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Towards the optimization of drug delivery to the cochlear apex: Influence of polymer and drug selection in biodegradable intracochlear implants

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ABSTRACT

There is growing need for new drug delivery systems for intracochlear application of drugs to effectively treat inner ear disorders. In this study, we describe the development and characterization of biodegradable, triamcinolone-loaded implants based on poly(lactic-*co*-glycolic acid) (PLGA) and polyethylene glycol–poly(lactic-*co*-glycolic acid) (PEG-PLGA) respectively, prepared by hot-melt extrusion. PEG 1500 was used as a plasticizer to improve flexibility and accelerate drug release. The sterilization process was performed by electron beam irradiation, resulting in minimal but acceptable polymer degradation for PEG-PLGA implants. The implants have been characterized by texture analysis, differential scanning calorimetry and X-ray powder diffraction. Compared to PLGA implants, PEG-PLGA implants offer similar flexibility but with improved mechanical stability, which will ease the handling and intracochlear application. A controlled release over three months was observed for dexamethasone and triamcinolone extrudates (drug load of 10%) with similar release profiles for both drugs. PEG-PLGA implants showed an initial slow release rate over several days regardless of the amount of PEG added. Mathematical simulations of the pharmacokinetics of the inner ear based on the *in vitro* release kinetics indicate a complete distribution of triamcinolone in the whole human scala tympani, which underlines the high potential of the developed formulation.

1. Introduction

According to current estimates by the WHO, almost half a billion people worldwide are affected by a hearing impairment (WHO, 2023) and it is estimated that around 10–14% of the world's population will develop some form of relevant hearing impairment in the course of their lives (Hoffman et al., 2017). Since spoken language communication is an essential part of our lives, a functional hearing loss is a significant burden not only for the person concerned, but also for society. Hearing impairment can lead to social isolation and stigmatization along with psychological complications (Erler and Garstecki, 2002) and significantly contributes to the risk of cognitive decline and dementia (Livingston et al., 2020).

Access to the inner ear fluids with systemic therapy is limited by a tight blood-labyrinth barrier (Salt and Hirose, 2018). High systemic doses are therefore required, which may cause side effects or the drugs are exposed to "first-pass" effects (Devare et al., 2018; Plontke et al., 2017; Szeto et al., 2020). One way to overcome these disadvantages is the approach of inner ear drug therapy by local drug release. The advantages of local drug delivery to the inner ear include bypassing the blood-labyrinth barrier, avoidance of "first-pass" metabolism, and overall dose reduction. Administration can be extracochlear (e.g. intratympanic), intracochlear or intralabyrinthine, the latter referring to the vestibular labyrinth (Salt and Plontke, 2009). Intratympanic application is less invasive and clinically more feasible than intracochlear application since the inner ear is not opened. However, due to various

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aspects, such as rapid drug clearance from the middle ear, limited permeability through the round window membrane, additional anatomical variations of the middle ear (e.g. obstruction of the round window with mucosal membranes), this leads to a high variability in intracochlear drug concentrations or even insufficient concentrations (Alzamil and Linthicum, 2000; Hahn et al., 2006). Recently, various polymer-based systems were preclinically investigated for sustained drug delivery via extracochlear administration (Gehrke et al., 2019; Lehner et al., 2021; Mäder et al., 2018; Mau et al., 2022; Rathnam et al., 2019). Intracochlear application is more invasive and technically more difficult than intratympanic application but can overcome significant disadvantages and problems of extracochlear therapy strategies. It paves the way for a better control of drug concentrations and drug distribution in the inner ear, and extends the range of usable substances (Hahn et al., 2012). Currently, intracochlear drug delivery with controlled release characteristics is mainly linked to drug eluting electrode carriers of cochlear implants (Briggs et al., 2020; Eshraghi et al., 2019; Liebau et al., 2020; Manrique-Huarte et al., 2020; Simoni et al., 2020), but is also promising without neuroprosthetic device (Pierstorff et al., 2018; Plontke et al., 2022a). We previously reported the development of biodegradable, intracochlear implants based on poly(lactic-*co*-glycolic acid) (PLGA) for sustained release of dexamethasone (DEX) over several weeks (Lehner et al., 2019). Mechanical properties and drug release profiles were controlled by varying the amount of non-covalently bound PEG. The general suitability of the administration of PLGA implants into the scala tympani of the human inner ear and co-administration with a cochlear implant electrode array was shown (Lehner et al., 2022). However, during handling the implants, slight deformation was observed due to forces by surgical instruments and mechanical stress of the co-administered cochlear implant (Lehner et al., 2022).

Therefore, we considered the block polymer polyethylene glycol – poly(lactic-co-glycolic acid) (PEG-PLGA) as implant matrix due to its inclusion of covalently bound PEG that act as plasticizer (de Souza et al., 2021). By changing the implant matrix, we aimed for an increased mechanical stability of the implants. In contrast to PLGA, PEG-PLGA does not undergo autocatalytic degradation. It avoids the development of an acidic microclimate and shows a more uniform polymer degradation (Witt et al., 2000). The flexibility of PEG-PLGA implants can be increased even further by adding non-covalently bound PEG (Kirchberg et al., 2020).

Glucocorticoids are widely used for inner ear therapy by intratympanic application (Patel et al., 2016; Plontke et al., 2022b). Most clinically available glucocorticoids, however, show rapid elimination from scala tympani, such as DEX with a half-time of 46 min (Salt et al., 2018). Short half-times lead to steep baso-apical concentration gradients in cochlear perilymph with very low amounts in the apex or the apex is not even be reached (Ayoob et al., 2019; Leong et al., 2023). Pharmacokinetic measurements in guinea pigs showed an extremely prolonged half-time in scala tympani of 700 min for the glucocorticoid triamcinolone (TCM), whereas the half-time for the more lipophilic triamcinolone acetonide is reduced to 12 min (Salt et al., 2019). Therefore, we decided to load the implants with TMC since its pharmacokinetic properties predicted to reach apical cochlear regions of the human ear in higher concentration. These regions are responsible for processing low-frequency sounds, such as vowel sounds and the fundamental frequencies of speech. In case of cochlear implantation, preservation of residual hearing in the apical, low-frequency region has become growing interest and importance (Gay et al., 2022; Kiefer et al., 2004).

In the present study, we investigated the suitability of TMC-loaded implants for intracochlear administration with controlled release properties. Implant formulations based on PLGA or PEG-PLGA were prepared using hot-melt extrusion. The impact of different amounts of non-covalently bound PEG was thoroughly characterized through texture analysis, differential scanning calorimetry (DSC), and X-ray powder diffraction. TMC distributions in the human scala tympani were predicted using computer simulations and compared with distributions of DEX-loaded implants based on their measured *in vitro* drug release profiles.

2. Material and methods

2.1. Materials

Triamcinolone (TMC) and dexamethasone (DEX) were purchased from Caesar & Loretz GmbH (Hilden, Germany). Polyethylene glycol (PEG) 1500 g/mol was purchased from Alfa Aesar (Haverhill, USA). Expansorb® polymer 10P019 DLG 50-2A (poly(lactic-*co*-glycolic acid); PLGA) was obtained from Merck KGaA (Darmstadt, Germany). Expansorb® 10P037 DLG 50-6P (polyethylene glycol–poly(lactic-*co*-glycolic acid); PEG-PLGA) was purchased from Seqens (Ecully Cedex, France) containing approximately 10% covalently bound PEG (5 kDa out of 37–77 kDa). Artificial perilymph was prepared by dissolving NaCl (137 mM), KCl (5 mM), $CaCl_2$ (2 mM), $MgCl_2$ (1 mM), $NaHCO_3$ (1 mM), and glucose (11 mM) in double-distilled water. To avoid microbial growth, sodium azide 0.02% was added to artificial perilymph. Acetonitrile and double distilled water were used for the HPLC method.

2.2. Preparation of biodegradable drug-loaded implants

Biodegradable implants containing TMC or DEX were prepared by hot-melt extrusion (ZE 5 ECO; Three-Tec GmbH; Seon; Swiss) with an extrusion screw frequency of 60 rpm. The three heating zones were set individually depending on the various implant formulations and an extrusion die of 0.3 mm was used. Samples were collected in falcon tubes and stored in a fridge between 2 and 8 °C. After at least 2 weeks of storage, the extruded material was cut under an Olympus SZX9 reflected light microscope (Olympus Optical Co., Hamburg, Germany) into 3 mm implants using a scalpel. In between, electron beam irradiation took place. Before extrusion, components of each formulation were pulverized with a cryomill (Retsch GmbH, Haan, Germany) using the following settings: automatic pre-cooling, 4 milling cycles at 25 Hz for 90 s, 30 s lasting phase between the milling cycles at 5 Hz. The grinding jar was continually cooled with liquid nitrogen. Components of each formulation are shown in Table 1. We perform physicochemical characterizations on implants containing TMC since our previous work has already covered DEX-loaded implants (Lehner et al., 2019). DEX-loaded implants of PLGA-10 and PEG-PLGA-5 formulation were exclusively fabricated for the purpose of conducting drug release studies.

2.3. Electron beam irradiation

Electron beam irradiation was chosen as sterilization process. Extruded material was irradiated with 25 kGy at room temperature by a 10 MeV linear accelerator MB 10–30 MP (Mevex, Stittsville, Ontario, Canada) on a moving tray (95 cm/min). The repetition rate of the accelerator was 460 Hz with 8 μs pulses, using a scanning frequency of 3

Table 1
Composition of prepared implants in percent. Numbers in the implant name represents the amount of non-covalently bound PEG added.

Implant name	PLGA	PEG-PLGA	PEG	Triamcinolone	Dexamethasone
TMC PLGA-10	80	–	10	10	–
DEX PLGA-10	80	–	10	–	10
TMC PEG-PLGA-0	–	90	0	10	–
TMC PEG-PLGA-5	–	85	5	10	–
DEX PEG-PLGA-5	–	85	5	–	10
TMC PEG-PLGA-10	–	80	10	10	–

Hz and a scanning width up to 60 cm. The total dose of 25 kGy was achieved by administering two separate doses of 12.5 kGy each. Drug load of the TMC-loaded implants after sterilization was determined by HPLC (Section 2.10). Furthermore, the impact of electron beam treatment on the molecular weight of PLGA and PEG-PLGA was investigated by gel permeation chromatography (Section 2.8).

2.4. Drug load and homogeneity

1 mg samples were collected from different parts of sterilized and non-sterilized extruded material respectively. Samples were dissolved under vortexing in 100 µL acetone and filled up to 1 mL with acetonitrile. Subsequently, the solutions were analyzed by high performance liquid chromatography (HPLC) as described in 2.10. to determine the TMC drug load. Drug load was calculated by Eq. (1), where m_{TMC} is the mass of TMC and $m_{implant}$ is the mass of the weighed drug containing implant. Mean values for three replicate determinations and their standard deviations are reported.

$$Drugload[\%] = \frac{m_{TMC}}{m_{implant}} * 100\% \quad (1)$$

2.5. Mechanical stability

Mechanical properties of the sterilized implants were evaluated on a CT3 Texture Analyzer (Ametek GmbH, Hadamar-Steinbach, Germany) with the TexturePro CT V1.6 software. Flexibility of the implants was examined by measuring the required force to push a blade (accessory TA7, knife edge, Ametek GmbH, Germany) over a distance of 0.2 mm with a constant velocity into the implants using the deformation mode and a scan velocity of 0.01 mm/s. The trigger force was adjusted to 0.02 N. Additionally, a deformation test was performed with a 6 mm diameter cylinder (accessory TA41, cylinder). The compression settings were adjusted over a distance of 0.4 mm until the program stopped due to reaching maximum resistance, resulting in a complete deformation of the implants. Pictures were taken before and within one minute after compression with an UC30 camera connected to an Olympus SZX9 reflected light microscope (Olympus Optical Co., Hamburg, Germany). Both experiments were conducted at 20 °C room temperature.

2.6. Differential scanning calorimetry (DSC)

DSC measurements were recorded with a Mettler Toledo DSC 823e module (Mettler Toledo, Gießen, Germany) in standard aluminum sample pans. Every sample was cooled down to −30 °C and kept at this temperature for 4 min. The sample was then heated up to 70 °C with a heating rate of 5 K/min. Data recording and processing were carried out with the software STARe V15.00 (Mettler Toledo, Gießen, Germany). In general, first heating curves are displayed. In case of PLGA and PEG-PLGA, second curves are shown to avoid relaxation peaks of the polymers.

2.7. X-ray powder diffraction (XRD)

Wide angle X-ray scattering was performed on a STOE STADI MP (STOE & Cie GmbH, Darmstadt, Germany) powder diffractometer, equipped with molybdenum anode (50 kV and 30 mA) and a Ge (1 1 1) monochromator to select the Mo Kα radiation at 0.071073 nm. The samples were scanned in an angle range from 5° to 20°, in 1.995° steps with an exposure time of 120 s per step. The diffraction patterns obtained were processed using an STOE WinXPOW software package.

2.8. Gel permeation chromatography (GPC)

Molecular weights of PLGA and PEG-PLGA before and after electron beam irradiation were measured using a GPC system, consisting of a ViscotekGPCmax VE 2002 using HHRH Guard-17360 and GMHHR-N-18055 columns and a refractive detector (VE 3580 RI detector, Viscotek). Tetrahydrofuran (THF) was set as eluent. Implants were dissolved in THF to obtain a concentration of 3 mg/ml. The flow rate was 1 mL/min. Polystyrene standards of known molecular weights were used for calibration. Samples were filtered (0.22 µm) before measuring.

2.9. In vitro drug release

Release studies of TMC-loaded implants were performed and compared with release profiles of DEX-loaded implants of PLGA-10 and PEG-PLGA-5 formulation. 1 mg of each sterilized implant formulation was placed in 1.5 mL glass vials filled with 1 mL artificial perilymph and slightly agitated in a water bath shaker with light protection (Memmert GmbH + Co. KG, Schwabach, Germany) at 37 °C. Total sample solution was withdrawn daily and analyzed according to the described HPLC methods below (2.10.). Appropriate volume of fresh artificial perilymph was replaced after taking samples. Each experiment was conducted in triplicate.

2.10. High performance liquid chromatography (HPLC)

Modified methods from European Pharmacopoeia were used to analyze TMC and DEX. A Jasco HPLC system with a PU-1580 Pump equipped with AS-1559 Intelligent Auto Sampler and UV-1559 Intelligent UV/VIS Detector (all Jasco, Oklahoma City, USA) with an EC 250/4 Nucleodur® 100–5 C18ec column (Macherey-Nagel, Düren, Germany), operated at 40 °C, was used. Acetonitrile and double distilled water in a ratio 25/75 V/V and 40/60 V/V were used as the mobile phase at a flow of 1 mL/min to quantify TMC and DEX, respectively. 20 µL of sample were injected and analyzed at $\lambda = 239$ nm. Retention times for TMC and DEX were found to be 5.4 min and 5.8 min, respectively. Data recording and processing were carried out with the software ChromNAV Ver.2 (Jasco, Oklahoma City, USA).

2.11. Mathematical simulations of inner ear drug distribution

Simulations of TMC and DEX distributions in the scala tympani of the human inner ear were performed with FluidSim V4.05 (https://alecsalt.com) over a period of 90 days, using the obtained *in vitro* release data. Implant location was set 1 mm behind the round window membrane in the basal region of scala tympani. The dimensions of the implants for simulation were set to 350 µm in diameter and 3 mm in length with total drug amount of 35 µg. All other parameters remained at the program's default values.

3. Results and discussion

3.1. Hot-melt extrusion

Hot-melt extrusion led to a successful preparation of extrudates (Fig. 1). All PEG-PLGA extrudates exhibit a golden-brown color resulting from the combination of the brown raw polymer and the integrated drug. The brown color of the raw polymer is likely associated with the covalent bonding of PLGA and PEG blocks, as the incorporation of non-covalently PEG does not cause any color change. The diameter of all formulations is within a narrow range of 350 µm (Table 2). The larger diameter compared to the die (300 µm) can be explained by the viscoelastic behavior of PLGA-based polymers (Wang, 2012; Witt et al., 2000) Process parameters for the TMC PLGA-10 implants were comparable to the previous published DEX-loaded PLGA implants (Lehner et al., 2019). When using PEG-PLGA polymers, the heating zones had to be set to higher temperatures. Compared to TMC PLGA-10 with heating zones at 50, 50, 52 °C, extrudates of TMC PEG-PLGA-0 formulation could be obtained at 58, 58, 62 °C. Adding PEG to PEG-PLGA resulted in a decrease in the temperature of the heating zones, with a maximum

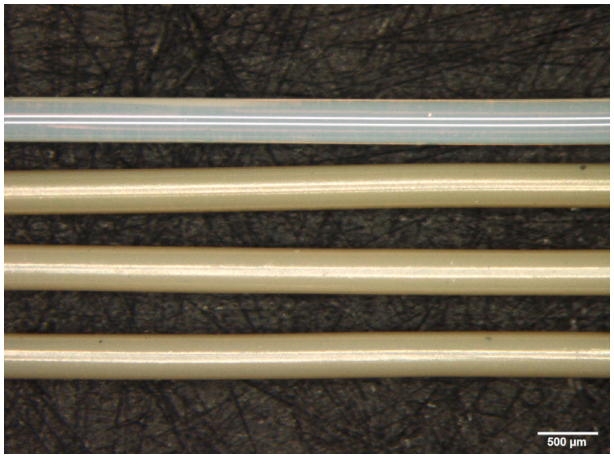

Fig. 1. Representative microscopic images of extrudates loaded with TMC from top to bottom: PLGA-10, PEG-PLGA-0, PEG-PLGA-5, and PEG-PLGA-10. Scale bars represent 500 µm.

Table 2
Extrusion parameters and resulting diameters of TMC-loaded implants.

Implant name	Temperature of heating zones [°C]	Screw speed [rpm]	Diameter [µm]
TMC PLGA-10	50/50/52	60	349 ± 11
TMC PEG-PLGA-0	58/58/62	60	341 ± 8
TMC PEG-PLGA-5	56/56/58	60	353 ± 10
TMC PEG-PLGA-10	52/52/54	60	359 ± 18

temperature reduction for the TMC PEG-PLGA-10 formulation (52, 52, 54 °C). Only minor adjustments had to be made when the polymer matrix was varied.

Subjectively, extrusion was "easier" with PEG-PLGA. The TMC PLGA-10 formulation was far stickier and showed stronger adhesion to the extruder screws. Therefore, a minor product yield resulted with a longer extrusion duration.

3.2. Impact of electron beam irradiation

Drug delivery systems for use in the inner ear must ensure the absence of pathogenic microorganisms. Due to the physicochemical properties of the polymers, the implants cannot be the sterilized by dry or wet heat. If the glass transition temperature of PLGA and PEG-PLGA is exceeded due to high temperatures, the implants lose their cylindrical shape. Gas sterilization with ethylene oxide is another potential sterilization technique. Gradwohl et al. demonstrated that ethylene oxide had no impact on the molecular weight of PLGA (Gradwohl et al., 2021). However, Hsiao's research revealed that ethylene oxide caused a significant alteration in the morphology of PLGA composites (Hsiao et al., 2012). Considering workplace toxicity and the residue analysis of toxic ethylene oxide and some of its derivatives, electron beam irradiation with doses of 25 kGy appears to be a suitable sterilization method for the TMC-loaded implants. However, studies on effects of sterilization processes with TMC are limited. For ethylene oxide and gamma irradiation no or minor loss in content was observed in TMC samples (Van Cauwenbergh et al., 2022). Therefore, the impact of electron beam irradiation on the drug load had to be investigated. Drug content of TMC-loaded implants was measured before and after electron beam irradiation. Drug load of each implant formulation was expected to be 10%. Values determined by HPLC confirmed drug loads of approximately 10% for all implant formulations before and after sterilization process (Fig. 2A). Irradiation induced TMC degradation was not observed, therefore, irradiation sterilization can be performed. In addition, the low standard deviations illustrate a homogeneous TMC distribution within various sections of the extruded material.

Furthermore, the molecular weight of the polymers can also be affected by electron beam irradiation. Fig. 2B displays the molecular weight M_w of PLGA and PEG-PLGA of TMC-loaded implants before and after sterilization including the obtained polydispersity index (PDI). PLGA was not affected by electron beam irradiation and showed a molecular weight of 10 kDa and a PDI of 1.3 before and after irradiation, respectively. The initial molecular weight of PEG-PLGA in the respective implants was heterogeneous, which is linked to the wide range of the molecular weight of the unprocessed polymer (36–77 kDa). In contrast to PLGA, the molecular weight of PEG-PLGA decreased about 10–14%. The results also showed an increase in the PDI for PEG-PLGA that could be caused by cross-linking and chain scission reactions (Loo et al., 2005). At high doses, which are used for sterilization, chain scission reactions will dominate. In general, polymers based on PLGA with higher molecular weights are more vulnerable to degradation upon irradiation (Dorati et al., 2008).

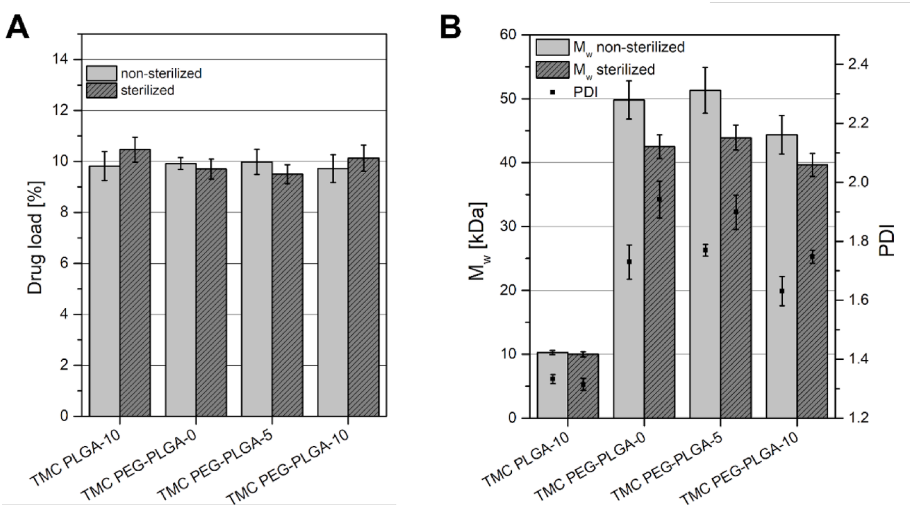

Fig. 2. Drug load **(A)** and in **(B)** molecular weight (M_w) and polydispersity index (PDI) of PLGA and PEG-PLGA of TMC-loaded implants before and after electron beam irradiation (mean ± SD, n = 3).

In the present study, all implants examined were treated under an oxygen atmosphere and at room temperature. The results indicate the suitability of this process. Further options to decrease the degradation processes of the polymers and drug molecules are sterilization under argon atmosphere or vacuum or at reduced temperatures (e.g. liquid nitrogen) (Fintzou et al., 2007).

All experiments were determined with sterilized implants, since irradiation-induced polymer degradation can have an impact on the mechanical properties and drug release kinetics.

3.3. Mechanical stability

Opening the round window of the cochlea (and even more so a cochleostomy) already is an invasive approach. It is therefore very important that insertion of the drug delivery system does not cause any additional trauma. Intracochlear implants should combine flexibility with sufficient mechanical stability for handling. Breakage or cracks in the implant during insertion may lead to uncontrolled drug release and sharp edges, which could harm e.g. the cochlea wall or basilar membrane. Texture analysis is a valid method for assessing the mechanical properties of implants (Esfahani et al., 2022; Kirchberg et al., 2020; Lehner et al., 2019). Fig. 3 shows the force path diagrams of the different sterilized implants. A small blade penetrated into the implants over a distance of 0.2 mm and the resulting force was measured. A linearity between penetration force and penetration depth was observed for all implants without any signs of breakage. Implant formulation TMC PEG-PLGA-0 had the highest maximum force (1.27 N) compared to the other implants. This maximum force could be reduced to 0.52 N and 0.07 N for TMC PEG-PLGA-5 and TMC PEG-PLGA-10 implants respectively, by adding PEG as a plasticizer. A plasticizer must be added when using PLGA as implant matrix to prevent the implants from breaking. We demonstrated cracking of PEG-free implants of the same diameter at a penetration distance of 0.04 mm with a measured maximum force of 5.33 N (Lehner et al., 2019). TMC PLGA-10 implants behaved quite similar to TMC PEG-PLGA-5 implants due to the use of 10% PEG. Summarized, when using PEG-PLGA polymer, additional PEG is not required to avoid breaking, but implants became softer depending on the PEG concentration.

In our recent studies, implants made from a combination of PLGA and 10% PEG showed good flexibility, but slightly deformed when subjected to external force, such as being inserted into the cochlea through the round window membrane with an alligator forceps (Lehner et al., 2022). Changing the cylindrical shape could lead to uncontrolled drug release (Kempe and Mäder, 2012; Suh et al., 2021). The deformation test with a cylinder offered major insights towards the mechanical properties of PLGA- and PEG-PLGA-based implants. Images of the respective implants were taken before and within one minute after deformation. Force applied to TMC PLGA-10 implants led to a complete destruction of the rod shape (Fig. 4A,B). In contrast, the TMC PEG-PLGA-5 implant showed elastic behavior immediately after mechanical stress (Fig. 4C,D). In terms of flexibility, implant formulations TMC PLGA-10 and TMC PEG-PLGA-5 are similar, but based on the deformation test, PEG-PLGA-based implants showed improved mechanical stability, which will ease the handling during intracochlear administration.

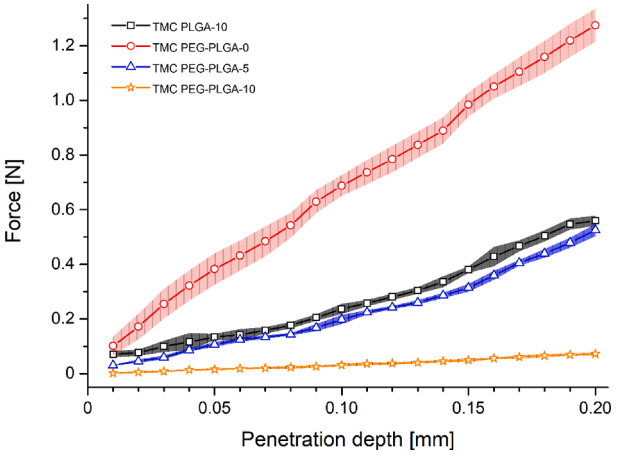

Fig. 3. Penetration test profiles of TMC-loaded implants (mean ± SD, n = 3).

3.4. Differential scanning calorimetry

To investigate the thermal properties of the sterilized TMC-loaded implants, DSC measurements were conducted, and the resulting thermograms are shown in Fig. 5. PLGA is an amorphous polymer with a glass transition temperature (T_g) at 35.3 °C. Incorporating 10% of crystalline PEG into PLGA decreases the glass transition temperature to 17.2 °C (TMC PLGA-10). Additionally, the glass transition temperature of PEG-PLGA was determined to be 23.1 °C, lower than the glass transition temperature of raw PLGA, due to the presence of covalently bound PEG (5 kDa).

Further addition of non-covalently bound PEG to PEG-PLGA results in a more substantial reduction in the glass transition temperature. For TMC PEG-PLGA-10 implants, a melting temperature of 41.6 °C was measured, indicating a semi-crystalline behavior of the non-covalently bound PEG. This PEG peak could lead to further recrystallization processes, causing a shift of the glass transition temperature to higher temperatures. The comparison with the unprocessed physical mixture (PM) of the lowest PEG-containing formulation (TMC PEG-PLGA-5 PM) identified this melting temperature as PEG. The observed temperature difference of 6 K in the melting points between raw (48.4 °C) and incorporated PEG (42.6 °C) could be explained by an interaction with the PEG-PLGA polymer. The PEG-PLGA matrix disrupts the crystal lattice and weakens the intermolecular forces, leading to a lower melting temperature (Nakafuku and Sakoda, 1993).

The behavior of the implants at room temperature is crucial for implantation. When the glass transition temperature is below the temperature in the operating theatre, the implants are in a flexible, rubbery state. Assuming a temperature in the operating theatre of around 20 °C, the implant formulations TMC PLGA-10, TMC PEG-PLGA-5, and TMC PEG-PLGA-10 are flexible during application. A summary of glass transition and melting temperatures is shown in Table 3.

3.5. X-ray powder diffraction

X-ray powder diffraction was conducted to receive conclusions about the physicochemical properties of TMC and PEG inside implants. The state of the drug i.e. crystalline or amorphous, in drug delivery systems can easily affect storage stability, release, solubility and therefore the bioavailability. X-ray traces of raw materials and the various sterilized TMC-loaded implants are displayed in Fig. 6. TMC diffraction patterns were found in TMC PLGA-10 implants and in each TMC PEG-PLGA implant, respectively, identifying the drug in crystalline state.

Since DSC measurements found a recrystallization peak of PEG in TMC PEG-PLGA-10 implants, X-ray powder diffraction could underline these findings. Therefore, a physical mixture (PM) of the implant formulation with the lowest amount of additional PEG (TMC PEG-PLGA-5 PM) was chosen to demonstrate the detectability of PEG alongside TMC. Once more, minimal signs of crystalline PEG could be found in TMC PEG-PLGA-10 implants, indicated by the most characteristic reflections of PEG (blue arrows). However, the right blue arrow points to an area consisting of overlapping PEG and TMC reflexes. The fact that PEG is not completely dissolved in the matrix could lead to further recrystallization processes and thus to storage instabilities and a lack of flexibility. Consequently, it should be carefully considered whether implants with PEG-PLGA-10 matrix have potential for use in further development. TMC PLGA-10 and TMC PEG-PLGA-5 implants show no characteristic PEG reflexes and, as displayed by the DSC results, appear

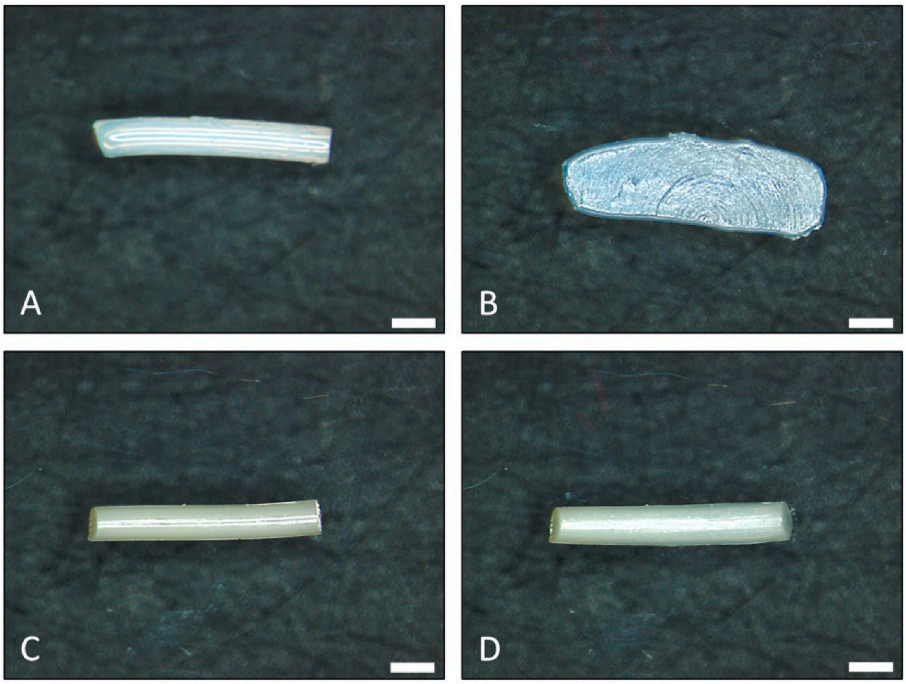

Fig. 4. Reflected light microscopy images of a TMC PLGA-10 implant (**A,B**) and a TMC PEG-PLGA-5 implant (**C,D**) before (**A,C**) and after (**B,D**) deformation tests. White scale bars represent 0.5 mm.

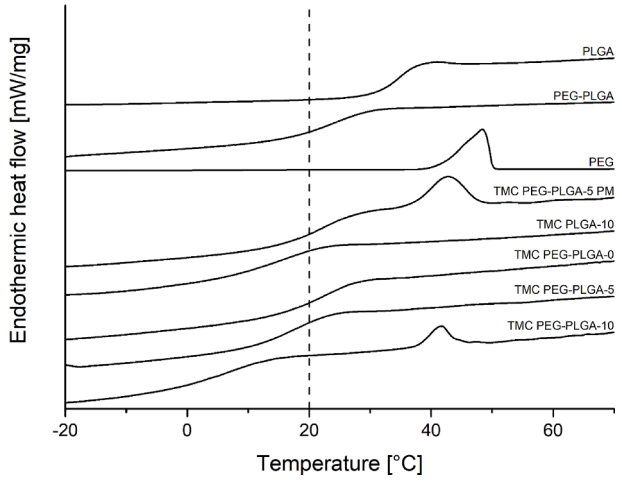

Fig. 5. DSC thermograms of implants and their components, consisting of PLGA, PEG-PLGA and PEG, and their physical mixture (PM). Measurements were carried out with a heating rate of 5 K/min. The vertical dotted line represents temperature in an operation room of approximately 20 °C.

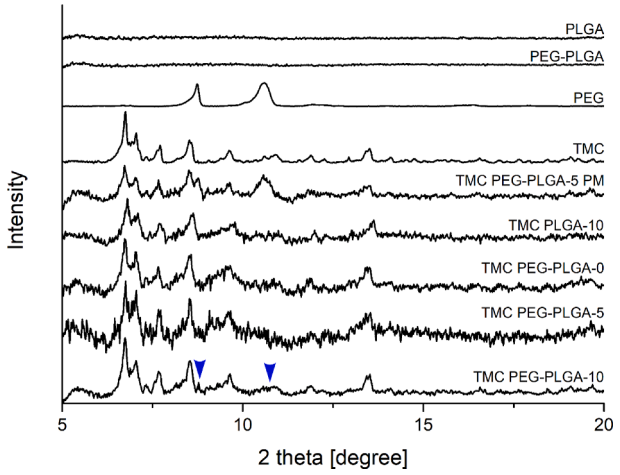

Fig. 6. X-Ray powder diffraction traces of implant components, physical mixture (PM) of TMC PEG-PLGA-5, and different implants. The blue arrow indicates the most characteristic reflections of crystalline free PEG in TMC PEG-PLGA-10 implants.

Table 3
Glass transition (T_g) and melting temperatures (T_m) of polymers, physical mixture (PM), and implants.

Sample	T_g [°C]	T_m [°C]
PLGA	35.3	–
PEG-PLGA	23.1	–
PEG	–	48.4
TMC PEG-PLGA-5 PM	23.6	42.6
TMC PLGA-10	17.2	–
TMC PEG-PLGA-0	22.9	–
TMC PEG-PLGA-5	18.7	–
TMC PEG-PLGA-10	7.9	41.6

to be stable after 14 days of storage.

3.6. *In vitro drug release*

Implants loaded with TMC were studied regarding their drug release profiles at 37 °C in artificial perilymph pH 7.4. Controlled release profiles over a period of 90 days are shown in Fig. 7A. PEG-PLGA implants showed a slightly longer release time than PLGA implants (7 to 11 days). After one week, 21.9%, 1.1%, 1.9%, and 6.6% were released from TMC PLGA-10, TMC PEG-PLGA-0, −5, and −10 implants, respectively. The typical lag phase and sigmoidal drug release profile for PLGA implants could be avoided by the addition of 10% PEG (TMC PLGA-10). Incorporation of non-covalently bound PEG in PEG-PLGA formulations accelerate the drug release that can be clearly seen at day 28.

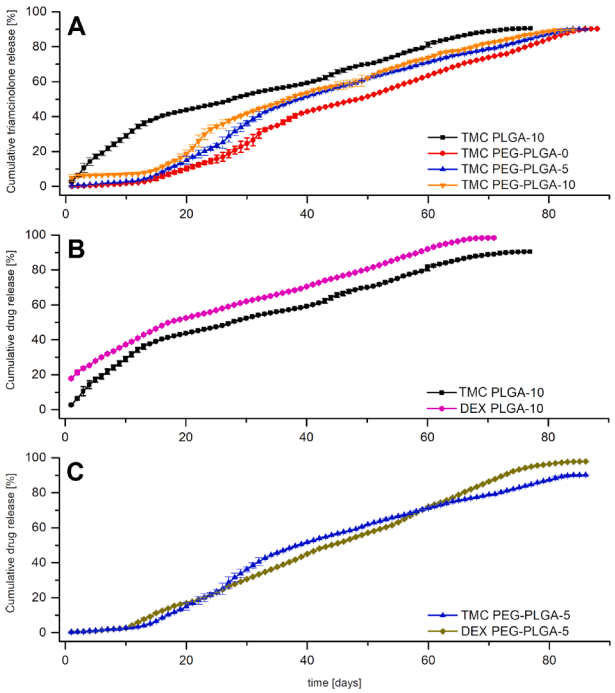

Fig. 7. *In vitro* drug release profiles of sterilized implants in artificial perilymph at 37 °C. (**A**) Cumulative release of sterilized TMC-loaded implants. Comparison of release profiles of TCM and DEX in PLGA-10 (**B**) and PEG-PLGA-5 (**C**) implant matrix. Data are presented as mean ± SD, n = 3.

Surprisingly, lag times for all TMC PEG-PLGA implants regardless of the added PEG amount were observed. PEG-PLGA microparticles produced by de Souza et al. showed no lag time and a risperidone release of 50% after three days (de Souza et al., 2021). However, release profiles of implants and microparticles are different due to various factors, including size and shape, porosity and surface area, and the type of drug. Previous experiments show a porous structure of PEG-PLGA microparticles (de Souza et al., 2021) and a rapid water penetration into the PEG-PLGA polymers (Mäder et al., 1998). However, TMC has a limited water solubility and therefore, contact with water will not result in immediate release. The overall release kinetics will depend also on the solubility and mobility inside the polymer matrix. For PEG-PLGA water penetration will lead to the formation of hydrophilic nanodomains inside the extrudate, which might act as a "distribution barrier". Further investigations are needed to understand release kinetics of these implants in detail.

Daily sampling was necessary for (a) reducing degradation products of TMC and (b) having sink conditions. Redasani et al. showed that TMC is quite stable under acidic environment, but highly unstable under alkaline condition (Redasani, 2015). Information on degradation in artificial perilymph is not available. After incubation of TMC in artificial perilymph for 7 days at 37 °C, a small degradation peak of 8% of the TMC peak at a retention time of 4.1 min was found (Suppl. 1). The amount of 90% cumulatively drug released proves that TMC remains stable over a period of three months in all implant formulations and degradation takes place in artificial perilymph of released drug. TMC released *in vivo* would not have a long residence time to form degradation products, but instead would act fast at glucocorticoid receptors or be eliminated. In addition to daily sampling, the volume of the release medium also determines whether sink conditions are achieved. The highest drug release was measured for TMC PEG-PLGA-10 implants at day one (4.81 µg/ml). This corresponds to 6% of the solubility of TMC (80 µg/ml). In relation to the volume of perilymph in the human scala tympani (30 µL) (Glueckert et al., 2018), 1 mL release volume does not correspond to physiological conditions, but considering the fast elimination rate of glucocorticoids in the scala tympani it is an acceptable compromise. In our previous study, 1 mL was used for release of DEX-loaded implants (Lehner et al., 2019). These implants were re-evaluated to compare the release profiles with TMC using identical release conditions, since the experimental setup (agitation, sampling interval, release medium) is of high importance (Bassand et al., 2022). Fig. 7B showed a similar release profile for DEX-loaded implants (DEX PLGA-10), but compared with TMC (TMC PLGA-10) a nearly seven-fold higher initial release within the first day was measured (17.9% compared to 2.7%). With a solubility of 89 µg/ml for DEX, the initial release could be even faster since no sink conditions were met for day one sampling point (20% released). Sink conditions were maintained for further DEX measuring points with a highest release rate of 2.8%. Instabilities could not be observed for DEX demonstrated by a release rate of 98.5%.

TMC PEG-PLGA-5 turned out to be the most promising formulation of all PEG-PLGA implants regarding TMC release, since TMC PEG-PLGA-10 showed physicochemical instabilities (Figs. 5 and 6) and TMC PEG-PLGA-0 showed the slowest release rate and higher mechanical resistance in texture analysis (Fig. 3). We tested whether the lag phase in the PEG-PLGA-5 formulation could be overcome by switching the drug to DEX, since a burst release was observed for DEX in the PLGA-10 matrix. The lag phase could be reduced from 14 to 11 days and a more linear release profile was observed over three months when using DEX (Fig. 7C). Adding a drug-loaded hydrophilic coating to the drug-loaded implants could overcome the lag-phase (Wulf et al., 2022). Qnouch et al. used small amounts of the more hydrophilic dexamethasone phosphate to provide a burst release (Qnouch et al., 2021).

3.7. Simulation of drug distribution in the human scala tympani

Using mathematical simulation for intracochlear drug distribution, the expected perilymph concentrations of TMC and DEX following the application of PLGA-10 or PEG-PLGA-5 implants containing 35 µg of the drug, were calculated. The resulting perilymph concentrations of TMC and DEX as a function of distance along the scala tympani (ST) and time are displayed in Fig. 8. Simulation of the PLGA-10 implant resulted in an even distribution of TMC, which quickly reach the cochlear apex (Fig. 8A). The simulations indicate that relevant concentrations of TMC will be present in all parts of the scala tympani during a prolonged period as indicated by the black line that show a concentration of 50 ng/ml (representing the effective therapeutic concentration for inflammatory suppression reported for DEX) (Bas et al., 2016; Liebau et al., 2020; Liu et al., 2015). TMC delivered by PEG-PLGA-5 implants will reach the cochlear apex in high concentrations after an initial delay of 14 days, and relevant levels will be maintained for the period of almost three months throughout the whole scala tympani (Fig. 8C). As expected due to the previously published short half-time of DEX in the inner ear (Salt et al., 2018), the placement of DEX-loaded PLGA-10 and PEG-PLGA-5 implants in the basal turn of the cochlea will not result in an even distribution of the glucocorticoid along the length of the cochlea (Fig. 8B, D). The simulation predicts high concentrations in the basal part of the cochlea, followed by a steep decline of drug levels. Therefore, DEX is expected to reach less than 20 mm of scala tympani length. Based on the published data on cochlear TMC pharmacokinetics (Salt et al., 2019) and the release kinetics of the PLGA-10 and PEG-PLGA-10 implants presented in this publication, both implants show a more favorable intracochlear glucocorticoid distribution than their DEX-loaded counterparts. Even in the cochlear apex, TMC perilymph concentrations significantly higher than 50 ng/ml will be constantly maintained during the whole observation period. The reason for these variations in distribution can be solely attributed to the differing half-times, as there are no notable disparities in physicochemical characteristics, including molecular size, polarity, lipophilicity, and solubility. Additional animal investigations would help validate the superior distribution, as the implants possess an analogous release profile and can be likened

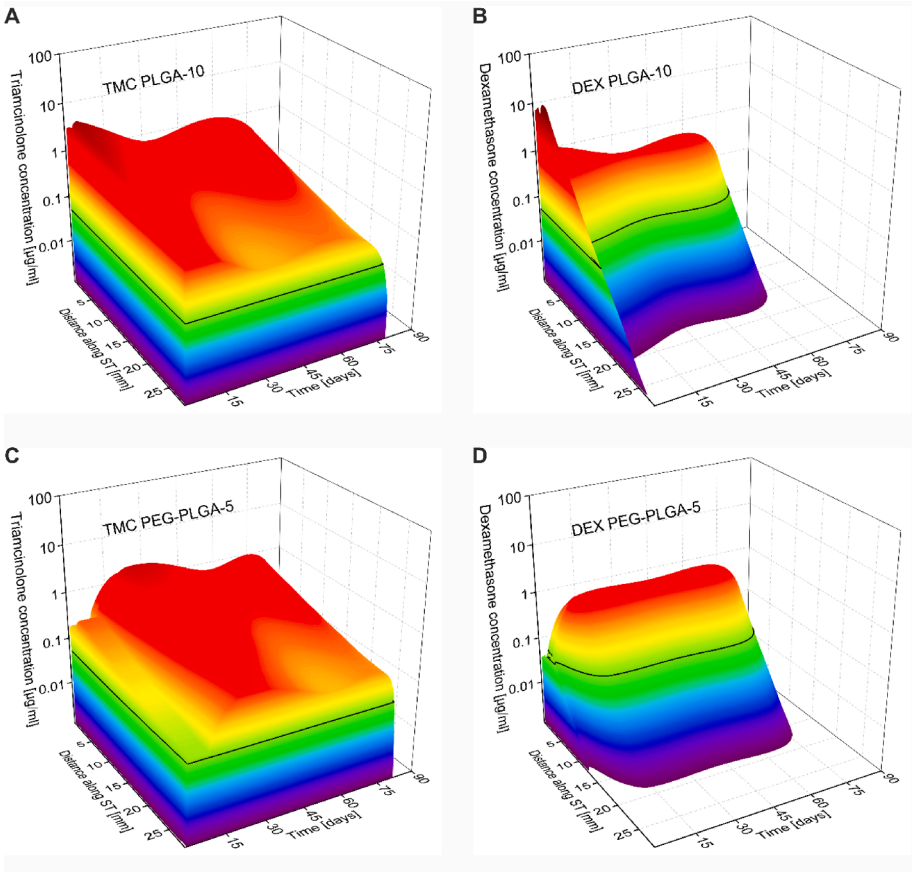

Fig 8. Calculated drug distribution in the perilymph of the scala tympani (ST) over 90 days after intracochlear application of a 0.35 × 3 mm implant of the formulation PLGA-10 (A, B) and PEG-PLGA-5 (C, D) loaded with TMC (A, C) and DEX (B, D), respectively. Horizontal black lines on surface plots represent minimal therapeutic concentration of 50 ng/ml DEX for inflammatory suppression (Bas et al., 2016; Liebau et al., 2020; Liu et al., 2015).

accordingly.

The potency of TMC is listed six times lower than DEX in most standard medical and pharmacological textbooks after oral administration. However, glucocorticoid potencies for human inner ear tissues remain undefined.

In our opinion, the presented (PEG-)PLGA implants possess a better risk–benefit ratio compared to previously evaluated drug delivery devices. An obvious disadvantage of intracochlear drug delivery systems in comparison to drug delivery systems designed for intratympanic application, like hydrogels or gelfoam (Lambert et al., 2016) is the need to open the inner ear for the placement of the implant, with certain risks, e.g., for infection or inflammatory responses. Nevertheless, given the soft texture and small size of the implants (0.35 mm × 3 mm), an atraumatic insertion into the human cochlea seems feasible. Especially in comparison to other intracochlear drug delivery systems like cochlear implants or catheters which are deeply inserted into the inner ear (Briggs et al., 2020; Prenzler et al., 2018), the application of the short and soft (PEG-)PLGA implants is most likely less traumatic.

A different intracochlear steroid delivery strategy, is based on polyvinyl alcohol-coated fluticasone propionate particles (Pierstorff et al., 2018). Even though the rationale behind the application of small particles to reduce structural trauma is tempting, polyvinyl alcohol is not biodegradable, and the long-term fate of the particles in the inner ear remains unknown. Another drug delivery system used for controlled inner ear glucocorticoid delivery is the DEX-releasing implant Ozurdex®, which has previously been evaluated by our group (Plontke et al., 2022a). Ozurdex® is approved for intravitreal injection to provide sustained delivery of DEX to the eye (Allergan, 2014). In comparison to the Ozurdex® implant, the presented implant formulations are softer and therefore the insertion is expected to be less traumatic, They also exhibit a more favorable drug release and distribution profile. Even though Ozurdex® implants contain a larger amount of steroids (350 µg DEX for ½ intracochlearly inserted implant) and therefore lead to higher initial perilymph concentrations and to a slightly higher apical spread of DEX when compared to the DEX-releasing (PEG-)PLGA implants, the cochlear apex is not reached, and there is a remarkable delay in DEX release. Such a delayed release was also seen for the TMC PEG-PLGA implant (Fig. 8C), which represents a certain tradeoff of this implant, which on the other hand provides a better surgical handling in comparison to the TMC PLGA-implant. Regarding these delayed release characteristics and potential intracochlear pH-changes due to the degradation of the implant, follow-up *in vivo* studies are warranted. Enzymatic processes in the inner ear could accelerate the degradation of the polymer and thereby reduce the delay in drug release, whilst pronounced chances of the intracochlear pH could result in inner ear trauma (Stawicki et al., 2014; Tanaka et al., 2004).

We think that another relevant advantage of the presented PLGA-10 and PEG-PLGA-5 implants is their potential applicability for different indications, including the salvage therapy of sudden hearing loss and hearing preservation cochlear implantation. Using a (PEG-)PLGA implant in combination with a cochlear implant in such cases could reduce regulatory hurdles significantly and thereby accelerate the development of a clinically available intracochlear drug delivery system regardless of a necessary modification of the cochlear implant.

4. Conclusion

In this study, we described the investigation of biodegradable implants with different polymer compositions for controlled inner ear drug delivery. Implants with a diameter of 350 µm and a drug load of 10%

were successfully prepared by hot-melt extrusion and sterilized by electron beam irradiation. Compared to recently published DEX-loaded PLGA implants, the implants characterized in the current study presented two major upgrades. (1) The use of a PEG-PLGA matrix resulted in an improved mechanical stability, which will ease the handling and intracochlear application. (2) Mathematical simulations of TMC-loaded implants predict an even distribution of the drug in the scala tympani reach the cochlear apex. Surprisingly, initial drug release was decreased in all PEG-PLGA implants despite of the added PEG amount.

CRediT authorship contribution statement

E. Lehner: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **C. Honeder:** Formal analysis, Investigation, Writing – original draft. **W. Knolle:** Formal analysis, Investigation. **W. Binder:** Methodology, Formal analysis, Investigation, Writing – review & editing. **J. Scheffler:** Formal analysis, Investigation, Writing – review & editing. **S.K. Plontke:** Conceptualization, Resources, Writing – review & editing. **A. Liebau:** Conceptualization, Methodology, Investigation, Writing – original draft. **K. Mäder:** Conceptualization, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2023.123268.

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