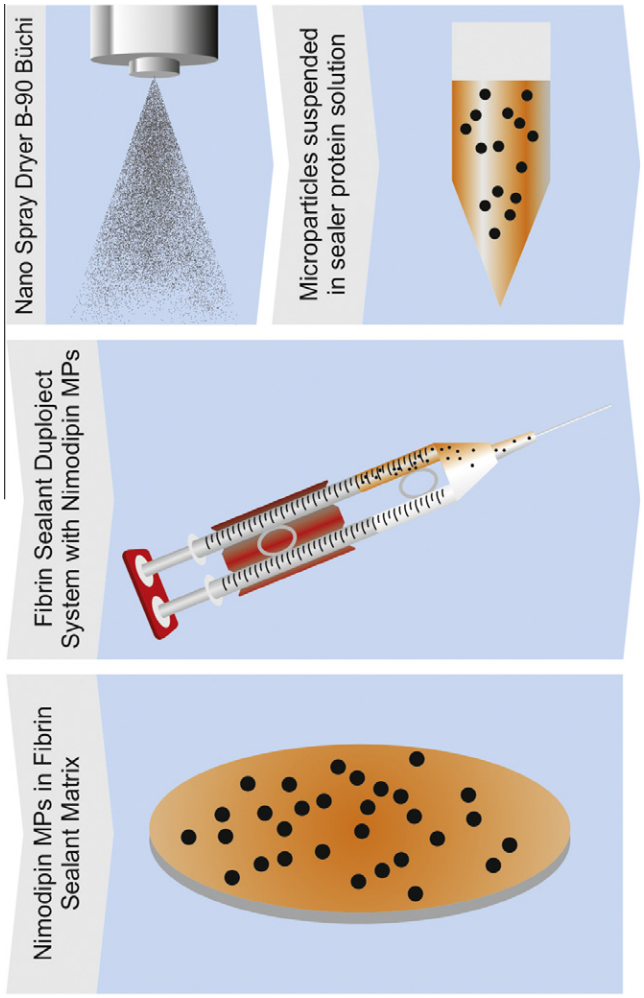

Fig. 1. Preparation of *in situ* forming nimodipine depot system. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characterization of spray-dried PLGA microparticles (MP).

Particles	Loading [% (w/w)]		Encapsulation efficiency (%)	Particle size (µm)	T_g (°C)
	Theoretical	Measured			
PLGA	–	–	–	2.25 ± 1.45	38.1
Nimodipine/PLGA	10%	9.78 ± 0.61	97.8 ± 6.1	2.19 ± 1.14 [a]	36.7
Nimodipine/PLGA	20%	18.74 ± 0.43	93.7 ± 2.1	2.37 ± 1.33 [a]	32.5
Nimodipine/PLGA	30%	28.57 ± 0.83	95.2 ± 2.8	1.90 ± 1.19 [a]	28.0
Nimodipine/PLGA	40%	37.33 ± 1.06	93.3 ± 2.6	1.96 ± 0.95 [a]	23.6
Coumarin-6/PLGA	0.5%	0.46 ± 0.02	91.9 ± 4.3	1.90 ± 1.08 [a]	–

[a] At the 0.05 level, the size mean of PLGA-MPs compared to the size means of each nimodipine/PLGA batch or coumarin-6/PLGA is not significantly different.

2.3. Drug loading and encapsulation efficiency

The amount of nimodipine encapsulated in NMPs was estimated by UV spectrophotometry (Ultrospec 3000, Pharmacia Biotech, Uppsala, Sweden). A defined amount of NMPs was dissolved in 2 mL acetonitrile and diluted appropriately, and absorbance was recorded at 347 nm. The concentration of nimodipine was determined and the actual drug loading was assessed. The relative encapsulation efficiency (EE) was calculated using the following equation:

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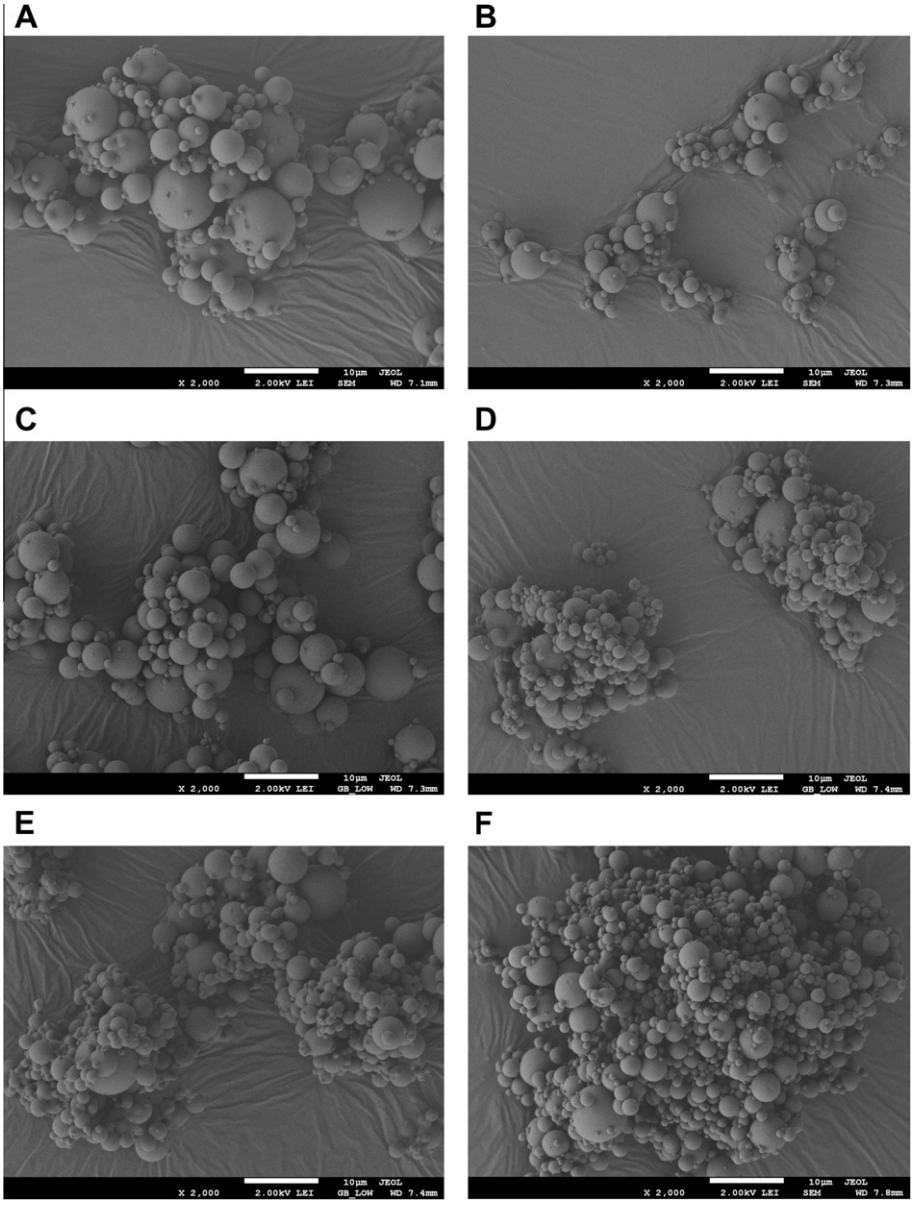

Fig. 2. Scanning electron microscopy. Scanning electron micrographs of spray-dried PLGA microparticles: PLGA only (A), 10% (B), 20% (C), 30% (D), 40% (E) nimodipine-loaded and 0.05% coumarin 6 (F)-loaded PLGA microparticles.

$$EE = \frac{agent_{ACTUAL}}{agent_{SET}} * 100 \quad (1)$$

The drug loading and encapsulation efficiency of coumarin 6 loaded particles (CMPs) was determined by fluorescence spectroscopy (LS50B, Perkin–Elmer, Juegesheim, Germany). Therefore, the dye loaded microparticles were dissolved in acetonitrile. Then, 200 µL of the adequate dissolved solution was placed in a white 96 well plate (Brand GmbH, Wertheim, Germany) and measured at an excitation wavelength of 457 nm with an emission wavelength of 500 nm [18]. After measurement of fluorescence, the loading and the encapsulation efficiency was determined.

2.4. Particle morphology

Scanning electron microscopy (SEM) was employed to examine the size and morphology of samples. Therefore, the particles were spread on a specimen mount prepared with a conductive carbon adhesive tab. All samples were sputter-coated with a platinum layer (Gatan Alto-2500, Gatan, München, Germany). The coated microparticles were then observed with a JSM-7500F SEM (JEOL, Eching, Germany) instrument.

2.5. Particle size measurements

The particle sizes of spray-dried particles were obtained by analysis of SEM images. Particle dimensions were calculated by averaging at least 100 particle diameters [14,15,19]. The analysis results have been reported as mean particle size values ± standard deviations.

2.6. Differential scanning calorimetry (DSC)

DSC measurements were carried out on a DSC 7 (Perkin–Elmer, Waltham, MA, USA) at a heating rate of 20 K/min using dry nitrogen purge gas. The samples were first heated to 140 °C, subsequently cooled to 0 °C with liquid nitrogen and heated again to

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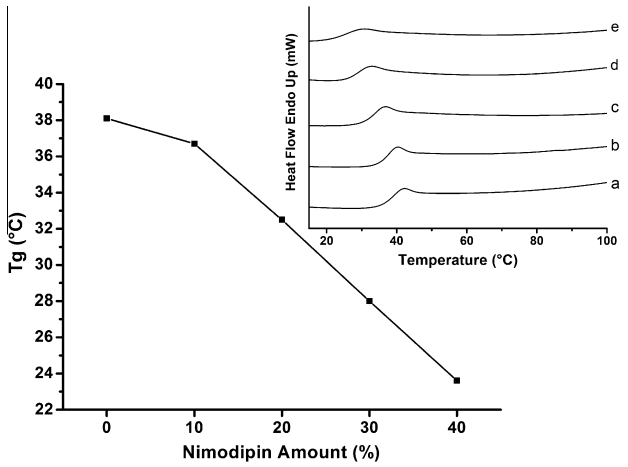

Fig. 3. DSC of nimodipine-loaded PLGA microparticles. DSC curves of nimodipine-loaded PLGA microparticles. (a) PLGA only microparticles, (b) 10%, (c) 20%, (d) 30%, and (e) 40% nimodipine-loaded PLGA microparticles.

140 °C. Thermograms were normalized to sample weight. The DIN midpoint of the slope change of the heat flow plot of the second heating scan was considered as the glass transition temperature (T_g), and the heat flow capacity change (Δc_p) was determined. The melting temperatures (T_m) were taken as the maximum of endothermic peaks. DSC studies were conducted after 7 days of lyophilization. Nimodipine loaded as well as unloaded PLGA nanoparticles were compared to bulk nimodipine powder.

2.7. Homogeneity of microparticles in the depot system

To visualize the homogeneity of microparticles in the Tisseel™ matrix, the coumarin 6 loaded PLGA microparticles were used. The dye loaded MPs were incorporated in the Tisseel™ matrix as described above. Subsequently, the formed device was examined by confocal laser scanning microscopy (CLSM) with a Zeiss Axiovert 100M microscope coupled to a Zeiss LSM 510 scan module. The homogeneity of the particles in Tisseel™ was detected using an argon laser with an excitation wavelength of 488 nm. The green fluorescent dye was identified with a 505–550 nm broad pass filter. Z-stacks of the matrix and 3D pictures of the Tisseel™ device (thickness: 42 μm) were prepared.

2.8. In vitro release studies of coumarin 6 from the Tisseel™ matrix

For drug release studies, 1% coumarin 6 loaded MPs (CMPs) were used. CMPs and blanks (BMPs) were homogeneously suspended in the sealer protein solution as described above. The loaded sealer protein solution and the thrombin solution were pipetted 50/50 (v/v) in wells of a 24-multiwell plate. The components were mixed in the plate to prepare matrices with identical volumes.

Due to the low solubility of coumarin 6 in aqueous media [20], a 50/50 (w/w) mixture of PBS (pH 7.4) and ethanol was used as release medium to maintain sink conditions. The lipophilic drug coumarin 6 is practically insoluble in aqueous media [20] like nimodipine. The solubility in phosphate buffered saline (PBS) has been reported to be 0.049 μg/mL [18]. To generate sink conditions, the solubility needs to be enhanced by the use of surfactants. The use of ethanol for release studies of lipophilic drugs is common [4,18,21,22]. The solubility of coumarin 6 in PBS/ethanol (1/1 w/w) was published to be 22.2 μg/mL [18]. So, the use of 30 mL PBS/ethanol (1/1 w/w) release medium guarantees sink conditions, which are necessary to obtain valid results.

The loaded and unloaded matrices were placed in 30 mL release medium in plastic tubes. Incubation occurred at 37 °C during slight horizontally shaking (KS-15 shaker with TH15 temperature chamber, Edmund Buehler, Hechingen, Germany). Also, samples with an equal amount of dissolved free model drug were prepared to detect loss of coumarin 6 during incubation time of 5 days. Samples of 1 mL were taken at predetermined time points; the volume was replaced with 1 mL release medium. The samples were suitable diluted and 200 μL was transferred to a 96-well plate. For quantification, a fluorescence plate reader (LS50B, Perkin–Elmer, Juegesheim, Germany) was adopted. Measurements were arranged at an excitation wavelength of 472 nm and an emission wavelength of 506 nm [18]. The coumarin 6 content was calculated using a calibration curve (R^2 = 0.999) with linearity between 5 and 70 ng/mL. The samples were protected from light exposition during the experiment. Measurements were carried out in triplicate.

2.9. Statistics

All measurements were carried out in triplicate and values are presented as the mean ± standard deviation unless otherwise noted. One-way ANOVA with Bonferroni's post *t*-test analysis was carried out to identify statistically significant differences. Probability values of $p < 0.05$ were considered as significant.

3. Results and discussion

3.1. Microparticle characteristics

The new Nano Spray Dryer B-90 was used to prepare nimodipine-loaded microparticles (NMPs). This system enables the production of fine powders on a laboratory scale in high yields [23]. The feasibility of the Nano Spray Dryer B-90 to produce NMPs with different loadings and high encapsulation efficiencies (EE) was examined in this study.

For microencapsulation processes by the solvent evaporation method or spray-drying, suitable organic solvents are mandatory. These solvents need to display tailored characteristics: dissolution of polymer and API, non-flammable, non-explosive, non-toxic for animals, humans, and the environment. Among the limited number of solvents available which meet the described properties, halogenated solvents like dichloromethane are commonly employed during microparticle preparation in research and for commercial microparticle products (e.g., Decapeptyl SR, Lupron Depot and Suprecur MP). Only an accurate adjustment of the process parameters employed during microparticle preparation by spray-drying would allow for a minimization of the residual amount of organic solvent in the final microparticle product [24]. Moreover, a final drying step via vacuum-drying will further minimize the amount of residual solvents far below the tolerable value described in the Pharmacopoeias. Therefore, the spray-drying setup was adjusted with the aim to meet the stringent requirements regarding residual organic solvents in the spray-dried microparticles (inlet temperature 45 °C, drying gas flow rate 120 L/min, pressure 46 mbar). Moreover, a final vacuum-drying step for microparticles was applied.

It was possible to prepare high yields of NMPs with dichloromethane as a solvent, a low concentrated spraying solution and the mentioned spray-drying setup. Differently loaded (10%, 20%, 30%, and 40% (w/w)) NMPs were synthesized. As shown in Table 1, the EE for nimodipine-loaded microparticles ranged between 93.3 ± 2.6% and 97.8 ± 6.1%. On balance the encapsulation efficiency of the lipophilic nimodipine in PLGA is high, which enables the production of adequately loaded nimodipine depots. Also, fluorescent dye loaded PLGA microparticles were prepared by the same methodology. Coumarin-6 is a green fluorescent dye, which

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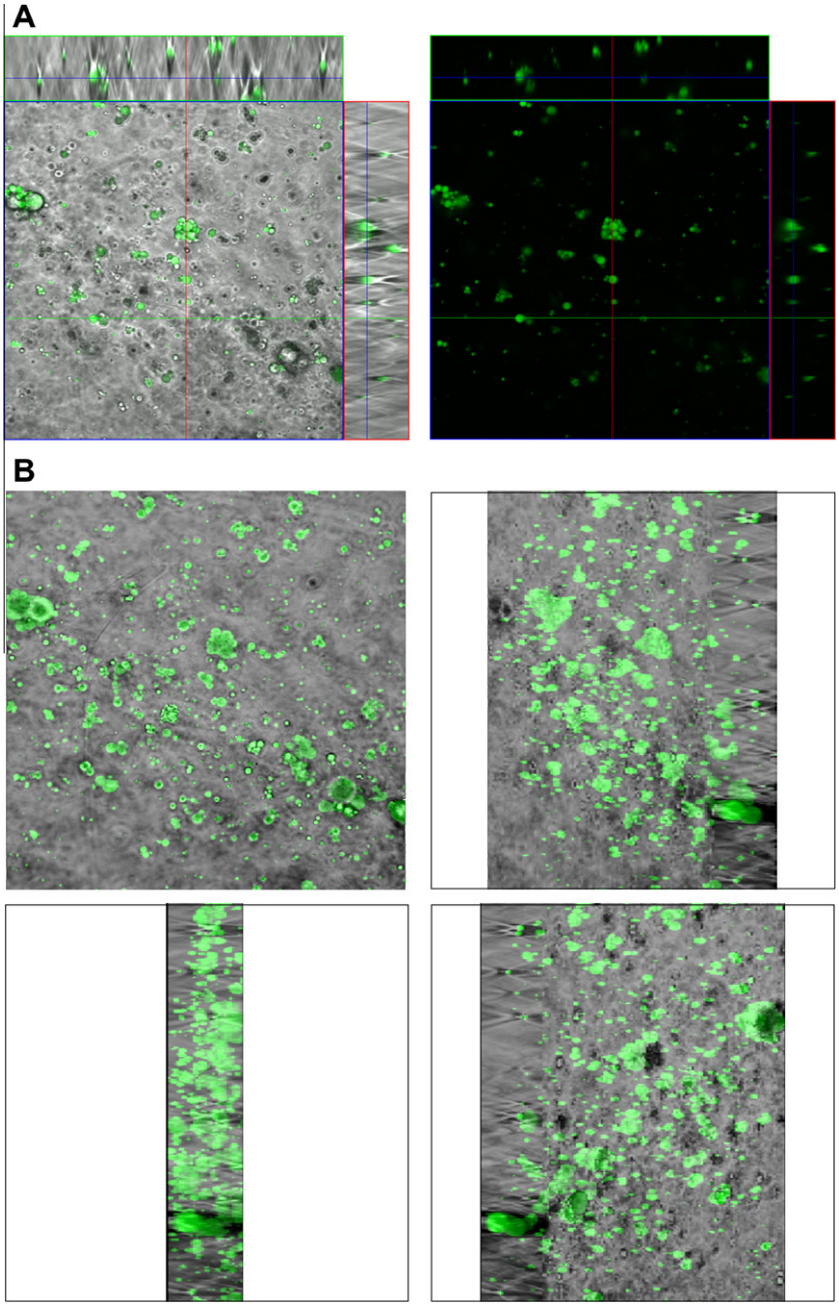

Fig. 4. Homogeneity of coumarine 6 loaded PLGA particles in Tisseel™. Confocal laser scanning images of coumarin-6 loaded PLGA microparticles in Tisseel™. (A) Z-stacks of the matrix were performed. Channel overlay of fluorescence and transmitted light (left) and fluorescence channel (right) is shown. Magnification 63 times. (B) 3D pictures of the Tissucol matrix (thickness: 26 μm). Channel overlay of fluorescence and transmitted light is shown. Magnification 63 times. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

can be used for visualizing microparticles by confocal scanning microscopy. The EE of coumarin 6 loaded microparticles (CMPs) with 91.9 ± 4.3% is high. A cause for the lower EE of CMPs compared to NMPs might be the inclusion of coumarin 6 into the feeding tube of Nano Spray Dryer B-90. A yellowish color of the tube after particle preparation was examined.

Fig. 2 reports SEM micrographs of spray-dried powders. The particle sizes in Table 1 were derived from the SEM pictures. This procedure was selected as it requires less material than standard laser diffraction methods. Pure PLGA microparticles (blanks, BMPs) showed a particle size of 2.25 ± 1.45 μm. As shown in Table 1, the particle sizes of the drug loaded NMPs were in the range of ca. 2 μm with relatively large standard deviations. The drug loading did not significantly affect the particle sizes. The particles are small enough to pass the syringe needle of the Duplojet Tisseel™ System.

For morphology studies, the spray-dried samples only in the upper part (2 cm) of the collection cylinder were examined. Large-scale particles are more rapidly captured by the high voltage system than smaller ones. Therefore, a particle segregation effect over the cylinder length can be noted [14]. Generally, the spray-dried microparticles in the collection cylinder were obtained as a fine powder. The SEM micrographs in Fig. 2 demonstrate spherical microparticles with a smooth surface structure. Samples of BMPs, NPMs (10%, 20%, 30%, 40%), and CMPs are shown. The microencapsulation of nimodipine using PLGA by spray-drying is technically feasible. For formulation of fibrin glue based devices, the particle size and particle

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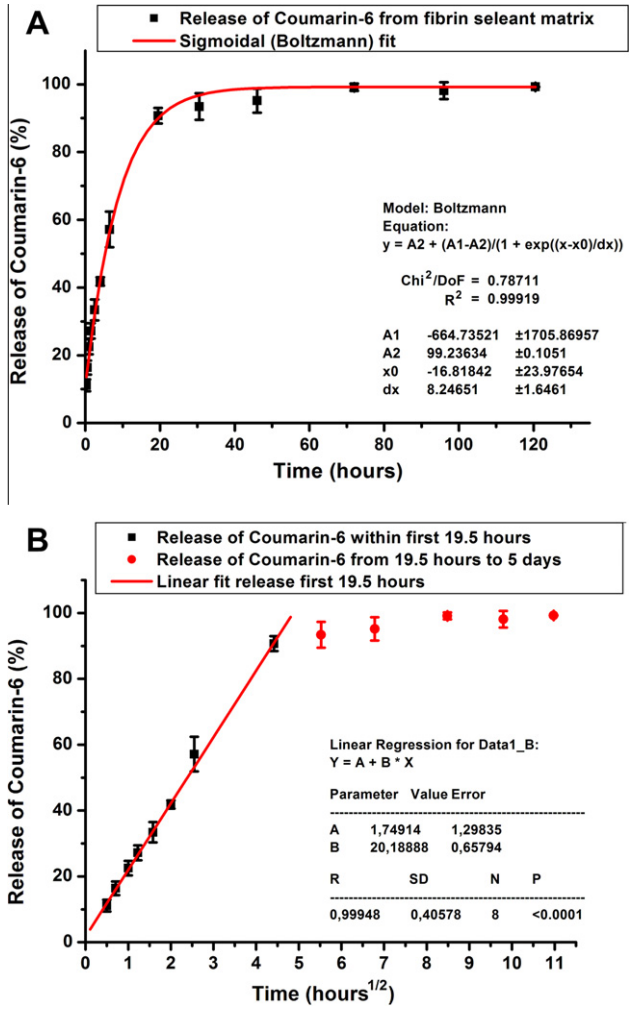

Fig. 5. 5-Day *in vitro* model drug release in 50% EtOH/PBS. (A) Release in % of coumarin-6 from fibrin sealant matrix loaded with C6-MPs ($n = 3$, mean ± STD). (B) Release in % of coumarin-6 plotted against the square root of time ($\sqrt{t}$) ($n = 3$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

distribution were found to be in an acceptable range and miscibility with components of the tissue adhesive was not problematic.

3.2. Thermal analysis (DSC)

DSC allows characterization of physical properties such as crystallinity or amorphous state of samples [25]. The effect of nimodipine loading on PLGA was measured by DSC. As shown in Table 1 and Fig. 3, the glass transition temperature of BMPs was 38.1 °C. Increasing the amount of nimodipine led to a decrease in T_g as shown in Fig. 3. At a drug loading of 40% nimodipine, the T_g was 23.6 °C. Linearity in T_g decrease was examined between 10% and 40% loading. With additional 10% drug loading, the T_g decreased about 4.4 K. Measurements were done between 0 and 140 °C (in Fig. 3 a 20–100 °C section was shown). No sharp peak for the melting temperature of nimodipine (about 125 °C [26]) could be found. The drug was homogeneously dissolved in the PLGA matrix [27]. The DSC data showed that interactions between nimodipine and PLGA occurred, so that nimodipine was dissolved in the PLGA matrix. The glass transition temperature of all NMPs was lower than 37 °C, which is important for the following release study. At a release temperature above the T_g, the polymer matrix is in a rubbery state [28]. Consequently, the incorporated drug is able to diffuse easier through PLGA and can reach the target region faster.

Moreover, the glass transition temperature of polymers is directly correlated with the amount of residual solvent (plasticizer effect) [29]. Higher solvent content results in a decreased glass transition temperature. As the blank microparticles reveal the same glass transition temperature compared with the bulk polymer employed for microparticle preparation, it is obvious that the residual content of methylene chloride in the final microparticle product is low.

3.3. Homogeneity of microparticles in the depot system

Due to the properties of the PLGA matrix [10], the microparticles were well miscible with the sealer protein solution of the Tisseel™. For construction of fibrin sealant devices, the loaded sealer protein solution and the thrombin solution were mixed and formed simultaneously as shown in Fig. 1. The *in situ* forming device was generated on a glass slide covered by a cover slip.

To investigate the homogeneity of the loaded microparticles in the fibrin sealant, the fluorescent dye coumarin-6 was incorporated into PLGA. Coumarin-6 acts as lipophilic model drug instead of nimodipine. This fluorescent dye can be detected via confocal scanning microscopy. Therefore, information concerning homogeneity of the drug in the PLGA matrix and of the homogeneity of microparticles in the Tisseel™ matrix was achieved respectively.

In Fig. 4A, Z-stacks of the loaded Tisseel™ matrix are shown. The microparticles were dispersed homogeneously in the matrix in each layer. Some small agglomerates were examined. These small agglomerates are negligible in relation to drug release.

Fig. 4B indicates 3D pictures of the sealant matrix with a thickness of 26 µm. In the four pictures, the loaded matrix was completely rotated so that the particle dispersion was examined in each layer. In summary, the microparticles were homogeneously dispersed in the sealant by the Duploject injection system.

3.4. Drug release

The model drug coumarin-6 instead of nimodipine was used as lipophilic loading component to allow for sensitive analytics. The CMPs were homogeneously dispersed in the sealer component and the *in situ* forming devices were built. The lipophilic drug coumarin 6 is practically insoluble in aqueous media [20] like nimodipine. So, to generate sink conditions, it was necessary to use the surfactant ethanol for release studies. The solubility of coumarin 6 in PBS/ethanol (1/1 w/w) was published to be 22.2 µg/mL [18]. So, the use of 30 mL PBS/ethanol (1/1 w/w) release medium guarantees sink conditions, which are necessary to obtain valid results.

Three individual CMP loaded matrices were examined during 5 days, and the amount of released coumarin 6 with time was determined by fluorescence spectroscopy (Fig. 5). The release study revealed that *in vitro* about 90% of the drug was released within the first 19 h.

In Fig. 5A, the release profile was fitted sigmoidal with a correlation coefficient of 0.999. This kinetic revealed that after 19.5 h, a climax has been reached and no additional drug can be released. The first 8 data points were fitted linear against the square root of time (Fig. 5B). Here, the amount of drug release is directly proportional to the square root of time. This kinetic of drug release can be described by the Higuchi Equation [30], which expresses diffusion controlled drug release. The release kinetic of the first 19.5 h was following Eq. (2) (linear fit) (correlation coefficient of 0.999).

Eq. (2), where Q is the amount of released drug in % of the total drug amount at time t

$$Q(t) = 1.75\% + 20.19\frac{\%}{\sqrt{s}} \cdot \sqrt{t} \qquad (2)$$

It was examined that the incorporated drug will be released and not detained by the fibrin sealant. The release is diffusion controlled, so the first step is the diffusion of coumarin 6 out of the PLGA matrix into the Tisseel™ layer and the second process is the diffusion of the compound from the sealant into the target region.

In summary, the release shows a sigmoidal release curve meaning that in the beginning, nimodipine was released to a higher amount. As drug was depleted close to the surface of the *in situ* forming device, the nimodipine release rate decreased. This phenomenon can be explained by a diffusion controlled process.

An actual release study with coumarin 6 loaded PLGA nanoparticles which were incorporated into Nanofiber Non-Wovens revealed release duration of about 1 h [18]. The *in situ* forming loaded Tisseel™ system offers much longer drug release, which is needed for vasospasm treatment.

We hypothesize that this *in situ* forming device will be ideal for a local treatment of vasospasm after subarachnoid hemorrhage. At this time, the nimodipine-loaded matrix systems are under investigation in animal studies with Wistar Rats to test the postulated behavior *in vivo*. First feasibility, effectiveness, and dose-finding experiments in the treatment of subarachnoid hemorrhage revealed a reduction in angiographic vasospasm after experimental subarachnoid hemorrhage [31].

4. Conclusion

In this study, we have shown the feasibility to incorporate nimodipine-loaded biodegradable polymer MPs into Tisseel™ fibrin sealant. Smooth and round-shaped nimodipine PLGA microparticles with high encapsulation efficiency were suspended in fibrin sealant. This system yielded an *in situ* forming device where the particles were homogeneously arranged and immobilized in this second matrix system. Thermal analysis revealed solubility of nimodipine in the PLGA matrix and a glass transition temperature lower than body temperature. Clearly, a prolonged release of coumarin 6 was obtained which followed the Higuchi kinetic and is therefore diffusion dependent. So, the nimodipine *in situ* forming device is a promising candidate for local treatment of a vasospasm after a subarachnoid hemorrhage.

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