Materials Science and Engineering C 33 (2013) 4244–4250

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Novel paclitaxel-coated angioplasty balloon catheter based on cetylpyridinium salicylate: Preparation, characterization and simulated use in an in vitro vessel model

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ARTICLE INFO

Article history:
Received 8 February 2013
Received in revised form 4 May 2013
Accepted 18 June 2013
Available online 26 June 2013

Keywords:
Drug delivery
Implant coating
Ionic liquids
Drug-coated balloons

ABSTRACT

Drug-coated balloons (DCB), which have emerged as therapeutic alternative to drug-eluting stents in percutaneous cardiovascular intervention, are well described with regard to clinical efficiency and safety within a number of clinical studies. In vitro studies elucidating the correlation of coating method and composition with DCB performance are however rare but considered important for the understanding of DCB requirements and the improvement of established DCB. In this context, we evaluated the applicability of a pipetting, dip-coating, and spray-coating process for the establishment of DCB based on paclitaxel (PTX) and the ionic liquid cetylpyridinium salicylate (Cetpyrsal) as novel innovative additive in three different compositions. Among tested methods and compositions, the pipetting process with 50 wt.% PTX resulted in most promising coatings as drug load was less controllable by the other processes and higher PTX contents led to considerable drug crystallization, as visualized by electron microscopy, accelerating PTX loss during short-term elution. Applying these conditions, homogeneous coatings could be applied on balloon catheter, whose simulated use in an in vitro vessel model revealed percental drug losses of 36 and 28% during transit and percental drug transfers of 12 and 40% under expansion for coatings applied in expanded and folded balloon condition, respectively. In comparison to literature values, these results support the high potential of Cetpyrsal as novel DCB matrix regarding low drug loss and efficient drug transfer.

1. Introduction

Vascular Intervention as a clinical alternative to bypass graft surgery for the treatment of coronary and peripheral artery disease caused by arteriosclerosis became famous with the first balloon angioplasty by Grüntzig et al. in 1977 [1]. Most important limitations of this minimally invasive technique as abrupt vessel re-narrowing or closure resulting from elastic recoil could be effectively solved by the implantation of balloon expandable bare metal stents (BMS) [2]. However, 15–20% of treated patients still required re-intervention within 6–12 months due to occurring in-stent restenosis [3], which was in turn addressed by the concept of drug eluting stents (DES), allowing the delivery of antiproliferative drugs in a controlled manner to arterial wall with the purpose to reduce or prevent excessive neointimal proliferation [4]. Although DES have become the mainstay of Vascular Intervention, they came under scrutiny when late stent thrombosis (LST) and delayed healing were identified as potential associated risks [5–7]. The short-term transfer of the similar antiproliferative drugs to the arterial wall by the use of drug-coated balloons (DCB) either as adjunct therapy to BMS for guaranteeing mechanical vessel stability or as standalone intervention has hence emerged as a therapeutic alternative to DES about ten years ago [8,9]. Major potential advantages of DCB include: i. homogeneous drug transfer not restricted to areas covered by stent struts, ii. high initial drug delivery with little impact on long-term healing possibly limiting the risk of LST and iii. high deliverability opening the opportunity of use in small vessels, bifurcations, long lesions, etc. hardly accessible by stents [10,11]. While the drug of choice on currently investigated DCB is paclitaxel (PTX), which has proven rapid uptake by the intima, high retention rate and sustained biological effect [12], various types of surface designs are discussed. Besides porous balloons [13] and microporous balloon surfaces (DIOR®, Eurocor, Bonn, Germany) these primarily focus on surface coatings of PTX and adjunctive transfer agents (SeQuentTM Please, B. Braun Melsungen AG, Melsungen, Germany; In.Pact™, Medtronic Invatec, Roncadelle, Italy; Pantera Lux, Biotronik AG, Bülach, Switzerland). As PTX alone is very lipophilic and hence sticks to the balloon surface, transfer agents as the mainly studied contrast agent iopromide [14] but also urea [15] and plasticizers [16] are applied in order to enhance the drug transfer capability. However, losses during transit of the device through the vascular system,

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0928-4931/$ – see front matter
http://dx.doi.org/10.1016/j.msec.2013.06.021

especially when applying water soluble transfer agents, should not be underestimated. For instance, while Kelsch et al. [17] reported percental PTX losses of up to 26 and 36% for urea- or iopromide-based DCB respectively, Berg et al. [18] even observed drug losses of 42% for the iopromide-based Paccocath formulation both during in vitro passage through a hemostatic valve and a guiding catheter. In this context we aim at an innovative design of DCB based on ionic liquids (IL), which potentially combines both, physical maintenance of the drug on the surface during transit of the device through the vascular system with a rapid, uniform, and efficient drug transfer to the vessel wall during balloon expansion. IL are assumed to be attractive as matrix for DCB, because important physical, chemical and biological properties are tuneable by combination of various anions and cations within a broad range [19]. For instance, solubility and behavior of IL in water can be finely adapted [20] regarding delayed solubility allowing low drug losses by short-term elution during insertion, swelling for efficient drug transfer to the vessel wall during dilatation and full solubilization for risk reduction of particle creation after balloon expansion. Moreover, IL can be composed of pharmaceutically active ions [21–23], which might additionally support cardiovascular intervention.

Although until to date, comprehensive clinical data for DCB has been provided in a number of publications, only very few studies describe the correlation of coating method and composition with DCB performance. Furthermore, according to our knowledge, no studies have so far been presented, describing the simulated use of DCB in an in vitro vessel model. However, such in vitro studies should be considered as highly important for the understanding of the DCB coating requirements, the resulted drug delivery and hence the improvement of established DCB. In the present study, we provide such data for PTX-coated balloon catheter using the IL cetylpyridinium salicylate (Cetpyrsal) as novel innovative additive. Besides the correlation of coating method and Cetpyrsal to PTX ratio with coating morphology and reproducibility in terms of drug load, determined by means of electron microscopy and chromatography respectively, we address the drug and particle transfer of promising IL-based DCB during simulated use in an in vitro vessel model.

2. Experimentals

2.1. Materials

All chemicals were purchased from Sigma-Aldrich (Taufkirchen, Germany), Mallinckrodt Baker (Griesheim, Germany), SERVA Feinbiochemica (Heidelberg, Germany), Thermo Scientific (Karlsruhe, Germany) or Merck (Darmstadt, Germany) in p.a. quality or higher if not indicated differently. For characterization of morphology, drug loss by elution and drug load accuracy polyetherblockamide tubes (PEBAX 7033 SA01) of 5 mm in length and diameter, provided by Biotronik AG (Bülach, Switzerland), were drawn on glass bars of the same diameter (5 mm) for better handling and used as model balloon surface. Examined PEBAX balloon catheter of 4 mm in diameter and 20 or 30 mm in length were kindly supplied by Biotronik SE & Co. KG (Erlangen, Germany).

2.2. Synthesis of cetylpyridinium salicylate

We synthesized the IL cetylpyridinium salicylate (Cetpyrsal), composed of the cation cetylpyridinium used as cetylpyridinium chloride in antimicrobial mouth rinses [24] and the anion salicylate, mostly known by its derivative acetylsalicylic acid, having a wide-spectrum of activities, including anti-inflammatory, anti-neoplastic, and antimicrobial actions [25] (Fig. 1), according to Bica et al. [22]. Briefly, 10.32 g cetylpyridinium chloride and 4.48 g of sodium salicylate were dissolved in 50 mL of water/acetone (1:1, v/v) and the solution was stirred at 23 ± 2 °C overnight. Subsequently, 100 mL of water was added to the reaction solution prior to extraction with

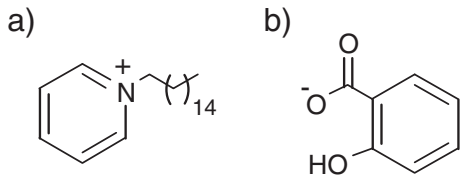

Fig. 1. Cetylpyridinium salicylate as combination of a) anti-bacterial cation and b) anti-inflammatory anion.

dichloromethane for at least 5 times. In order to remove residual sodium chloride (NaCl), the combined extracts were washed with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution). Finally, the extract was dried over a molecular sieve and dichloromethane was evaporated under reduced pressure. The resulting ionic liquid was a crystalline slightly yellow powder. ^1H and ^{13}C NMR data were recorded in d_6-DMSO at 23 °C on a Bruker AVANCE 300 III spectrometer (Coventry, UK) for verification of the structure.

2.3. Coating

2.3.1. Pipetting process

PTX (Cfm Oskar Tropitzsch e.K., Marktredwitz, Germany) and Cetpyrsal were separately dissolved in methanol (MeOH) to yield concentrations of 4.72 mg/mL. The PTX solution was diluted 1:1 with either pure MeOH and/or Cetpyrsal solutions in different ratios in order to obtain PTX concentrations of 50, 75 and 90% in Cetpyrsal (w/w). 100 μL of the resulting Cetpyrsal-PTX solution was then slowly pipetted per each PEBAX tube (78.54 mm^2), in order to approach a PTX surface load of 3 $\mu g/mm^2$. The volume of 100 μL turned out to be best manageable for the coating of a surface of the aforementioned 78.54 mm^2 in preliminary experiments. The constant PTX concentration of 2.36 mg/mL in the solution thus resulted from the predefined volume of 100 μL and PTX surface load of 3 $\mu g/mm^2$.

For the coating of balloon catheter, which were either dilated (p = 2 bar) prior to coating or left in folded condition, the pipetted volume was adapted in accordance to the surface to be covered. During manual pipetting, tubes and balloons were rotated and a weak air stream was applied to guarantee evaporation of the solvent. Finally, all coatings were dried at 23 ± 2 °C overnight.

2.3.2. Dip-coating process

Manual dip-coating of PEBAX tubes was performed via five repetitive dipping processes with intermediate drying for 30 min at 23 ± 2 °C. The finally applied PTX concentrations in the methanolic coating solution of 15 mg/mL, 10 mg/mL and 5 mg/mL were chosen for 50%, 75% and 90% PTX in Cetpyrsal (w/w) respectively, as they yielded the highest drug load accuracy within the investigated concentration range of 5 mg/mL to 15 mg/mL (data not shown). The PTX and Cetpyrsal solutions were prepared separately at a concentration of 30 mg/mL and prior to coating mixed with each other and if necessary pure MeOH in the corresponding ratio. Finally, all coatings were dried at 23 ± 2 °C overnight.

2.3.3. Spray-coating process

For spray-coating, PTX and Cetpyrsal were separately dissolved in MeOH to yield concentrations of 0.80 mg/mL. The PTX solution was then diluted 1:1 with either pure MeOH and/or Cetpyrsal solutions in different ratios in order to obtain PTX concentrations of 50, 75 and 90% in Cetpyrsal (w/w). The constant PTX concentration of 0.40 mg/mL was chosen for the spraying solutions, since it turned out to allow for homogenous coating in manageable spraying times within preliminary experiments. For spraying, PEBAX tubes were inserted into a holder of an electropneumatic airbrush system, which guaranteed homogeneous coating by continuous rotation