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Fabrication and characterization of gefitinib-releasing polyurethane foam as a coating for drug-eluting stent in the treatment of bronchotracheal cancer

Weiluan Chen[a], Chiara di Carlo[b], Donal Devery[b], Donnacha J. McGrath[c], Peter E. McHugh[c], Kathrin Kleinsteinberg[d], Stefan Jockenhoevel[d], Wim E. Hennink[a], Robbert J. Kok[a,*]

[a] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[b] Vysera Biomedical Limited, BMR House, Parkmore Business Park West, Galway, Ireland
[c] Biomechanics Research Centre, Biomedical Engineering, College of Engineering and Informatics, National University of Ireland, University Road, Galway, Ireland
[d] Department of Biohybrid & Medical Textiles (BioTex) at AME-Helmholtz Institute for Biomedical Engineering, ITA-Institut für Textiltechnik, RWTH Aachen University, Germany

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ABSTRACT

The purpose of the present study was to develop gefitinib-loaded polymeric foams that can be used as coating of drug-eluting stents for palliative treatment of bronchotracheal cancer. Release of such an anticancer drug from such stent coating can retard tumor regrowth into the bronchial lumen. Gefitinib-loaded polyurethane (PU) foams were prepared by embedding either gefitinib micronized crystals or gefitinib-loaded poly(lactic-*co*-glycolic acid) microspheres in water-blown films, with up to 10% w/w loading for gefitinib microcrystals and 15% w/w for gefitinib microspheres (corresponding to 1.0% w/w drug loading). Drug-release studies showed sustained release of gefitinib over a period of nine months, with higher absolute release rates at higher drug loading content. By the end of the studied nine month release periods, 60–100% of the loaded gefitinib had been released. Foams loaded with gefitinib-PLGA microspheres at 15% w/w showed accelerated drug release after 4 months, coinciding with the degradation of PLGA microparticles in the PU foam as demonstrated by scanning electron microscopy (SEM). When applied on a nitinol braided bronchotrachial stent, PU coatings with gefitinib microspheres showed similar mechanical properties as the drug-free PU coating, which indicated that the loading of microspheres did not affect the mechnical properties of the PU foams. In conclusion, we have fabricated drug-loaded PU foams that are suitable for bronchotracheal stent coating.

1. Introduction

Lung cancer, being the most prevalent malignancy in men and the 3rd most frequent in women, has poor prognosis due to the advanced stage at the time of diagnosis (Hohenforst-Schmidt et al., 2016). About 20–30% of the patients with lung cancer will develop complications resulting from airway obstruction and up to 40% of the lung cancer deaths may be attributed to locoregional disease (Ernst et al., 2004). The gold standard treatment for airway obstruction is surgical resection and re-establishment (Saji et al., 2010), based on tumor ablation and debulking as palliative treatment (Inoue et al., 2012). Polymer coated stents are used as a supplement of surgery to prevent tumor regrowth and restenosis of airways (Shaikh et al., 2013). Polyurethane foams generally have a large tensile strength with a very high deformation at break and are particularly useful as covering material for stents which are compressed and flexed during their implantation but also upon their placement in the bronchotracheal lumen (Seo and Na, 2014). Importantly, polyurethane materials have good biocompatibility characteristics which makes them suitable for either coatings or controlled drug release systems (Cherng et al., 2013; Lee et al., 2003; Park et al., 2001; Yamaoka et al., 2000).

In this study we aim to develop a drug-eluting stent coating for a bronchotracheal stent. Gefitinib (chemical structure as shown in Fig. 1) is an anticancer drug that has good efficacy against pulmonary cancer, by virtue of its antiproliferative activity against epidermal growth factor receptor (EGFR)-overexpresssing tumor cells (Reck et al., 2013). Gefitinib eluting from the stent coating can suppress tumor regrowth into the bronchial lumen and hence can prolong the time span during which airway stenosis is prevented. In the present study, we now explored whether it is possible to load gefitinib in PU foams.

PU polymers are typically prepared by reacting diisocyanates with low-molecular-weight polyol polymers in the presence of additives (catalysts, surfactants, etc.), resulting in polymeric networks with high flexibility. The use of tri- and higher isocyanates in the polymerizing

* Corresponding author at: Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands.
E-mail address: r.j.kok@uu.nl (R.J. Kok).

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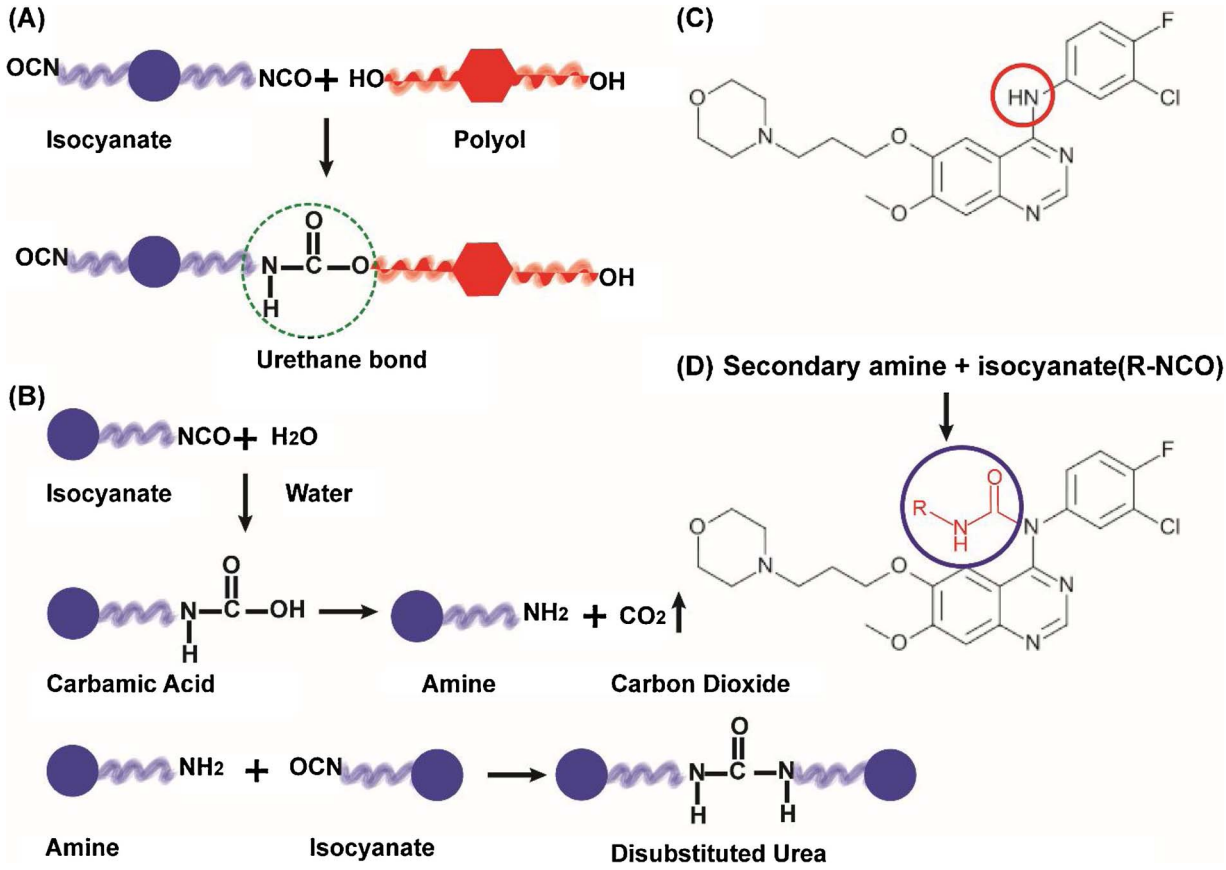

Fig. 1. Chemical reactions in the formation of polyurethane. A: schematic representation of polyurethane formation, the urethane bond is formed via the reaction of an isocyanate group with one of the alcohol function groups in a polyol compound. Frequently applied isocyanates for the production of commercial polyurethane are toluene diisocyanate, methylene diphenyl diisocyanate, hexamethylene diisocyanate, etc. Frequently used polyols are polyetherpolyol, polyesterpolyol, etc. The blue and red chains represent the hard and soft segment of PU, respectively. B: reaction of the isocyanate group with water generates carbon dioxide which serve as blowing agent in PU resulting in gas-filled foam cells. The formed amine group can react with another isocyanate group to yield a urea bond. C: Chemical structure of gefitinib. D: potential side reaction between an isocyanate prepolymer and gefitinib. Reaction of an isocyanate with a secondary amine results in urea derivatives. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mixture results in formation of crosslinked polymeric networks, while the presence of low amounts of water in the prepolymer solution generates carbon dioxide that functions as blowing agent (Fig. 1A) (Seyanagi et al., 2004). Anti-cancer drugs can be added to the polymerizing isocyanate/polyol mixture to form the drug-loaded PU foam. However, an important drawback of such an approach can be that the PU polymerization isocyanate-containing is influenced by the presence of the drug. Such problems can either arise from chemical interference due to side-reactions of molecules with gefitinib at the secondary amine functionality of the drug (Fig. 1B). Such problems can be avoided when drug is embedded in a different material prior to its mixing with the PU forming reactants. In the present study we therefore explored two strategies for drug incorporation in PU foam, either using gefitinib microcrystals or gefitinib-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres, which prevent the direct interaction of drug with the PU forming reactants. The latter approach furthermore offers opportunities to modulate drug release via the properties of the polymeric microspheres, rather than to rely on dissolution of micronized drug crystals.

2. Materials and methods

2.1. Materials

Gefitinib (free base, > 99%) was purchased from LC laboratories (Woodburn, MA, USA). This is a micronized powder with an average particle size of 10 µm. Gefitinib-PLGA microspheres were prepared according to a previously described method (Chen et al., 2017b) and had a size of 50–100 µm and drug loading of 7.2%. PPT-95A, a toluene diisocyanate polyol having 6.4–6.8 wt% −NCO groups and crosslinker solution were provided by Vysera Biomedical Ltd (Galway, Ireland). Phosphate buffered saline (PBS, 10 mM sodium phosphate, 140 mM NaCl, pH 7.4) was purchased from Braun (Melsungen AG, Germany), whereas dichloromethane (DCM) and acetonitrile were purchased from Biosolve (Valkenswaard, the Netherlands). Dimethyl sulfoxide (DMSO) was purchased from Sigma Aldrich, Germany. Machine-braided nitinol stents were kindly provided by ITA-Institut für Textiltechnik, RWTH Aachen University.

2.2. Compatibility of gefitinib with the PU forming polymerzing mixture

Potential reactivity of gefitinib with isocyanate groups of the diisocyanate polyol was investigated by monitoring the disappearance of the NCO bond in mixtures of drug/prepolymer by infrared spectroscopy (IR). IR measurements were carried our at room temperature on a Bruker Tensoe-27 Fourier transform infrared (FT-IR) spectrometer equipped with a deuterated triglycine sulfate detector. The sample compartment was flushed with dry air to reduce interference of H_2O. Spectra were recorded using a horizontal attenuated total reflection accessory (FastIR, Harrick Scientific Products) with a ZnSe crystal as the internal reflection element. The spectral resolution was 4 cm^{-1}, and 50 scans were accumulated with medium apodization for each spectrum.

PPT-95A prepolymer, non-loaded PU foam and gefitinib free base microcrystals were first loaded in the compartment and analysed by FT-IR. Subsequently, spectra were recorded of PPT-95A (25 µmol) mixed with either gefitinib microcrystals (11 mg, 25 µmol), a gefitinib solution in DMSO (25 µmol, 100 mg/ml), or water (450 mg, 25 µmol). The

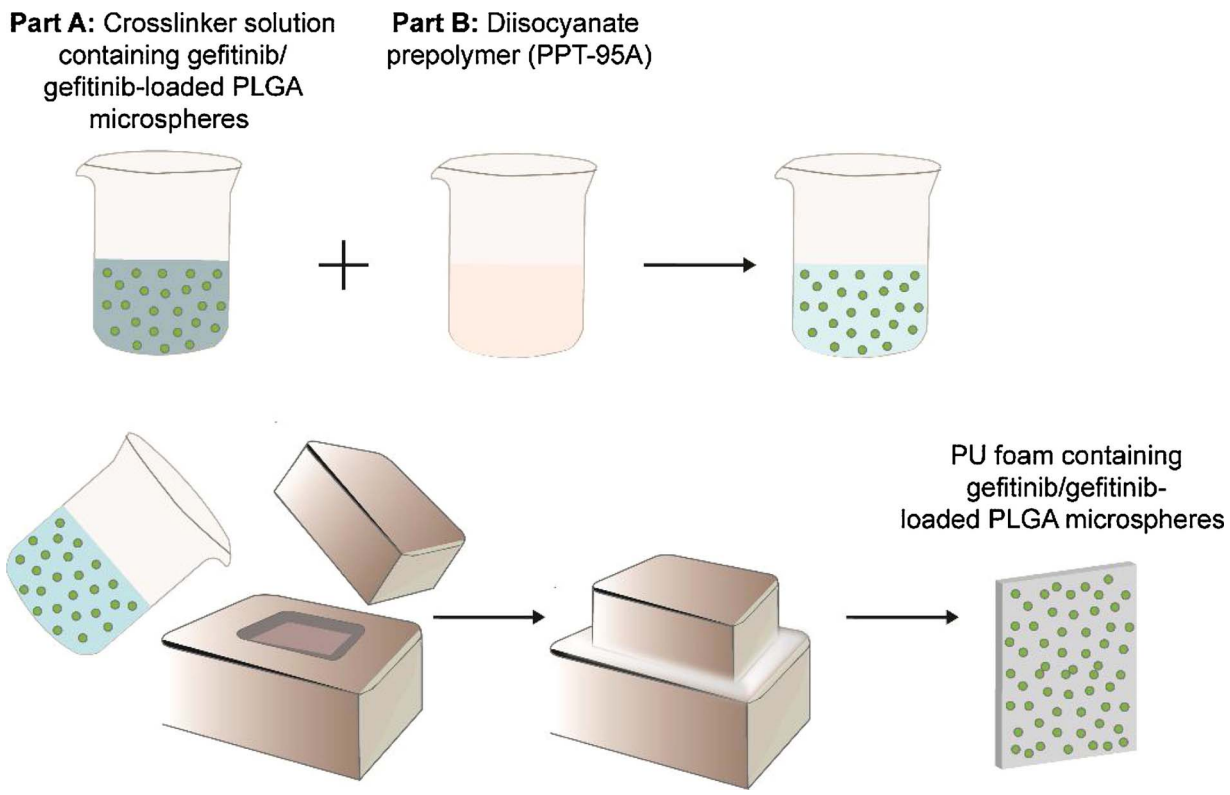

Fig. 2. Schematic picture of the fabrication of PU foam loaded with gefitinib/gefitinib-PLGA microspheres.

mixtures were incubated for 2 h before recording the infrared spectra. DMSO was dried with molecular sieves (5 Å) before use to remove the interference of water.

2.3. Fabrication of gefitinib-loaded PU foams

PU foams were prepared by Vysera Biomedical Ltd. using a one-pot procedure (Behan and Kumar, 2011). In brief, gefitinib microcrystals or PLGA microspheres (non-loaded or loaded with gefitinib) were dispersed in the crosslinker solution that contained silicon surfactant, bismuth neodecanoate (BICAT) gelling catalyst, DABCO blowing catalyst and diethanolamine branching agent (part A). The resulting dispersion was mixed with diisocyanate prepolymer PPT-95A (part B) using a mechanical stirrer at 600 rpm for 1 min. The mixture was poured into a mould (25 × 25 × 0.4 mm) as shown in Fig. 2 and kept at room temperature for 2 h to allow PU foam formation and hardening. Theoretical loading contents (% w/w) of gefitinib and gefitinib-loaded polymeric microspheres are listed in Table 1.

Table 1
Characteristics of gefitinib-loaded PU foams (n = 3).

Formulations	Loading capacity (wt%)	Drug recovery (%)
Gefitinib incorporated $PU_{gefitinib}$		
$PU_{0.4\%gefitinib}$	0.31 ± 0.03	86.1 ± 0.4
$PU_{1.1\%gefitinib}$	1.02 ± 0.03	94.4 ± 0.5
$PU_{2.0\%gefitinib}$	1.75 ± 0.07	87.5 ± 0.3
$PU_{5.0\%gefitinib}$	4.95 ± 0.55	99.0 ± 0.2
$PU_{10.0\%gefitinib}$	9.88 ± 0.03	98.8 ± 0.6
Gefitinib-PLGA microspheres incorporated $PU_{gefitinibMSP}$		
$PU_{5\%gefitinibMSP}$	0.32 ± 0.02	88.9 ± 0.3
$PU_{15\%gefitinibMSP}$	1.00 ± 0.04	92.6 ± 0.5

2.4. Characterization of PU foams

2.4.1. Analysis of gefitinib content

Samples of gefitinib-loaded PU foams (approximately 40 mg, accurately weighed) were immersed in 10 ml of DMSO and incubated at room temperature for 1–3 days to extract drug from the polymeric material. Samples of the extract (50 µl) were analysed for gefitinib concentration using reversed phase HPLC (a C_{18} (4.6 × 150 mm, 5 µm particle size; Sunfire™, Ireland), mobile phase of acetonitrile:methanol:water: trifluoroacetic acid (20:23:57:0.3 v/v/v/v, complemented with TFA 0.3% w/v); flow rate of 1.0 ml/min). Gefitinib standards (1–150 µg/ml dissolved in DMSO) were used for calibration and detection was done a 254 nm.

2.4.2. Morphology of the PU foams

PU foams (with and without gefitinib microcrystals or gefitinib-loaded microspheres) were cut into small pieces and glued onto 12 mm diameter aluminum sample holders using conductive carbon paint (Agar scientific Ltd., England). Specimens were covered by a platinum layer (4 nm) under vacuum using an ion coater. Cross-section of the samples as well as the surface morphology were examined by scanning electron microscopy (SEM, PhenomTM, FEI Company, the Netherlands).

Gefitinib distribution in PU foams was analysed by fluorescence microscopy making using of the autofluorescence of gefitinib ($\lambda_{excitation}$ = 265 nm and $\lambda_{emission}$ = 337 nm). The PU foam specimens were cleaned with destilled water, dried and microscopically examined under an ordinary optical microscope and fluorescence microscope (Keyence; BZ-9000).

2.5. X-ray diffraction study

X-ray diffraction (XRD) was used to determine the crystallinity of gefitinib in the PU foams. The X-ray diffraction patterns of gefitinib microcrystals, and PU foams (non-loaded foam and foams loaded with

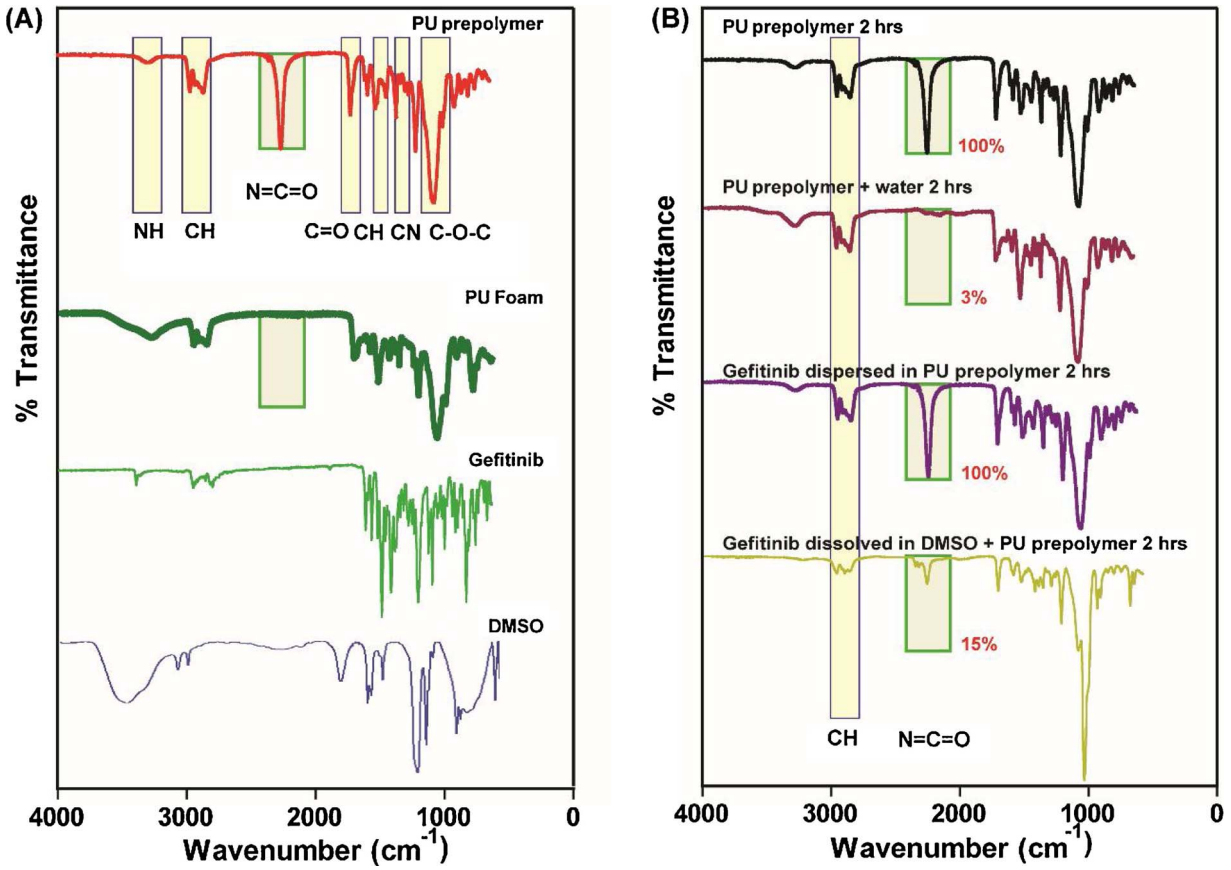

Fig. 3. FT-IR spectra of PU prepolymer in presence of gefitinib. A: reference FT-IR spectra of PU prepolymer, fully reacted PU foam, gefitinib and DMSO. B: FT-IR spectra of dedicated reactions of PU prepolymer with water, gefitinib microcrystals, and gefitinib dissolved in DMSO. Reactants were added at a 1:1 molar ratio to isocyanate groups and incubated for 2 h with the prepolymer.

gefitinib) were recorded using a Bruker-AXS D8 ADVANCE diffractometer coupled with a VANTEC detector and a Ni filter. The measurements were done using Co-Kα12 radiation (λ = 1.79026 Å) at ambient conditions. Scans were performed between 10 and 75 ° 2 theta, using a step size of 0.09 ° 2θ and a scan speed of 2 s. Separate reference runs were recorded to allow subtraction of air and capillary wall-scattering.

2.6. In vitro release of gefitinib from PU foams

In vitro release experiments were carried out in PBS buffer supplemented with 1% Tween 80 to ensure sink conditions for released gefitinib. The release buffer also contained 0.01% sodium azide to prevent bacterial growth. PU foams (sample size approximately 80 mg, accurately weighed) were transferred into tubes containing 15 ml of the release buffer and incubated in a shaking water bath at 37 °C. At different time points, 1 ml of the buffer was sampled and replaced with fresh buffer. The concentration of gefitinib in the different samples was determined by HPLC as described in Section 2.4.1. The LOD (limit of detection) was 0.30 μg/ml for gefitinib at a signal-to-noise ratio of 3:1. The LOQ (limits of quantitation) was determined as 0.85 μg/ml at a signal-to-noise ratio of 10:1.

Cumulative gefitinib release was fitted (Graphpad Prism version 5) according to the (Korsmeyer-peppas model: $Q = (M_t/M_0) = K_m t^n$ (Korsmeyer et al., 1983) in which Mt/M_0 stands for the cumulative fraction of released drug, t stands for the time since start of the release experiment, Km is the release constant that includes structural properties of the drug and structural and geometrical properties of the release construct, and *n* is release exponent which is indicative of the drug release mechanism.

Morphologies of gefitinib-PLGA microspheres in the PU foams during degradation process were analysed by SEM (as described in Section 2.4.2). Specimens of around 40 mg PU foams were transferred into 15 ml PBS buffer and incubated at 37 °C in a water bath under constant shaking. At different time points, samples were collected and washed twice with reverse osmosis water. After freeze-drying, the morphologies of the PU foams were investigated.

2.7. Fabrication of PU foam coated stent

The stent coating technique developed by Vysera Ltd. is a type of compression moulding technique in which the PU material is dispensed inside the mould and a system of clamp applies a certain pressure. A dedicated mould with dimensions matched to the dimensions of the machine-braided stents was used to prepare of PU coated stent with coating thickness of 400 μm. Non-loaded PLGA microspheres were embedded in the PU coating at a weight percentage of 5 and 15% via a similar procedure as described above.

2.8. Stent radial force testing

Stents were subjected to a radial force test which was carried out using an 8-faced crimping head (RCM-H60, MPT Europe) connected to a Zwick uniaxial testing machine (Zwick 7025-3, Zwick, Ulm, Germany). Machine-braided stent coated with non-loaded PU foam was compared to stents coated non-loaded PLGA microspheres loaded PU foams.

The stents were crimped from their free diameter (15 mm) to a constrained diameter of 7.5 mm (100% crimped state) at rate of 0.06 mm/s at 37 °C. After crimping, the stents were allowed to expand

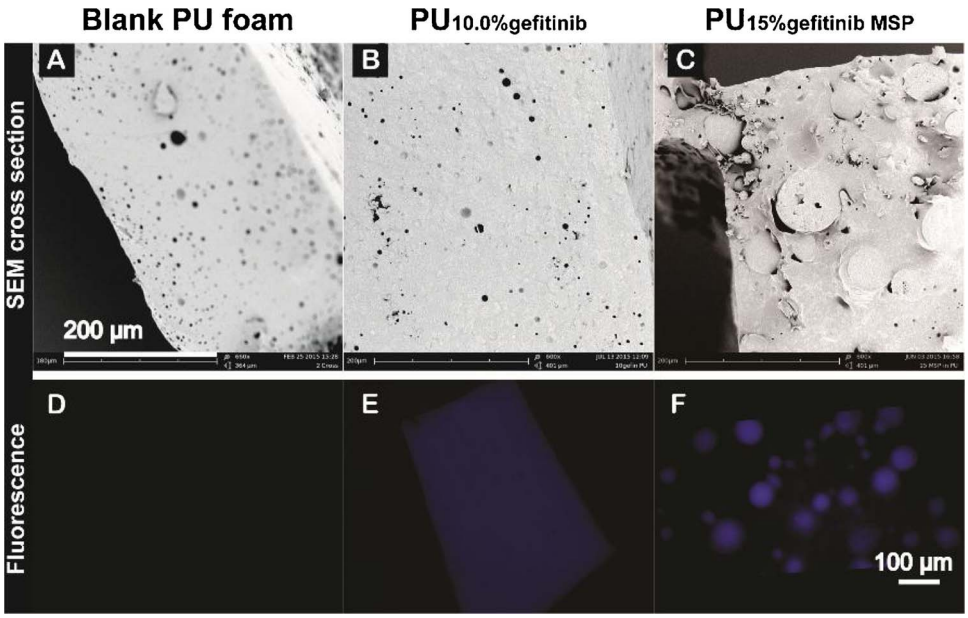

Fig. 4. SEM pictures with magnification ×600 of the cross-section blank PU foam (A), and PU foams loaded with 10% gefitinib (B) and 15% gefitinib-PLGA microspheres (C). (D)-(F): Corresponding fluorescence microscopy pictures of the samples of non-loaded PU, gefitinib and gefitinib-PLGA microspheres loaded PU foams (DAPI filter, ×4 magnification of D and E, ×20 magnification of F).

to their original diameters at the same rate. Testing a stent in this way mimics the loading it undergoes when inserted into a delivery device (crimping step) and developed into an airway (expanding step).

2.9. Statistics

The comparison of release rates between different gefitinib loading groups was performed by comparing regression coefficients using SUEST command in Stata v13. A p-value of < 0.05 was considered statistically significant.

3. Results and discussion

3.1. Compatibility of gefitinib with PU polymerization process

Isocyanates can potentially react with secondary amines, yielding urea products (Fig. 1D). We therefore investigated the stability of diisocyanate prepolymer PPT-95A in the presence of solid gefitinib and gefitinib dissolved in DMSO. Samples were studied by FT-IR spectroscopy by monitoring the disappearance of the −NCO band at 2270 cm^{-1}.

Fig. 3A shows the reference FT-IR spectra of the PU prepolymer, PU foam that had been formed by reacting the prepolymer with the crosslinker solution in absence of gefitinib (see Method, Section 2.3), gefitinib and DMSO. All typical transmission peaks have been indicated in the spectrum of the polyurethane prepolymer, such as those notable at 3330–3360 cm^{-1} (NH), 2855–2955 cm^{-1} (CH_2 and CH_3), 1724 cm^{-1} (C═O), 1360 cm^{-1} (C–N), 1110 cm^{-1} (C–O–C). The strong absorbance at 2270 cm^{-1} (NCO) was used to monitor the disappearance of isocyanate groups in the PU prepolymer upon reaction with a small amount of water (equimolar to the amount of isocyanate groups) for 2 h (Fig. 3B upper two spectra). Clearly, reaction with water resulted in complete disappearance of the isocyanate groups. Addition of gefitinib microcrystals, under conditions similar to the PU foam process, did not result in consumption of isocyanates of the prepolymer. A solution of gefitinib in DMSO, however, largely consumed the reactive groups in PPT-95A (only 15% left). This experiments confirms that isocyanate groups can react with secondary amines like gefitinib, but such a reactivity however is only observed with dissolved gefitinib. A plausible explanation for the difference between the two experiments with gefitinib is the poor solubility of the drug in the liquid prepolymer.

3.2. Preparation and characterization of gefitinib-loaded PU foams

3.2.1. Loading of gefitinib in PU foams

Gefitinib/gefitinib-PLGA microspheres were loaded in PU foams via a water blown procedure as described in Section 2.2. The drug loadings in the PU foams were measured by HPLC (see Section 2.3.1)

Drug loading of the foams used in this study are summarized in Table 1. High recoveries from 86 to 99% were found for each loaded PU after extraction of with DMSO. For gefitinib-PLGA microspheres incorporated PU foams, drug loadings were found of 0.32% and 1.00%, corresponding to recoveries of 89% and 93% of the loaded PLGA microspheres, respectively. The high drug recoveries indicate good drug extraction from the PU foam by soaking the material in DMSO, and indicate that the drug is primarily entrapped in its parental form. Extensive cross-reactivity with the isocyanate prepolymer is therefore unlikely, although such side-reactions cannot be excluded solely based on the found recoveries which are high but not complete. Another argument that makes it unlikely that gefitinib has reacted with the prepolymer is that similar recoveries were found after embedding of drug microcrystals and gefitinib-loaded polymeric microspheres, which protect the drug from interacting with the isocyanate groups.

3.2.2. Morphology of PU foams loaded with gefitinib/gefitinib-PLGA microspheres

Morphology of PU foams (with or without gefitinib/gefitinib-PLGA microspheres) were determined by SEM and fluorescence microscopy analysis of cross-sectioned materials (Fig. 4). Many micrometer-sized foam cells can be observed in the cross sections indicating a typical closed-cell structure of the PU foams (Fig. 4A and B). No apparent differences could be observed between non-loaded PU foam and PU foams loaded with gefitinib microcrystals, indicating that drug loading did not affect polymerisation and foam cell processes. Specimens of other drug loadings showed similar morphologies (data not shown, only the sample with $PU_{10\%gefitinib}$ is shown in Fig. 4B). Embedding of drug-loaded PLGA microspheres in PU foam resulted in a material in which 50–100 µm sized particles could be observed in both SEM and fluorescence microscopy (Fig. 4C and F). The size of these structures corresponds to the size of the embedded polymeric microspheres, while the observed fluorescence indicates that these are polymeric microspheres with high concentrations of embedded gefitinib.

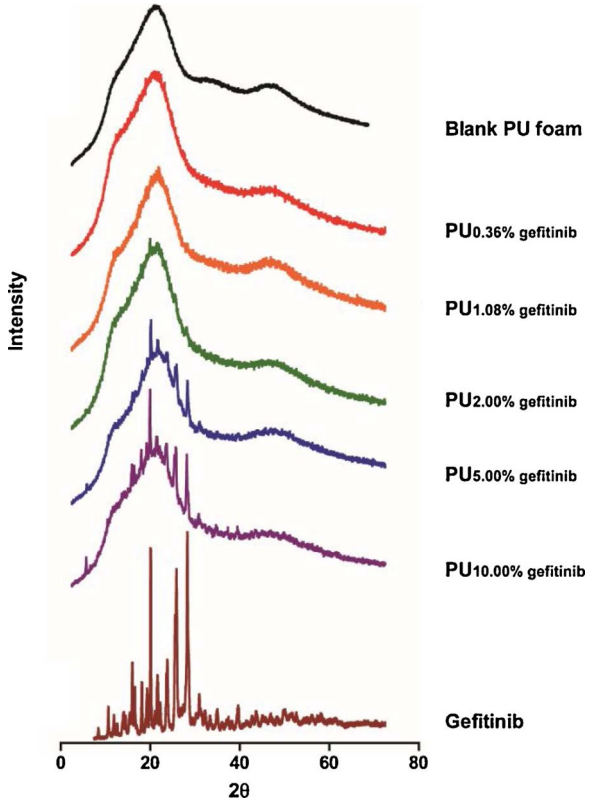

Fig. 5. X-ray diffraction patterns of gefitinib, blank PU foam, and foams with different loadings of drug.

3.2.3. XRD analysis of gefitinib crystallinity in PU foams

The physical state of gefitinib incorporated in the PU foams was studied by XRD crystallography, along with analysis of non-loaded PU foam and gefitinib microcrystals as reference material (Fig. 5). Gefitinib is highly crystalline and exhibited intense diffraction peaks at 18.6°, 19.2°, 24.2°, 26.2° and 26.4° as also reported by Lee et al. (Phillip Lee et al., 2009). PU foam showed no diffraction peaks which is in agreement with expectations that this polymeric material is fully amorphous. Gefitinib-loaded PU foams with drug contents of 5 and 10% showed peaks indicative for the presence of crystalline drug, while drug loading content below 5% did not show diffraction peaks, but this may be related to the detection limit of the technique. Previous studies have shown that gefitinib is embedded as amorphous drug in PLGA microspheres (Chen et al., 2017b), and hence it is likely that PU foams loaded with such microspheres also contain gefitinib in the amorphous state.

3.3. In vitro release of gefitinib from PU foams

Gefitinib release curves of different drug-loaded PU foams are shown in Fig. 6. When focusing at the release profiles of the PU foams loaded with micronized crystals of gefitinib (Fig. 6A and B), it can be concluded that the drug was released in a diffusion mechanism based manner (% release is proportional to the square root of time). Fitting of the curves by the Korsmeyer-Peppas model provided release constant that increased from 3.58 to 6.67%/day$^{1/2}$ for materials with increasing drug loading (from 0.4 to 10%), and release exponents of 0.5 (Table 2) indicative of a diffusion-based mechanism of release. Several mechanisms can account for the increment in relative release rates at increasing drug loading, such as faster water influx and hence faster dissolution at higher drug loading (due to osmotic effects) or connectivity of drug-loaded particles within the PU foam cell structure which forms a stronger barrier for diffusion than drug-loaded areas (Kaunisto et al., 2011).

PU foams loaded with gefitinib-PLGA microspheres demonstrated zero-order drug release for approximately 3 months followed by a phase in which drug release was accelerated and subsequently declined (Fig. 6C–E). During the first three months release was linear, with a release constant of 0.19 and 0.30%/day for $PU_{5\%gefitinibMSP}$ and $PU_{15\%gefitinibMSP}$, respectively (Fig. 6D). The initial phase was followed by an accelerated release phase which subsequently decreased until the end of the 8 months release experiment (Fig. 6E), which could be fitted well with the above described Korsmeyer-Peppas model (Table 3). Previously performed release studies with this type of 50–100 μm gefitinib-PLGA microspheres showed sigmodal release profiles, with almost complete release and erosion of the microspheres in 80 days (Chen et al., 2017b). Moreover, embedding of the same type of microspheres – which also have been used in the present study- in non-woven PU fleece provided zero order drug release for 7 months, with release constants ranging from 1.9-0.2%/day depending on the PU coating thickness (Chen et al., 2017a). The release rates for PU-foam embedded gefitinib-PLGA microspheres (approximately 0.25%/day during first phase) are hence in the same order of magnitude as observed for the thicker layer of PU fleece. Of note, the types of PU polymers used in both coatings are quite different, not only physically (foam vs fleece) but also chemically (commercially available Carbothane was used for PU fleeces, while PU foams were formed from prepolymers as described above). Moreover, also the strategies for embedding are quite different, since drug-PLGA microspheres had been embedded by a sandwich approach between two layers of non-woven PU fleece. Nevertheless, quite comparable release rates were found for both stent coatings. It seems likely that the accelerated release observed after 4 months (see Fig. 6C) coincided with erosion of the microparticles, in line with their complete erosion after 80 days when incubated in buffer at 37 °C (Chen et al., 2017b). Such an erosion process would eventually result in the presence of low-molecular weight PLGA acidic degradation products within the PU foam, which may help in solubilizing gefitinib, whose water solubility is pH-dependent (Bergman et al., 2007). Hence, one can expect faster release due to increased solubility of the drug, and maybe a plasticizing effect of water or lactic acid degradation products.

Overall, the sample with 10.0% w/w gefitinib microcrystals has the highest drug loading while it also provided sustained release for more than 270 days, which makes this drug-eluting coating the best for in vivo test in the future.

To confirm that accelerated release was related to erosion of the microspheres in the PU foams, we investigated their morphologies by SEM upon different incubation times in release buffer at 37 °C. Round structures most likely corresponding to microspheres could still be observed after 3 months (Fig. 7). However, after 4 months, these round structures were almost disappeared, and instead pores or small irregularly shaped-solids can be observed in PU foams, likely caused by the erosion of microspheres. Since the microspheres loaded in the PU foams are not in direct contact with water, it is likely that their erosion is retarded in comparison with incubation in buffer. Such as retarded erosion was also observed for microspheres embedded in the above discussed PU fleeces (Chen et al., 2017a).

3.4. Stent radial force testing

Embedding of drug microparticles or polymeric microspheres in PU coatings can negatively influence the tensile properties of the coating material. We therefore tested the radial force of a bronchotracheal stent that had been coated with PU foam loaded with different amount of polymeric microspheres, i.e. 5% and 15% w/w. Testing of drug-loaded coating was not feasible logistically, for risk of contaminating the equipment with anti-cancer drug-loaded in the PU foams.

Fig. 8A shows the image of a machine-braided stent (15 mm diameter, 30 mm long) coated with PU foam. As can be observed, the moulding process assured a perfect adhesion between the PU and the nitinol stent. Stents coated with PU foams loaded with either 5 or 15%

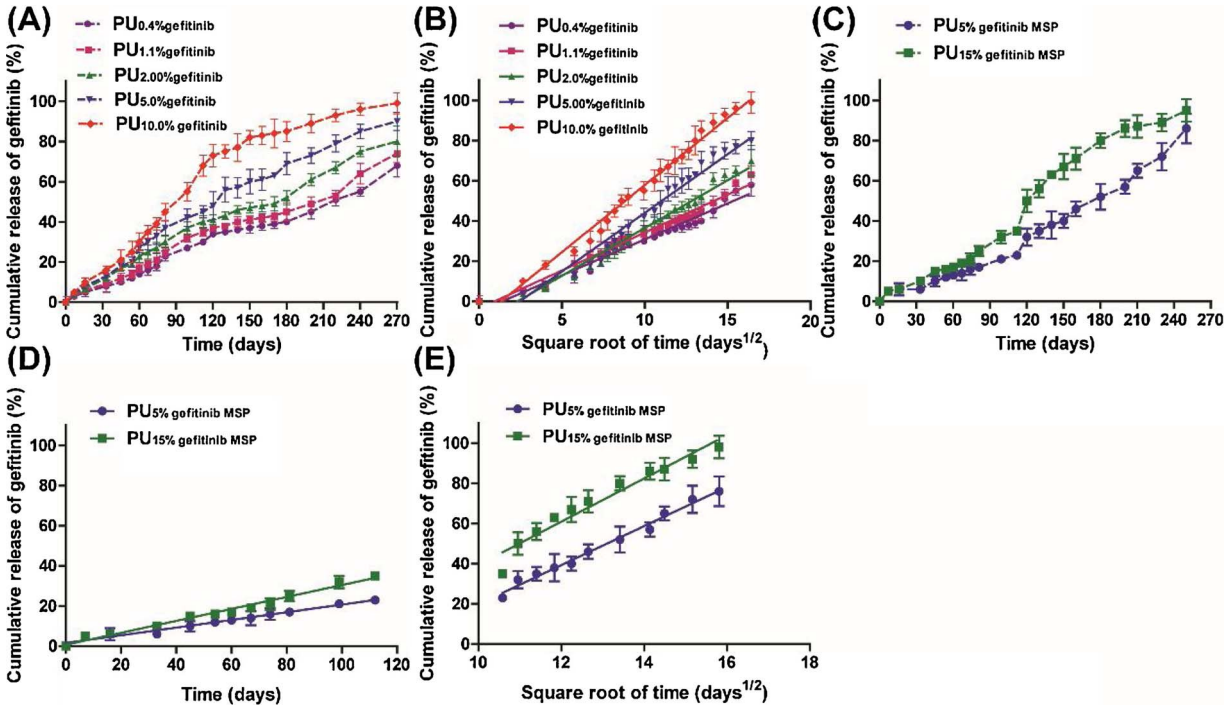

Fig. 6. Release curves of PU foams loaded with micronized gefitinib and PU foams loaded with gefitinib-PLGA microspheres. Cumulative release of gefitinib from PU foams loaded with micronized gefitinib, either plotted on a linear time scale (A), or plotted on a square root of time scale (B). Cumulative release of gefitinib from PU foams loaded with gefitinib-PLGA microspheres plotted on a linear time scale (C), and fitted release curve (D) plotted on a linear scale from 0 to 112 day, or plotted on a square root of time scale (E) from 112 to 270 days.

Table 2
Release rates and correlation coefficients of drug release from PU foams loaded with micronized gefitinib. Release curves were fitted with release exponent $n = 0.5$.

Samples	Release rate (%/day$^{1/2}$)	Correlation coefficient (r)	P value < 0.05 (release rate compared to other groups)			
			(1)	(2)	(3)	(4)
(1) $PU_{0.4\%gefitinib}$	3.58	0.9858				
(2) $PU_{1.1\%gefitinib}$	3.77	0.9910	–			
(3) $PU_{2.0\%gefitinib}$	4.75	0.9850	*	*		
(4) $PU_{5.0\%gefitinib}$	5.84	0.9812	*	*	*	
(5) $PU_{10.0\%gefitinib}$	6.67	0.9934	*	*	*	–

*p < 0/05.

Table 3
Release rates and correlation coefficients of drug release from PU foams loaded with gefitinib-PLGA microspheres.
Release curves were fitted with release exponent $n = 0.5$.

Samples	Zero-order model (0–112 d)		Korsmeyer-Peppas model (112–270 d)	
	Release rate (%/day)	Correlation coefficient (r)	Release rate (%/day$^{1/2}$)	Correlation coefficient (r)
$PU_{5\%gefMSP}$	0.19	0.9875	9.72	0.9937
$PU_{15\%gefMSP}$	0.30	0.9920	10.75	0.9736

w/w PLGA microspheres had a similar appearance (data not shown). Crimping and expansion curved of all three types of PU coated stents matched well (Fig. 8B–D). As can be observed, crimping of the stent from a diameter of 16 mm down to 7.5 mm outer diameter resulted in radial force of 60–70 N for all the PU coated stents, while expansion resulted in complete relaxation to the original non-crimping dimensions. This cycle was repeated three times for each stent. At 12 mm deployed state, all stents exerted an outward radial force of 10 N. The reported dimensions of the stents at 7.5 and 12 mm represent the maximally crimped state in an application device for bronchoscope assisted placement, and the dimensions of the stent after its placement in the bronchotracheal lumen. A small outward radial force was needed for proper retention of the stent at its intended implantation site. The currently observed radial force is similar to the chronic outward forces of commercially available airway stents (11–20 N) (Chen et al., 2016). We therefore conclude that PU foam coating with solid materials such as polymeric microspheres up to 15% did not adversely affect their mechanical properties.

4. Conclusions

Gefitinib was successfully loaded in PU foams either as micronized drug or as gefitinib-PLGA microspheres. Drug-loaded PU foams exerted sustained drug release over a time period of 9 months in a diffusion and in case of PLGA microspheres erosion based release mechanism. Initial experiments with coated stents suggest that the developed PU drug-eluting materials are suitable as stent coating for bronchotracheal stents.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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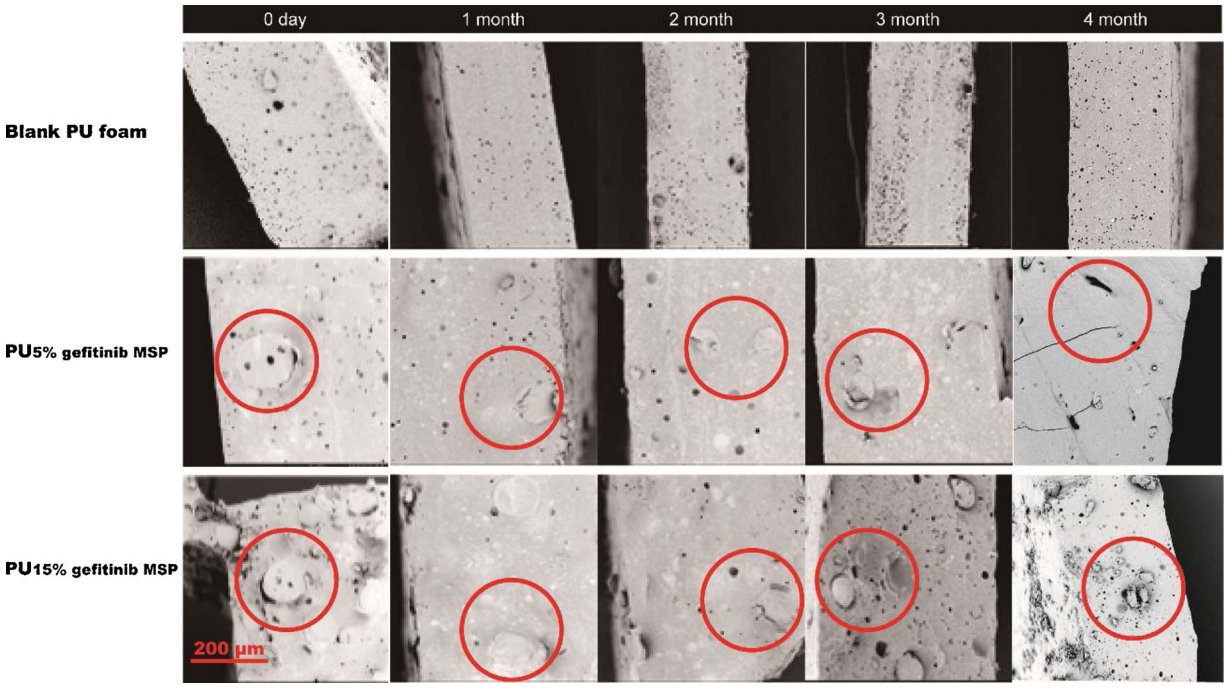

Fig. 7. SEM pictures of gefitinib-PLGA microspheres loaded in PU foams. The magnification is the same for all images (×600). Microspheres embedded in the PU foam have been circled and can be observed as circular objects with dimeter of 50–100 μm.

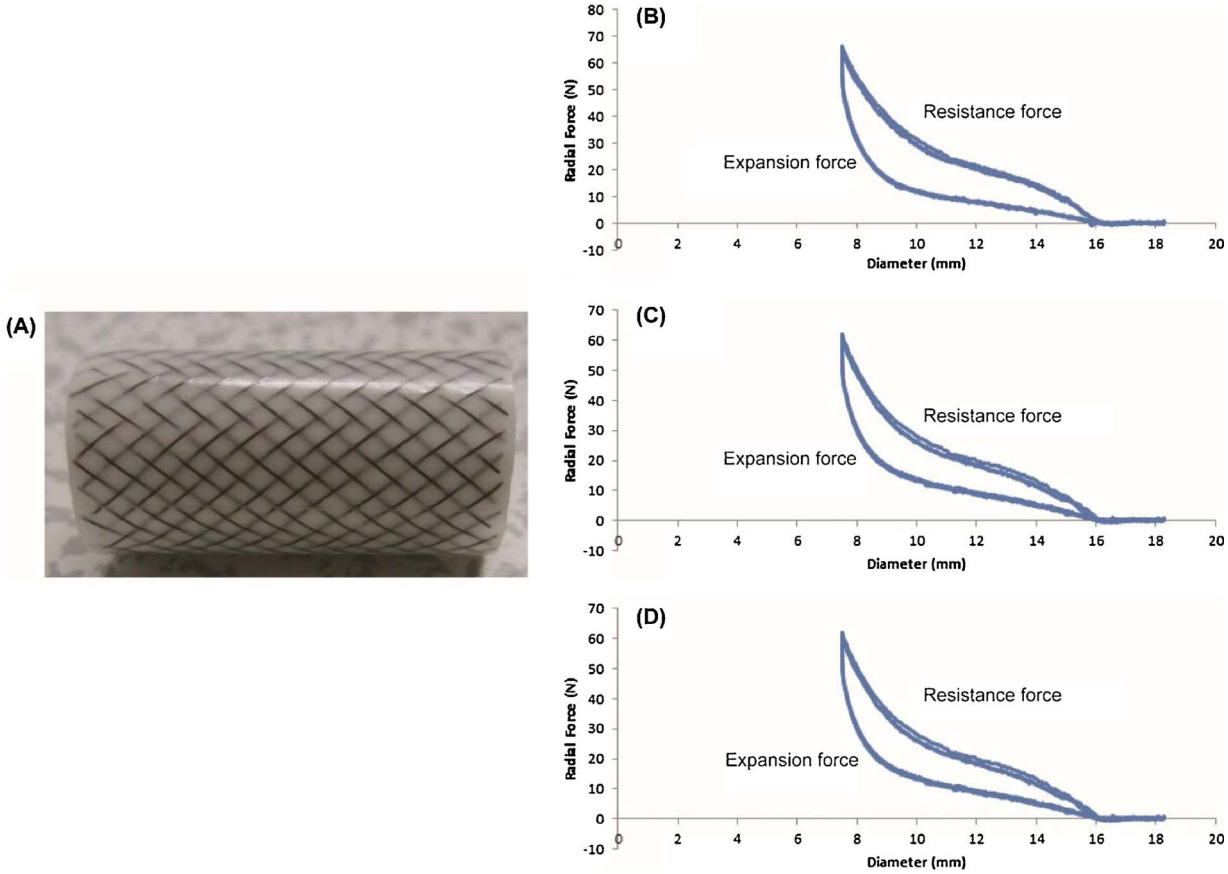

Fig. 8. Picture of PU-foam coated machine-braided stent (A). Radial force curves of blanc PU foam coated machine-braided stent (B) and PU coated stents with 5% (C) or 15% (D) w/w loading of blanc PLGA microspheres. The upper lines refer to the crimping cycles and the lower lines refer to the expansion cycles, the cycle was triplicated.

experiments.

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