

How Can DCB Design Impact Clinical Outcomes?

The technology and clinical outcomes of the Passeo-18 Lux DCB.

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Clinical performance of a medical device derives directly from its technical design and characteristics. Drug-coated balloons (DCBs) have to address several complex and contradictory demands. In an ideal case, a DCB must ensure a perfect balance between drug retention during the transfer to the lesion and an effective drug transit to the vessel wall to optimize the drug uptake. This transfer needs to be realized in a rather short time window, and the therapeutic drug dose should remain in the tissue for several weeks. This perfect balance can only be achieved through a combination of the balloon platform, the drug, the excipient, and the coating process.

DRUG

The most crucial component of every DCB is the drug. Paclitaxel has been the drug of choice for peripheral DCBs because of its highly lipophilic profile, fast tissue absorption, and the long tissue retention, which is a determinant for a positive long-term result, especially in the superficial femoral artery (SFA).

Paclitaxel's mode of action has been known since the 1960s and its use in oncology. It acts at the β -tubulin level,

impairs the microtubular assembly, and halts the cell cycle assembly between the G2 and M phase. The paclitaxel dose and coating formulation directly impacts biological performance. Excessive drug amount on the balloon can cause a systemic effect, and an amount that is too low impairs the effectiveness of the treatment.

There are different morphologic forms of paclitaxel used as coatings: amorphous, hybrid, macrocrystalline, crystalline, microcrystalline, and nano encapsulation; amorphous and microcrystalline are the forms most often used by medical device manufacturers. As shown by Granada et al, the type of crystallinity influences the pharmacokinetic behavior of the coating.¹ Despite releasing more particles than an amorphous coating, the crystalline coating allows a better transfer and much higher retention into the vessel wall.

COATING PROCESS

Coating homogeneity is key; uniform drug coating will lead to uniform vessel wall coverage during drug transfer. The coating process allows a good homogeneity as well as a dose control and reproducibility among the produced units.

The principal determinant of a DCB's biologic effect is the quantity and homogeneity of the drug transferred to the tissue wall. Unfortunately, due to the current technical capabilities, it is commonly accepted that only a reduced quantity of drug is actually transferred to the vessel wall. Some of the active component is washed off during navigation of the balloon to the target lesion, and some of the drug stays on the balloon after the inflation.

EXCIPIENT GOVERNS EFFICACY: BTHC, A HIGH-DRUG-RETENTION EXCIPIENT

The excipient is the other key element of a DCB coating. An excipient will protect the active drug component from washing off prematurely and optimize the drug uptake into the vessel wall. Excipient performance will determine the overall technical performance of the device, ensuring adequate balance between these two contradictory needs.

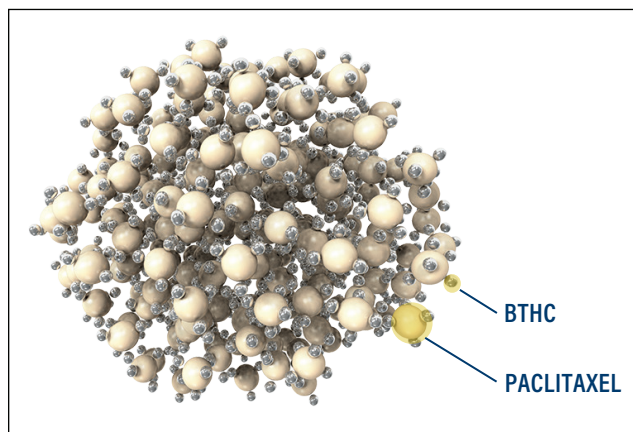


Figure 1. Paclitaxel and BTHC microcrystalline structure.

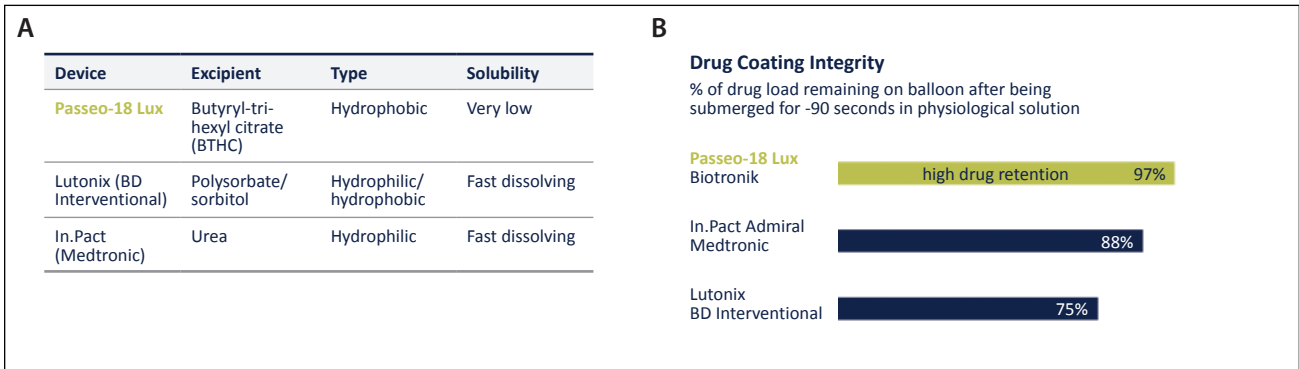
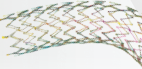


Figure 2. The Passeo-18 Lux's hydrophobic BTHC excipient is less soluble than hydrophilic alternatives (A), ensuring more drug is available at the lesion site (B).

Butyryl-tri-hexyl citrate (BTHC) is the excipient of the Passeo-18 Lux, which was screened among dozens of other excipients and selected for its capability to adhere to the balloon, low amount of particles generated, stability, and hydrophobic characteristics (Figure 1). BTHC is a hydrophobic excipient, meaning it tends to repel water. This characteristic helps prevent the drug from washing off prematurely during the transit to the target lesion, thus maximizing the drug availability at the target (Figure 2) (Data on file at Biotronik).

Does the presence of excipient correlate with clinical results? The only randomized controlled trial (RCT) conducted with a DCB without an excipient has been the only one that did not show significant improvement over the comparator percutaneous transluminal angioplasty (PTA) device.²

PROLONGED DRUG PRESENCE

The combination of BTHC and paclitaxel ensures an efficient performance of the drug at the target lesion over time. A preclinical porcine study demonstrated a prolonged presence of paclitaxel in the target vessel tissue up to 28 days following treatment (Figure 3) (Data on file at Biotronik). Systemic blood levels decreased to low levels after 7 days (Figure 4) and reached levels below quantification at day 28. There were no signs of adverse events related to the Passeo-18 Lux.

LIMITING DRUG LOSS DURING INSERTION

Keeping the drug safe and unaltered on the balloon during insertion in the introducer sheath is one of the main challenges for DCB manufacturers. Passeo-18 Lux uses a SafeGuard (Figure 5), a small plastic tube that protects the coating during handling, as well as protecting the user from getting in contact with the paclitaxel.

The principal benefit of the SafeGuard is to avoid contact between the coating and the valve of the introducer sheath and therefore protect the coating from scratches that could

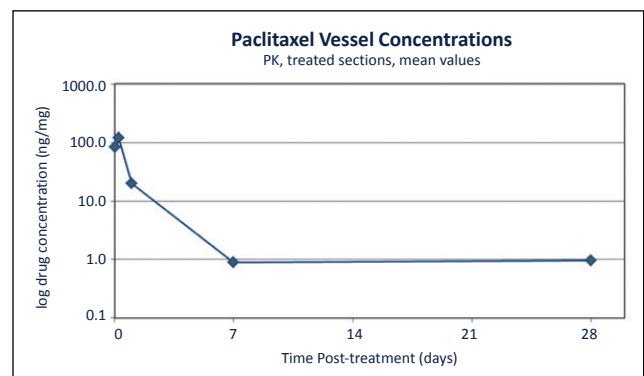


Figure 3. Local pharmacokinetic profile of paclitaxel in a porcine animal model.

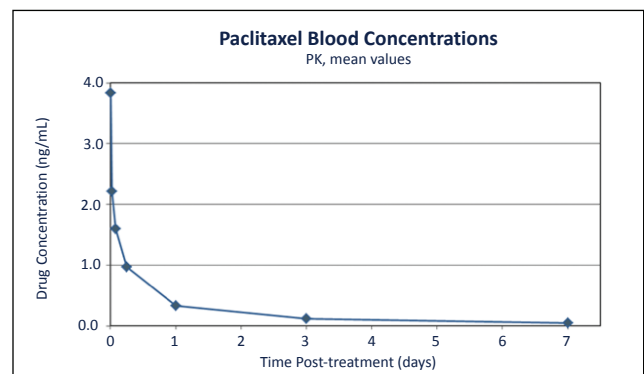


Figure 4. Normalized systemic paclitaxel blood concentrations over time.

result in drug loss or particulate generation. Independent testing demonstrated the benefit of SafeGuard in terms of drug loss (Data on file at Biotronik). It has been proven that the drug loss inside the introducer sheath valve was reduced by 94% (Figure 6). Using SafeGuard will result in a low 1.5% drug loss into the valve, thus offering very efficient protection against preliminary drug loss.

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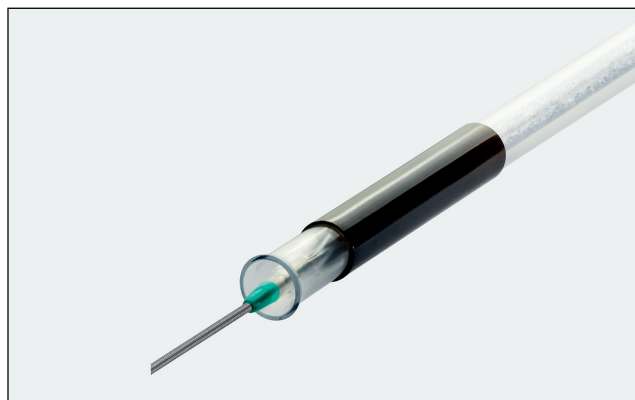


Figure 5. The SafeGuard is a small plastic tube that protects the Passeo-18 Lux's drug coating.

PARTICLE EMBOLIZATION

After release of the IN.PACT DEEP results,³ particle embolization became a highly discussed topic, but what is the real impact of downstream particle embolization? Histologically, there is an impact, as proven multiple times by Dr. Renu Virmani's research.⁴ In the clinical setup, the principal consequence of distal embolization would be amputation (minor or major), but it is difficult to correlate these findings to clear clinical consequences. Thus far, the main RCTs conducted in the SFA comparing DCB to standard PTA showed a very limited, if any, number of amputations. For the below-the-knee (BTK) indication, where particle embolization is considered the most harmful, the BIOLUX P-II RCT showed a 0% amputation rate at 30 days for the Passeo-18 Lux arm versus 2.8% for standard PTA (Figure 7).⁵ Though not statistically significant, these results show a trend toward safe use of Passeo-18 Lux in the BTK indication.

CLINICAL OUTCOMES FROM THE BIOLUX P-III REGISTRY

RCTs have proven the efficacy of DCB technology in the SFA region both in the short (≤ 12 months) and long

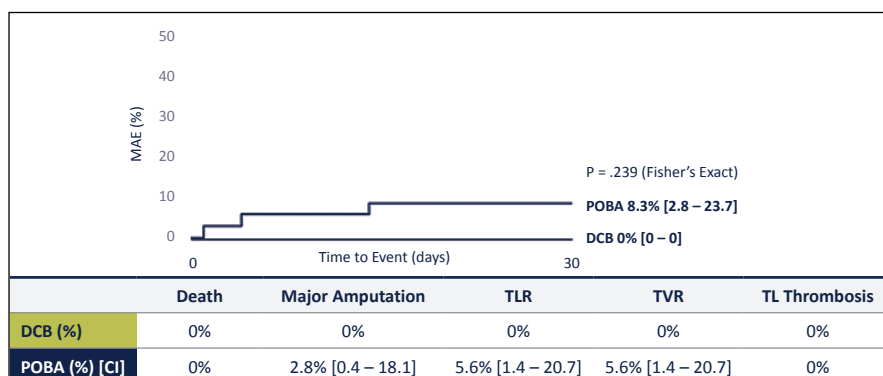


Figure 7. BIOLUX P-II showed a 0% amputation rate at 30 days for the Passeo-18 Lux arm.⁵

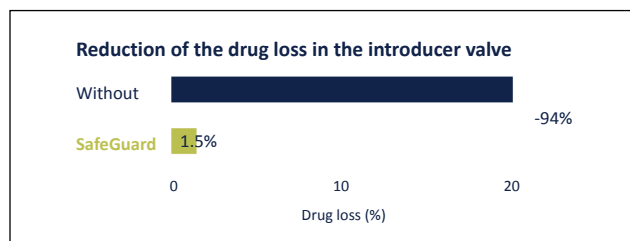


Figure 6. Independent testing demonstrated a 94% reduction in drug loss when SafeGuard was used. Data on file at Biotronik.

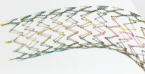
term. There are now published and reviewed data for a sustained benefit of up to 3 years for the In.Pact Admiral DCB (Medtronic).⁶

The transmission of this DCB data to real-world patients' symptoms and lesions is still a subject of debate. One of the main criticisms is that RCTs thus far have excluded a considerable number of patients, especially highly calcified and long, complex lesions as well as certain patient subsets, such as those with critical limb ischemia (CLI). All-comers registries try to overcome these issues. The BIOLUX P-III registry^{7,8} is one of the largest real-world DCB registries to date and has no exclusion criteria. It is a prospective, global, multicenter, all-comers registry, with the goal of further investigating the Passeo-18 Lux DCB's safety and efficacy in infrainguinal arteries in a real-world environment.

The primary endpoints are freedom from major adverse events (MAEs) at 6 months and freedom from clinically driven target lesion revascularization (CD-TLR) at 12 months. There were no limitations concerning patient characteristics or lesion characteristics, and use of additional devices was allowed. The registry was performed at 47 sites in 16 countries (Europe, Australia, Singapore, and Malaysia). The full cohort of the registry included 882 subjects with 1,085 lesions. There was an extension of enrollment to complete some predefined subgroups after the initially planned full cohort of 700 patients was completed. In the end, a total of 332 patients with CLI, 418 patients with diabetes, 150 patients with BTK lesions, 141 patients with heavily calcified lesions, 305 patients with complex lesions (TASC C/D), and 103 subjects with in-stent restenosis were included.

Patient and Lesion Characteristics

Compared to RCTs in this space, baseline patient characteristics included patients who were older (mean age, 70.1 ± 10.3 years), a higher percentage of women (36%), a high percentage of patients



with diabetes (47.6%), and 51.6% of patients had previous interventions. It is the only DCB registry thus far that has enrolled Rutherford 6 patients (9%).

Lesion baseline characteristics included a mean lesion length of 89 ± 77.1 mm, 54.1% were de novo lesions, 24.9% were total occlusions, 10.6% were in-stent restenosis, and 10.4% were restenotic lesions. Within this variety, 76.1% of lesions were calcified, with 44.6% showing either moderate or heavy calcification; 32.6% of lesions were TASC C/D, and 17.1% were located in the BTK area.

Procedural Approach

In 73% of the lesions, vessel preparation (mainly predilatation with standard PTA [88.3%], but other methods including cutting/scoring balloons and atherectomy were applied) was performed to increase drug uptake. The bailout stent rate was considerably low at 15.7%.

Results

At 365 days, freedom from CD-TLR was 93.5% (91.8%, 94.9%), and primary patency was 84.3% (81.8%, 86.4%). Not only was efficacy well proven, but there were no safety issues. Efficacy on one site was accompanied by a freedom from MAEs (defined by composite of device- and procedure-related mortality through 30 days, major target limb amputation, and CD-TLR) rate of 89.7% (87.4%, 91.6%). MAEs were adjudicated by an independent clinical events committee.

Although 332 patients with CLI were included in this real-world registry, the rate of freedom from major amputation at 12 months was 97.4% (96.1%, 98.3%).

These morphologic findings were consistent with clinical improvement—the most important finding for the patient; 81.9% of patients improved by at least one Rutherford classification after 1 year.

When we look at the BIOLUX P-III full cohort in context with other DCB registry data, it should be noted that:

- This registry addresses the largest CLI cohort so far (42.6% vs IN.PACT Global, 11%)⁹
- 47.6% of enrolled patients had diabetes versus an average of 40% in comparative registries
- 17.1% of BTK lesions were treated within the full BIOLUX P-III cohort compared to no BTK lesions included in any other real-world DCB registries so far
- Freedom from TLR was no different from other DCB registries (93.5% vs IN.PACT Global's 92.6%)

CONCLUSION

Despite the fact that most DCBs are efficient, they are not equal. Excipient and coating characteristics will govern the overall performance of a DCB and impact the clinical outcomes. A hydrophobic excipient such as BTHC will prevent paclitaxel from being prematurely washed off, enabling better

transfer of the drug to the lesion. Microcrystalline paclitaxel will ensure that drug remains in the tissue up to 28 days after treatment to inhibit the restenosis process.

These factors allow Passeo-18 Lux to claim significant advantage over standard PTA in terms of safety and efficacy in the SFA indication¹⁰ and safety over standard PTA in BTK treatment.⁵ The more recent real-world registry, BIOLUX P-III, showed excellent results in a very complicated patient population that included a high rate of patients with CLI and diabetes, especially in the BTK subgroup, which sends a strong signal that a DCB could be a valuable option for this indication.^{7,8} The Passeo-18 Lux technology is providing a robust clinical program to prove the safety and efficacy of this DCB in varied patient populations. ■

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