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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

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* 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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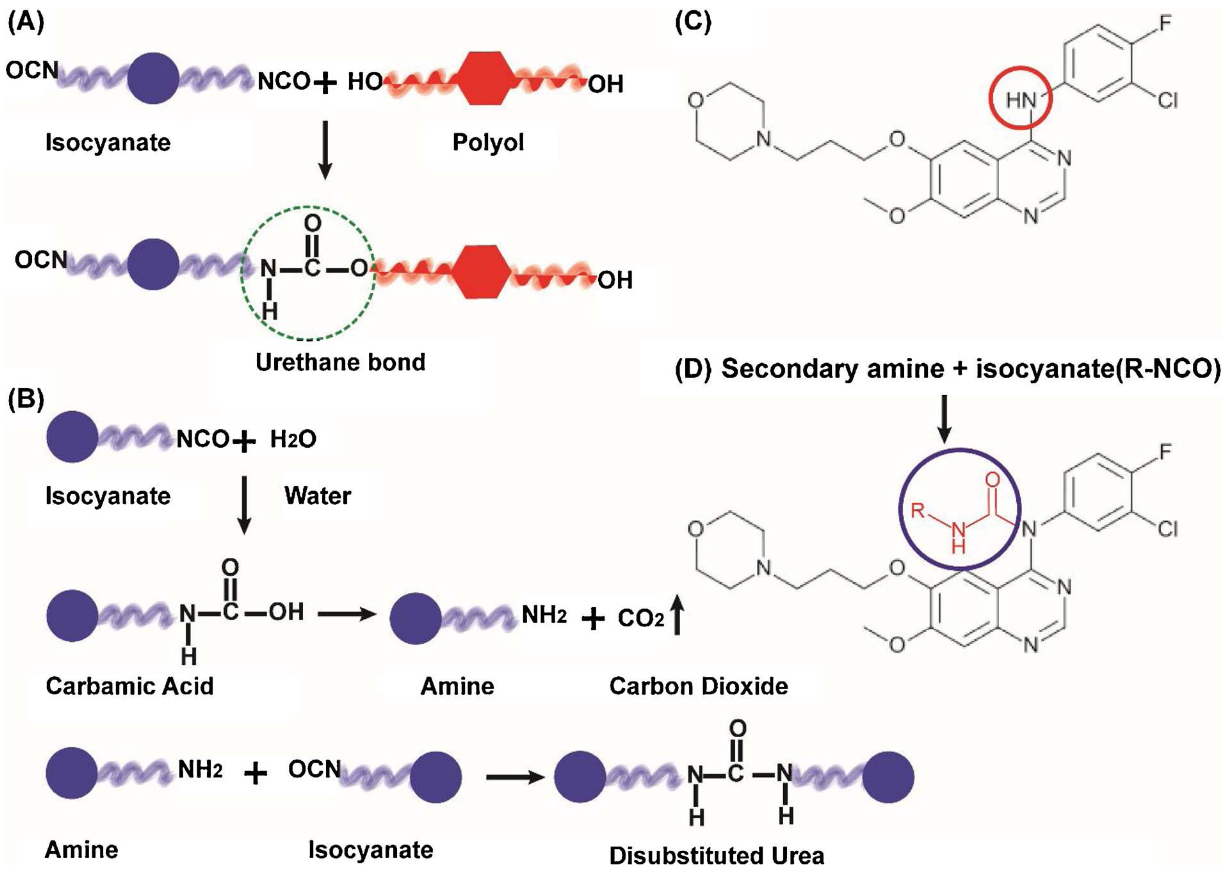

Fig. 1. Chemical reactions in the formation of polyurethane. A: schematic representation of polyurethane formation, the urethane bond is formed via the reaction of an isocyanate group with one of the alcohol function groups in a polyol compound. Frequently applied isocyanates for the production of commercial 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