Drug Release Profiles of Different Drug-coated Balloon Platforms

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Abstract

Drug-coated balloons are a new tool for the treatment of *de novo* or in-stent stenosis; as yet little is known about the principle by which these devices apply their therapeutic agents during intervention. Concerns remain regarding clinical safety and efficacy of different coatings, mainly influenced by the amount of drug transferred into the arterial tissue and lost into the bloodstream. To assess whether the chemical or mechanical set-up influences drug migration and wash-off, we compared four paclitaxel-coated balloon platforms differing in surface structure (folded versus non-folded) and coating compounds (pure paclitaxel versus paclitaxel plus excipient) in a porcine coronary model. The study revealed high wash-off rates for all devices, exceeding 54.4% of the initial coating contents. In terms of tissue concentration significant differences could be observed between the coating compounds independently from the device platform. For the paclitaxel versus paclitaxel plus excipient balloons tissue concentrations of 0.02 and 0.33µg/mm^2, respectively ($p<0.01$), were detected; for the paclitaxel versus paclitaxel plus excipient-wrapped balloons tissue concentrations were 0.13 and 0.53µg/mm^2, respectively ($p=0.04$). The main driver of drug migration from drug-coated balloon surfaces into arterial tissue is the chemical set-up of the coating. Hydrophilic excipients allow higher tissue concentrations of paclitaxel independent from the mechanical platform. The wash-off from the surface coating remains an unsolved safety issue and may be solved by mechanical modifications of these devices.

Keywords

Drug-coated balloons, paclitaxel-coated balloon platforms, drug migration, hydrophilic excipients, clinical safety, efficacy

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Drug-coated balloons (DCBs) are a nascent technology gaining a lot of attention among cardiologists and angiologists worldwide. As opposed to drug-eluting stents (DES) they allow intraluminal drug application to diseased arterial tissue without leaving an implant such as a metal scaffold behind. This may be beneficial where a stent is already in place or where stenting is problematic due to challenging anatomy.

DES are characterised by sustained drug release into the arterial wall. The release kinetics of the contained drugs are crucial for the efficacy of DES; the most common way to control this process is embedding the drug into durable or bio-erodable polymers. Multiple human trials have shown that no class effect can be observed for DES coated with the same antiproliferative drug.[1,4] The safety and efficacy of DES depend on the delicate interaction of stent architecture, antiproliferative drug and polymer from which the drug is released.

Recently, multiple DCBs have received the CE mark and are available to European physicians. Yet, human trials with DCBs are scarce and the technology behind DCBs is little understood by the medical community. As opposed to DES, DCBs apply drug to the vessel wall only over a period of 30–60 seconds.[2,3,7,10] To reach therapeutic drug dosages in the arterial tissue DCBs contain significantly higher amounts of antiproliferative drugs than DES. Similar to DES there are differences in the chemical set-up of the coating of DCBs that influence the release of the drug and the migration of the drug into the vessel wall. European physicians can currently choose between DCBs coated with paclitaxel alone or paclitaxel with one of the following additives: butyryl-tri-hexyl-citrate, iopromide, shellac and urea.

These DCBs have a rather smooth polytetrafluoroethylene (PTFE) surface. The surface area does not significantly differ between relaxed and expanded balloons because of the semi-compliant balloon material. In order to achieve a small entry profile of the balloon catheter the balloons are folded in an umbrella-like manner (see *Figure 1*). Depending on the employed coating methods such surface coatings can be very uneven, showing high concentrations within the balloon folds and lower concentrations at the outer balloon.

An alternative mechanical system that insures a more uniform drug coating (and drug transfer into the tissue) is the drug-coated wrapped balloon (DCW). These balloons feature a highly elastic wrap around the folded balloon (see *Figure 1*). This wrap may be manufactured

from latex or synthetic materials. These materials often possess micropores that partially open if the balloon is expanded. This might be favourable for the surface coating and drug transfer. On the other hand, a drug on the surface is more exposed to the blood, which might cause a higher wash-off. Little is known about the efficacy of such a mechanical platform.

For the paclitaxel-plus-iopromide-coated balloon (PACCOCATH® Technology) there are several animal and human studies showing that a short-term administration of paclitaxel can inhibit neointima proliferation.[5,8,11] Yet, a recent animal study comparing this balloon with a DCB coated with paclitaxel alone (DIOR®) showed significant differences in the inhibition of neointima proliferation between the two DCB.[3]

Apart from efficacy data, little is known about possible side effects of these devices. The above-mentioned additives are commonly described as 'hydrophilic spacers'. Yet a hydrophilic coating in the aqueous environment of the bloodstream invariably leads to a 'wash-off' of parts of the surface coating. The amount of washed-off antiproliferative drug and its effects in the peripheral vascular bed or adjacent organs are of particular interest for assessing the safety of DCBs.

To evaluate the differences between several DCB platforms the investigators sought a model that describes the chemical distribution of the therapeutic agent during DCB application. We assessed the percentage of drug transferred into the vessel wall (tissue concentration) as well as the percentage of drug lost into the bloodstream (wash-off) for four different DCB platforms in the porcine coronary overstretch model.

Materials and Methods

Used Drug-coated Balloons and Drug-coated Wrapped Balloons

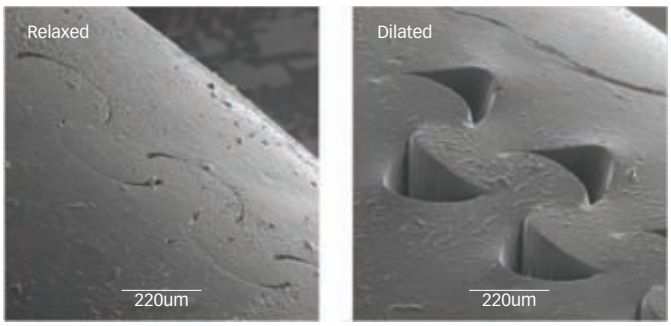
The study compared CE-marked DCBs with DCWs manufactured by the investigators. The main mechanical differences between DCB and DCW balloons are the material carrying the drug and the geometry of the coated surface. DCB have a rather smooth PTFE surface. The surface area does not significantly differ between relaxed and expanded balloons because of the semi-compliant balloon material. In order to achieve a small entry profile of the balloon catheter, the balloons are folded in an umbrella-like manner. Depending on the employed coating methods such surface coatings can be very uneven, showing high concentrations within the balloon folds and lower concentrations at the outer balloon.

DCW balloons feature a highly elastic wrap around the folded balloon. This wrap may be manufactured from latex or synthetic materials. These materials often possess micropores, leading to a certain roughness that is favourable for surface coating. In contrast to the umbrella-like folding of DCBs the wraps used for the present study always have a cylindrical shape whether the underlying balloon is relaxed or expanded, yet the surface of the wrap significantly increases when the balloon is expanded and decreases when the balloon is relaxed. With the change of surface area of the wraps, the opening size of the micropores also changes.

Figure 1 compares the cross sections of DCB and DCW balloons and *Figure 2* shows scanning electron microscope (SEM) images of the surface of DCWs. Note that for this study DCWs were not laser

Figure 1: Drug-coated Balloon Versus Drug-coated Wrapped Balloon

Figure 2: Structured Surface of AVIDAL WOMBAT®



structured as shown in *Figure 2* to ensure comparability with PTFE balloon surfaces.

Two different surface coatings for the DCB study groups were chosen, one being a pure paclitaxel coating (ELUTAX© Balloon Catheter, Aachen Resonance GmbH, Germany) and the other being a matrix coating of paclitaxel plus hydrophilic X-ray contrast medium iopromide (SeQuent® Please Balloon Catheter, B|Braun Melsungen AG, Germany). They were referred to as paclitaxel DCB (Ptx balloon) and paclitaxel plus iopromide coated balloon (Ptx+I balloon). For the initial drug concentration contained in the surface coating the investigators adopted the values stated in the instructions for use, being 2µg of paclitaxel per mm^2 balloon surface for the Ptx balloon and 3µg of paclitaxel per mm^2 balloon surface for the Ptx+I balloon.

For the DCW balloons (DCW) we manufactured two versions closely matching the used CE-marked DCB. The DCW coated with pure paclitaxel contained an initial drug concentration of 3.31±0.08µg of paclitaxel per mm^2 balloon surface. The matrix-coated DCW contained a mixture of paclitaxel plus a hydrophilic substance that currently cannot be disclosed due to patent issues. The initial drug concentration of the matrix-coated DCW was 3.37±0.29µg of paclitaxel per mm^2 balloon surface. They were referred to as paclitaxel DCW balloon (Ptx wrap) and paclitaxel plus X DCW balloon (Ptx+X wrap).

Animal Study

Nine domestic pigs were pre-sedated by intramuscular injection of 6ml ketamine and 4ml xylazine. A venous access was provided, and anaesthesia was induced by intravenous injection of propofol, followed by orotracheal intubation. All animals received 5,000IU unfractionated heparin, 250mg aspirin, and 200µg intracoronary nitroglycerine. The coronary arteries were imaged using a standard angiographic technique via the left carotid artery. Target segments were selected in

Table 1: Distribution of Paclitaxel During Percutaneous Coronary Intervention – Values in µg/mm²

	Ptx Balloon (n=4)	Ptx Wrap (n=9)	Ptx+I Balloon (n=9)	Ptx+X Wrap (n=5)
Initial ptx surface conc.	2.00*	3.31 ± 0.08	3.00*	3.37 ± 0.29
Tissue concentration	0.02 ± 0.01	0.13 ± 0.10	0.33 ± 0.31	0.53 ± 0.36
Residual ptx surface conc.	0.90 ± 0.17	0.48 ± 0.19	0.13 ± 0.03	0.29 ± 0.07
Wash-off	1.09 ± 0.17	2.70 ± 0.22	2.55 ± 0.31	2.56 ± 0.34

**According to manufacturer.*

the right (RCA), left anterior descending (LAD) and circumflex (CX) coronary arteries, and vessel diameters were estimated by comparison with the diameter of the angiographic catheter.

Prior to DCB/DCW application we implanted standard 316L stainless steel stents (Apolo 3®, IBERHOSPITEX S.A., Spain, diameters 3.0 and 3.5mm, length 18mm) to mark the drug application area and to induce a vessel response similar to prior DCB animal trials.[2,5,11] Stents were implanted with an oversize ratio of ~1.2 (implantation pressure 12atm). Immediately after stent implantation a DCB/DCW was placed into the stented lesion, inflated with 12atm over 30 seconds, and withdrawn from the target lesion. The CE-marked DCB and the manufactured DCW balloons were available in 3.0 and 3.5mm diameters and lengths of 20 or 21mm.

Overall 27 lesions were treated in a randomised fashion and DCB/DCW were selected from one of the four groups: paclitaxel DCB (Ptx balloon, n=4), paclitaxel DCW balloon (Ptx wrap, n=9), paclitaxel plus iopromide coated balloon (Ptx+I balloon, n=9), paclitaxel plus X DCW balloon (Ptx+X wrap, n=5).

After the procedure the animals were sacrificed and the hearts rapidly excised. The coronary system was flushed with 0.9% saline before the treated artery segments were dissected and stored at -20°C.

Tissue and Drug-coated Balloons/ Drug-coated Wrapped Balloon Extraction

The frozen tissue samples were weighted and wrapped in aluminum foil. After freezing in liquid nitrogen the tissue was pulverised with a hammer and quickly transferred to a glass tube containing 6ml ethanol (absolute). The suspension was vortexed and sonicated for 30 minutes in an ultrasound bath (Fisher Scientific Model FB15046). After repeating the vortexing and ultrasound procedure the suspension was centrifuged for three minutes at 3,000*g* (Eppendorf centrifuge 5702). The ethanolic supernatant was collected. The pellet was resuspended in 4ml ethanol and extracted as described above. After centrifugation the ethanolic supernatants were combined and filtered for high-performance liquid chromatography (HPLC) analysis. The recovery was nearly quantitative (98%) if homogenised tissue amounts of up to 3g were extracted. Re-extraction of tissue samples from the angioplasty experiments revealed paclitaxel levels of about 1% of the first extraction. The DCBs/DCWs were eluted with 5ml ethanol (absolute) and sonicated for five minutes.

High-performance Liquid Chromatography Analysis

Ethanolic extracts were separated by RP18 chromatography on a 5µm column (UltrasepES, 250 x 3mm, Separation Service Berlin) in a Shimadzu LC-2010A HT chromatograph. Gradient elution with acetonitril: water mixtures were used. Starting conditions: Acetonitrile/water 30%; 70%, linear gradient to 95%; 5% within 15 minutes and 95%; 5% for five minutes. Compounds were detected at 228nm and quantified by LC-Solution software (Shimadzu, Japan).

Calculations and Statistical Analysis

For the initial drug concentration contained in the surface coating the investigators adopted the values stated in the instructions for use, being 2µg of paclitaxel per mm² balloon surface for the Ptx balloon and 3µg of paclitaxel per mm² balloon surface for the Ptx+I balloon. For the Ptx wrap and Ptx+X wrap we examined four sample products manufactured in the same fashion as the DCW balloons used in the animal study. The initial paclitaxel concentration of the surface coating was 3.31±0.08µg/mm² for the Ptx wrap and 3.37±0.29µg/mm² for the Ptx+X wrap.

To allow a comparison of absolute values for the different balloon sizes (3.0 and 3.5mm diameters; 20 and 21mm length) all measurements where standardised to µg/mm². For the balloon outer surface as well as for the vessel inner surface the area was calculated using the area formula for cylindrical bodies without the top or bottom ($A=2\pi rh$). The absolute values are shown in *Table 1*.

To standardise for the different initial drug concentrations (2.00–3.37µg/mm²) and allow the characterisation of drug release profiles, the absolute amounts of paclitaxel found in the tissue and the residual surface coating of the DCBs/DCWs are set in relation to the initial drug concentration of the surface coating and expressed as percentages. The percentage values are shown in *Table 2*.

The statistical analysis was per DCB/DCW or per lesion and the discrete variables are expressed as counts or percentage. Continuous variables are expressed as mean + standard deviation (SD). The two-tailed Mann-Whitney U-test was chosen for statistical testing. Statistical significance was accepted for $p<0.05$. Statistical analysis was performed with SPSS 15.0 (SPSS Inc., Chicago, US).

Results

Tables 1 and *2* show initial concentrations, the tissue concentrations of paclitaxel after intervention and the corresponding paclitaxel wash-off rates. The wash-off rates represent the difference between the initial concentration and the sum of the remaining concentration on the balloon after the intervention and the tissue concentration.

When comparing tissue concentration and residual surface concentration of paclitaxel for the different DCB platforms, significant differences could be found: the tissue concentrations of paclitaxel were found to be generally higher in the paclitaxel plus excipient-coated balloons, independent of the mechanical platform of the balloon used.

We could detect three to four times higher tissue concentrations for the DCBs/DCWs coated with paclitaxel + excipient when compared with DCBs/DCWs coated with paclitaxel alone (coating comparison). The tissue concentrations of paclitaxel for the Ptx balloon and the Ptx+I balloon showed significant differences (0.8 versus 10.9%, $p<0.01$). For the comparison of the Ptx wrap versus the Ptx+X wrap we also observed great differences (3.9 versus 15.3%, $p=0.04$).

Table 2: Distribution of Paclitaxel During Percutaneous Coronary Intervention – Percentages of Initial Surface Coating

	Ptx Balloon (n=4)	Ptx Wrap (n=9)	p value	Ptx+I Balloon (n=9)	Ptx+X Wrap (n=5)	p value	Pure ptx versus ptx+excipient p value
Initial ptx surface concentration (%)	100.0	100.0		100.0	100.0		
Tissue concentration (%)	0.8 ± 0.5	3.9 ± 3.1	0.03	10.9 ± 10.2	15.3 ± 9.9	0.30	<0.01
Residual ptx surface concentration (%)	44.8 ± 8.4	14.5 ± 5.8	< 0.01	4.2 ± 0.9	8.4 ± 1.9	<0.01	<0.01
Wash-off (%)	54.4 ± 8.4	81.6 ± 7.0	< 0.01	84.9 ± 10.2	76.3 ± 11.6	0.24	0.11

When comparing balloon versus wrap (device architecture comparison) the differences were not as pronounced. While the comparison of Ptx balloon versus Ptx wrap showed significant differences (0.8 versus 3.9%, p=0.03), there were no significant differences observed between Ptx+I balloon and Ptx+X wrap (10.9 versus 15.3%, p=0.30) (see *Figure 3*).

The comparison of residual paclitaxel concentration after intervention revealed significantly higher remaining paclitaxel amounts on the balloons that were coated with paclitaxel alone. The comparison of residual surface concentration after intervention revealed significant differences for all devices. The coating comparison showed differences in the order of up to 10 times higher surface coating retention for DCBs/DCWs coated with paclitaxel alone compared with DCBs/DCWs coated with paclitaxel plus excipient. The residual paclitaxel surface concentrations where 44.8 versus 4.2% for Ptx balloon versus Ptx+I ballon (p<0.01) and 14.5 versus 8.4% for the Ptx wrap versus Ptx+X wrap (p=0.04).

Taken together, our data show that higher tissue concentrations of paclitaxel can be achieved by utilising hydrophilic excipients, but these excipients may lead to higher wash-off rates of the paclitaxel coating. These findings were independent from the mechanical platform (DCB versus DCW). Furthermore, all devices showed high wash-off rates, ranging from 54.4 to 84.9% of their initial coating concentration. This phenomenon may be characteristic for DCB due to the passage of the coating through the bloodstream.

Discussion

This is the first study comparing the differences between two different DCB platforms with regard to drug release during normal angioplasty intervention.

The two platforms have great differences in mechanical set-up. Standard angioplasty balloon catheters are tightly folded like umbrellas and may protect parts of the surface coating in the folds against the bloodstream. Newly developed wraps for angioplasty balloons in contrast have no folds but an elastic material that changes in diameter during balloon inflation. Without surface modification these are more prone to drug wash-off, a process constituting the sum of mechanical loss (sheath passage, collisions with the vessel wall) and dissolution of the coating in the bloodstream. Despite these great mechanical differences, we did not find great differences in wash-off rates between the different platforms. In fact, the greatest differences between the devices were achieved by the addition of hydrophilic excipients to the paclitaxel coating. There was a platform-independent increase of tissue concentration of paclitaxel for excipient-based coatings (see *Figure 3*).

Figure 3: Tissue Concentration of Paclitaxel in Per Cent of Initial Coating Concentration

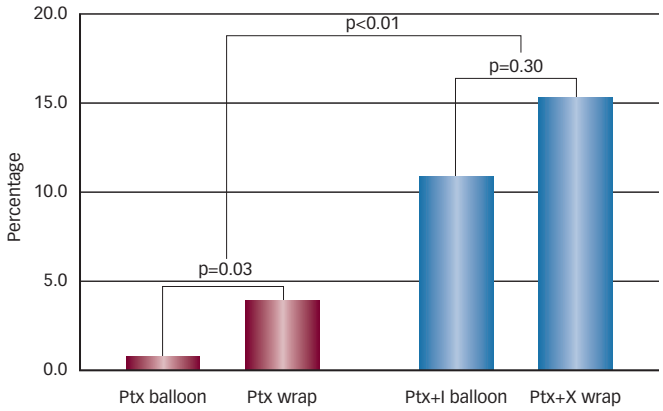
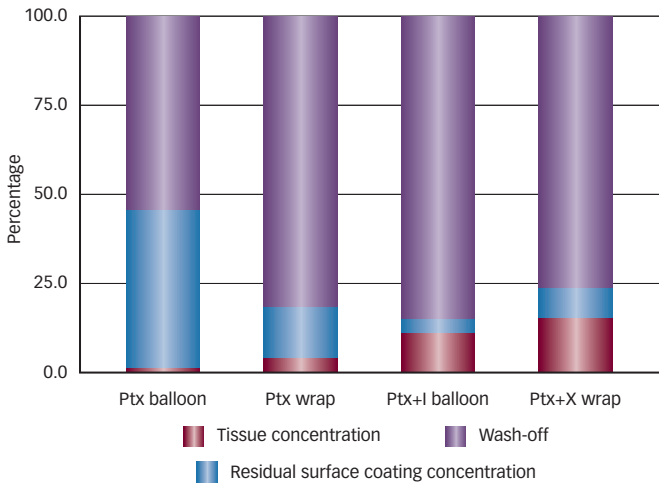


Figure 4: Comparative Drug Release Profiles for Four Different Drug-coated Balloon Platforms



It is supposed that higher tissue concentrations of paclitaxel are indicative of more effective inhibition of neointima proliferation. This hypothesis is supported by prior animal studies where paclitaxel-coated balloons showed inferior neointima suppression when compared with paclitaxel plus iopromide-coated balloons.[3] Our data suggest that the main driver of clinical efficacy is the chemical set-up of the DCB platform.

One very new aspect related to DCBs is the relatively low drug amount administered into the arterial tissue when compared with initial drug coating concentrations. *Figure 4* shows the drug release profile results of the four investigated devices. For oversight

bodies it will be of particular interest how much of the initial antiproliferative drug concentration can be detected in the tissue, how much is withdrawn from the body with the device (coating after intervention), and how much is washed off. So far, little is known about potential systemic effects of the washed-off drug coating even though we detected an 84.9±10.2% wash-off for the currently best-evaluated device on the market (SeQuent® Please, B. Braun Melsungen).

When interpreting the drug release profiles in *Figure 4*, one can easily appreciate that the ideal DCB would have no wash-off (only red and blue areas). All of the drug that is not transferred into the arterial tissue should be withdrawn with the device. The lower systemic drug loss would also allow for lower initial concentrations, which would further contribute to the safety of such devices.

Yet, our data suggest that the beneficial effect of hydrophilic excipients for higher tissue concentrations is counteracted by higher wash-off of these coatings. We observed a platform-independent lower residual paclitaxel concentration for excipient-based coatings when compared with pure paclitaxel coatings (see *Table 2*). Due to these counteracting processes, we believe that the safety of DCB platforms can primarily be enhanced by the mechanical set-up of the device to protect the hydrophilic coating against wash-off in the aqueous environment of the bloodstream.

Such mechanical solutions may include protective sheaths over the coated balloons or surface modifications that allow the drug to be embedded in the balloon material. Another possible approach to such a mechanical solution can be the wrapping of the balloon with a drug delivery platform, the surface of which can be optimised for intraluminal drug application as shown in *Figure 2*.

In conclusion, from the initial data from our chemical drug distribution model there are great differences between the coatings of different devices that will most likely lead to pronounced differences in terms of efficacy as well as safety. As for DES, we expect no class effect for DCBs that use the same therapeutic agent. It is clear that in the future we will see devices with very different chemical and mechanical set-ups to manage the safety and efficacy of intraluminal drug application become available on the market. Comprehensive animal and human data are warranted for each of these devices. ■

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