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Research Paper

In vitro evaluation of paclitaxel coatings for delivery via drug-coated balloons

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ABSTRACT

Lately, drug-coated balloons have been introduced in interventional cardiology as an approach to treat occluded blood vessel. They were developed for the rapid transfer of antiproliferative drugs during the angioplasty procedure in stenosed vessels with the intent to reduce the risk of restenosis. In this study five different paclitaxel (PTX) balloon coatings were tested *in vitro* in order to examine how solvents and additives influence coating stability and drug transfer rates. PTX-coated balloons were advanced through a guiding catheter and a simulated coronary artery pathway under perfusion and were then inflated in a hydrogel acceptor compartment. The fractions transferred to the gel, remaining on the balloon and the PTX lost in the simulated coronary pathway were then analysed. The results obtained suggest that the solvent used for the coating process strongly influences the surface structure and the stability of the coating.

Ethanol/water and acetone based PTX coatings showed the lowest drug transfer rates to the simulated vessel wall (both <1%) due to their high drug losses during the prior passage through the coronary artery model (more than 95%). Balloons coated with PTX from ethyl acetate-solutions showed smaller drug loss (83% ± 9%), but most of the remaining PTX was not transferred (mean balloon residue approximately 15%).

Beside the solvent, especially the use of additives seemed to have a great impact on transfer properties. The balloon pre-treatment with a crosslinked polyvinylpyrrolidone (PVP) film was able to increase the PTX transfer rate from less than 1% (without PVP) to approximately 6%. The best results in this study were obtained for balloon coatings with commercially available SeQuent© Please balloons containing the contrast agent iopromide. For this formulation drug transfer rates of approximately 17% were determined. Fluorescence microscopic imaging could visualize the particulate transfer of labelled PTX from the balloon surface during dilatation. The findings of this study underline the importance of drug adhesion and coating stability for the efficiency of PTX transfer.

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1. Introduction

Drug coated-balloons (DCBs) are marketed in Europe since 2009 as a treatment option during percutaneous transluminal coronary angioplasty (PTCA). Since the late 1970s stenosed vessels were successfully reopened by the inflation of balloons during PTCA and were combined with bare metal stents (BMS) in order to avoid elastic recoil of the vessel. However, restenosis as an excessive response to the controlled injury of the artery wall is an important drawback of PTCA. To counteract this process, anti-inflammatory and antiproliferative drugs have been used locally, either coated onto drug-eluting stents (DES) or lately as DCB, to reduce the inflammatory processes and the proliferation of vascular smooth muscle cells, which leads to neointima growth and late lumen loss.

Currently the drug of choice for DCB is paclitaxel (PTX). Other drugs, such as zotarolimus are also under investigation [1]. Several studies have shown a significant superiority of PTX-coated balloons in the treatment of in-stent restenosis compared to uncoated balloons concerning clinical outcomes [2–4]. In contrast to DES with their sustained drug release, DCBs have to transfer the drug rapidly during the short time of vessel contact. This time is limited

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to approximately 1 min in order to avoid ischaemic events through PTCA-related vessel occlusion. It has been proposed, that due to the absence of a potentially harmful polymeric matrix [5] and avoidance of a foreign body remaining after DCB angioplasty, the duration of antiplatelet therapy and thereby the risk of bleeding could be reduced compared to DES [6].

CE-marked balloons are typically loaded with 3 μg PTX per mm^2 of balloon surface area [6,7] and can also contain additives such as butyltrihexylcitrate, shellac, urea or polysorbate and sorbitol [8–11]. However, so far the most investigated DCB is the SeQuent© Please (SQP) balloon with the contrast agent iopromide as an excipient for the PTX-coating. There is a lot of clinical evidence regarding its efficacy and safety from clinical studies [12,13]. Even though a fair number of *in vivo* evaluations of DCB have been published, relatively little is known about the mechanism of PTX transfer and how it can be influenced by the type and structure of the coating.

Mechanical requirements for the balloon coatings are high since they should quickly release the drug during dilatation but not on the way to the application site. As the crystallinity of the coating may influence its stability, different PTX coatings, generated by the use of different solvents, were investigated in this study. Depending on the vapour pressure of the solvent, the drying of the applied solution may proceed faster or slower, which then may result in different coating morphologies. Furthermore, coating additives seem to play an important role.

In this study DCB with crosslinked polyvinylpyrrolidone (PVP) and DCB with iopromide (SQP) were examined along with the DCB coated with pure drug regarding drug loss and transfer in an *in vitro* model. In a previous study, Kaule et al. investigated three self-established DCB-matrices (one containing PVP as well) regarding their coating characteristics and their performance during a simulated angioplasty, similar to the one presented here [14].

The aim of this study was to gain a deeper understanding of how PTX is transferred during dilatation and how solvents and coating additives can affect this process.

2. Materials and methods

2.1. Materials

PTX was purchased from Cfm Oscar Tropitzsch e.K. (Marktredwitz, Germany). Uncoated fast exchange PTCA balloon catheters (nominal expanded diameter 3.5 mm, length 20 mm, foil made of polyether block amide) were kindly provided by Biotronik AG (Bülach, Switzerland). Polyvinylpyrrolidone (PVP K90, Mw = 360,000 g/mol) was obtained from Sigma Aldrich Chemie GmbH (Taufkirchen, Germany). Fluorescence-labelled PTX (Oregon Green© 488 Taxol) was obtained from Life Technologies (Carlsbad, USA). Commercially available SeQuent® Please balloon catheters were acquired from B. Braun Melsungen AG, Germany. Sodium alginate was purchased from Fagron GmbH Co. KG, Germany. Porcine carotid arteries were obtained as an animal by-product from a local slaughterhouse. Solvents and all other substances used were of analytical grade.

2.2. Methods

2.2.1. Balloon coating

A micro-pipetting technique was used for the coating of the folded balloon catheters. PTX was dissolved in different solvents (ethanol, ethyl acetate, acetone) yielding a concentration of 7.45 mg/mL. While rotating the balloon catheter in a weak airstream, 100 μL of the solutions was slowly pipetted onto the balloon surface. Drying of the DCB was carried out in a vacuum chamber at 40 °C and 40 mbar overnight. For the PVP-hydrogel coating PVP was dissolved in chloroform (22.62 mg/mL) and pipetted on the balloon as outlined above. After drying, PVP coatings were crosslinked by UV irradiation. Therefore balloon catheters were positioned and intermediately rotated at a distance of 15 mm beneath a 3UV lamp (Ultra Violet Products, P/N 95-0343-02, 254-302-365 nm, 8 W/230 V, ~50 Hz/0.16 A, UK). Balloons were irradiated for 10 min with the lamp set to 254 nm, which produces a radiant flux of 1670 μW/cm^2 at 2″ distance. Afterwards, PTX was incorporated via pipetting and drying as described above. Commercially available SQP balloons were used as received. An overview of the different balloon coatings is given in Table 1. For fluorescence imaging PTX-coatings based on ethanol/water were generated with Oregon Green© 488 Taxol substituting 100 μg of the total PTX load.

2.2.2. Model vessel wall compartment

Alginate gel film rolls were prepared as formerly established [15]. Sodium alginate solutions (3% m/m in purified water) were spread with a doctor blade (slot width 500 μm) onto a glass plate and gelled with calcium chloride solution (6% m/m in purified water) for 10 min. After removing the overlaying liquid, resulting gel films were cut into 50 mm × 80 mm rectangles and coiled around a stainless steel rod (diameter 3 mm). Thereby gel film rolls with a length of 50 mm and approximately five layers of film were formed. When the inserted steel rod was pulled out a rolled up gel film cylinder with a central lumen of 3 mm in diameter was generated and used for drug transfer testing immediately after preparation. In one set of experiments, porcine carotid arteries were additionally used to investigate drug transfer to the vessel wall. Arteries were selected by their luminal size to ensure a tight fit of the balloon during inflation.

2.2.3. Coronary artery pathway model

In order to simulate blood flow, shear and friction forces during the insertion of a DCB *in vivo*, a polymethacrylate model was used for *in vitro* testings. The model, which has been described previously [15,16], is based on the ASTM standard F 2394-07 [17]. It is composed of three polymethacrylate plates. In the middle plate a route with a straight upper part followed by a part simulating the coronary artery pathway is inserted. Of the three branches in the ASTM standard only the main branch was considered. A sche-

Table 1
Composition of paclitaxel (PTX) balloon coatings, PVP: polyvinylpyrrolidone.

Nr.	PTX concentration of coating solution	Solvent	Balloon pre-treatment
1	7.45 mg/ml equal to 3 μg/mm^2	Ethanol/demineralized water (8:2, V/V)	–
2	7.45 mg/ml equal to 3 μg/mm^2	Ethanol/demineralized water (8:2, V/V)	PVP coating (PVP dissolved in chloroform 22.62 mg/mL, pipetted and crosslinked by UV radiation)
3	7.45 mg/ml equal to 3 μg/mm^2	Ethyl acetate	–
4	7.45 mg/ml equal to 3 μg/mm^2	Acetone	–
5	SeQuent® Please: 3 μg/mm^2 PTX embedded in carrier matrix containing approx. 10% iopromide		

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