TITLE

Technology, Pharmacology, And Clinical Outcomes of Sirolimus Coated Balloons for Peripheral Arterial Interventions.

ABSTRACT

Introduction: Peripheral arterial intervention is a rapidly evolving field with a significant impact on an aging population.

Areas covered: Treatment concepts evolve rapidly, with new therapies providing sustainable and cost-effective solutions for complex patients.

Expert opinion: Metal stenting has been replaced by the "leave-nothing-behind" approach, and plain balloon angioplasty devices have been replaced by drug-coated balloons (DCBs). While paclitaxel was initially used, sirolimus has more recently shown promising outcomes. This review article provides an overview of the technology and pharmacology behind sirolimus-coated balloons (SRL-DCB) and presents existing clinical evidence of their use.

KEYWORDS

Peripheral vascular disease; Drug coated balloons; Restenosis; Sirolimus

ARTICLE HIGHLIGHTS

1. Peripheral arterial disease exerts a substantial global socioeconomic impact. The endovascular approach is often first line of intervention, and Drug-coated balloons (DCBs) have been developed to provide a "leave nothing behind" treatment.
2. Paclitaxel has been the primary drug used in drug-coated balloons. Sirolimus formerly in drug-eluting stents (DES) has now been recently adapted for balloon platforms.
3. The main challenges with drug-coated balloon technology are safe drug delivery and tissue distribution without distal drug migration. The arterial wall can act as a reliable reservoir for hydrophobic drugs like sirolimus. Sirolimus is distributed throughout the tunica media and adventitia and binds with vascular smooth muscle cells, preventing hypertrophy and vessel restenosis.
4. Nanoparticle-encapsulated sirolimus in phospholipid-based nanocarriers have been developed to minimize drug loss during delivery, enhance bioavailability, and accelerate drug uptake.
5. Early clinical data suggest sirolimus-coated balloons may achieve outcomes comparable to paclitaxel DCBs and superiority over plain angioplasty; yet long-term randomized trial data are required to confirm non-inferiority and safety.

1. Introduction

Peripheral arterial disease (PAD) is a chronic condition affecting the arterial tree of the lower limbs. The prevalence is very high in the general population (20 million cases in the US in 2015);

the rate increases continuously due to the aging of the population with a substantial global socioeconomic impact [1]. Endovascular interventions are an established form of management of patients with PAD aiming to alleviate symptoms, increase quality of life, and reduce amputation rate [2]. This is a continuously evolving field of medicine that embraces novel technology. The era of permanent metal stenting has evolved toward "leave-nothing-behind" strategies, in which DCBs deliver therapy without leaving a scaffold. The chemotherapeutic drug paclitaxel (PTX) has been the drug of choice for DCBs due to its effective tissue uptake during balloon inflation and prolonged retention in vessel walls. Although PTX was initially used in the first and second generations of coronary drug-eluting stents (DESs), it has been dominating the field and was linked to severe complications, and this triggered the necessity to look for other agents. Limus analogues have largely replaced PTX due to concerns about its cytotoxicity. Sirolimus (SRL), or rapamycin, an immunosuppressant drug, has recently been used in DCBs. SRL is considered safer, though its lower lipophilicity presents challenges for tissue absorption; it also exhibits lower stability, necessitating protective coating strategies or nanocarriers to achieve effective arterial concentrations. [3–6]. This review article aims to offer an overview of the technology and pharmacology behind those novel devices and present the existing clinical evidence of their use.

2. The -limus drug family

The first of the -limus family drugs used on endovascular prostheses was SRL, a natural macrocyclic lactone. All -limus family drugs are rapamycin derivatives used for various therapeutic contexts [7]. These drugs bind to FK-binding protein 12 and act as signal transduction inhibitors by inhibiting the mammalian target of rapamycin (mTOR), thus arresting the cell cycle

in the G1 phase (Figure 1). This mechanism prevents the degradation of p27Kip1, a cyclin-dependent kinase inhibitor, which prevents restenosis, promotes healing, and regulates protein synthesis, cell growth, proliferation, and angiogenesis [8].

The -limus family of drugs consists of amphilimus, everolimus, novolimus, pimecrolimus, sirolimus, tacrolimus, umirolimus, and zotarolimus (ZRL). These drugs exhibit structure, molecular weight, lipophilicity, and potency variations. For instance, ZRL, a relatively lipophilic analogue of SRL, boasts a shorter half-life [9]. Everolimus shows markedly elevated interaction with the mechanistic target of rapamycin complex 2, resulting in greater bioavailability and a lesser half-life when contrasted with SRL. It also diminishes vascular inflammation and illustrates faster endothelialisation [10]. Umirolimus is designed for local delivery to coronary arteries. It takes the top position for lipophilicity among the typical -limus drugs, facilitating its use in low-dose incorporation into free-polymer stents [11]. Novolimus is a metabolic transformation molecule of SRL and has shown strong suppression of smooth muscle cells in laboratory investigations. A study by Lee et al. indicated that sirolimus-eluting stents (SESs) outperform paclitaxel-eluting stents (PES) regarding anti-restenotic efficacy [12]. The main physicochemical properties of the -limus family of drugs is shown in Table 1.

3. Drug delivery concepts for DCBs

Achieving efficient drug delivery to ensure their precise vessel wall delivery can be challenging. Drugs adhere to the balloons' surface and are transferred to the specific location that needs to be treated. This adherence allows efficient and uniform drug transfer to the target area. The balloon can be deflated and withdrawn once the drug has been transferred to the vascular wall. This process

enables drug uptake by the tissue rapidly, ensuring immediate delivery to the target area, as shown in Figure 2. The medicines endure in the vessel wall, which facilitates and maintains the retention of drug release in its designated location. This is crucial for achieving a sustained therapeutic effect. The drug delivery mechanism should also prevent unintended distal migration. This is essential to reduce systemic toxicity. Moreover, the delivery mechanism should not stimulate restenosis, which can result from the injury induced by the delivery process.

4. Tissue distribution

Tissue distribution plays a crucial role in drug therapeutic efficacy DCBs. The primary objective of DCBs is the prompt administration of a large single dose to the vessel wall. The wall is a reliable drug reservoir for hydrophobic therapeutics, emphasizing the significance of efficient tissue uptake and sustained retention for DCB drugs [13]. Hydrophobic therapeutics can cross the inner hydrophobic core of cell plasma membranes in the endothelium [14]. This function grants for the effective distribution of the medication to the desired tissues. A case in point for hydrophobic therapeutic agents is the family of limus drugs, encompassing SRL and ZRL. These therapeutic agents exhibit substantial lipophilicity, (log P ≈4.2–4.5), favouring tissue retention [15]. The log value of the distribution constant serves as a more precise indicator of a molecule's lipophilicity [16]. Higher log values and increased hydration energy enhance permeability [17]. The limus family is highly lipophilic, with a log P of approximately 4. SRL, in particular, has a substantial apparent volume of distribution (5.6–22.8 L/kg), indicating extensive distribution across organs and tissues, contributing to its prolonged half-life [18–21]. The pharmacokinetics of ZRL, administered at a 2.5 mg/kg dose either intravenously or orally to rats and cynomolgus monkeys,

demonstrate high volumes of distribution (from 8.5 to 27.9 L/kg) and a prolonged apparent elimination half-life [22].

Table 2 highlights the differences between PTX and SRL. PTX accumulates in cytoskeleton-dense areas when thrombi are present due to its affinity for tubulin, allowing it to persist longer in deeper arterial layers for extended therapeutic effect [23]. In contrast, SRL's targeted distribution in the tunica media is linked to the expression of its binding target, FKBP12, in vascular smooth muscle cells (VSMCs), which are vital in hyperplasia. Additionally, after angioplasty, FKBP12 is upregulated in neointimal smooth muscle cells, enhancing SRL's activity in hyperplastic tissues and supporting its role in preventing restenosis [24]. An animal model study comparing various drugs employed in DCBs found that PTX maintains better tissue retention than SRL [25, 26]. However, disease-induced physiological changes in the arterial wall composition can affect the drug distribution. It is worth mentioning that the lipid constitution and complexity of the arterial wall can influence the sensitivity of SRL derivatives less than that of PTX [27]. ZRL shows comparable uptake and efficacy but has a different distribution pattern, concentrating mainly in shallower layers, while PTX reaches greater depths, as shown in Figure 2 [28].

5. Coating

5.1. Crystalline coating

Crystalline drug coatings have emerged as a promising advancement in medical technology, particularly for DCBs. Recognized as first-generation DCBs, these coatings have several benefits compared to their amorphous alternatives. One of the distinctive strengths of a crystalline drug coating is its slow dissolution rate. The drug's crystalline arrangement enables a sustained release of the active compound, guaranteeing a controlled and long-lasting transport of the drugs to the intended tissues. This sustained drug delivery can play a pivotal role in increasing the effectiveness of the treatment and improving patient outcomes. An additional benefit of crystalline coatings is their capacity to enhance stability, which can extend the shelf-life of the coated device. Achieving the desired coating crystallinity heavily depends on manufacturing and precise drying techniques. Through diligent management of these variables, manufacturers can maintain the durability and functionality of the crystalline coating over an extended period. While the use of crystalline coatings in DESs of -limus drug family is still relatively limited compared to paclitaxel-coated devices, recent advancements have revealed some promising outcomes. Solvent-free electrostatic coating processes were introduced to create crystalline coatings for DESs [29]. Moreover, a crystal seeding process utilizing SRL seeds has been implemented to promote the growth of crystalline coatings [30]. Crystalline SRL coatings offer drug stability and prolonged release[29,- 31].

5.2. Non-crystalline or hybrid/amorphous coating

Technological evolution led to the development of non-crystalline or hybrid/amorphous coatings. This approach utilizes a unique drying process on the balloon's surface. A study conducted by Clever et al. investigated an exclusive drying process to obtain amorphous and crystalline coatings

using identical excipients, namely iopromide. The scientists successfully dispersed a precise volume of organic solvents containing SRL and different matrix-forming additives onto the balloon's surface, yielding SRL dosages of 7 $\mu g/mm^2$ or lower. Non-crystalline coatings provide numerous advantages. Initially, amorphous coatings have demonstrated superior drug release kinetics compared to their crystalline counterparts. Accordingly, the drug is released in a more controlled and sustained manner, ensuring a prolonged therapeutic effect. This attribute plays a critical role in preventing restenosis and improving patient prognosis. Furthermore, amorphous coatings have shown enhanced adherence to the balloon surface, preventing premature drug release or displacement during the balloon's deployment and inflation. The drug's uniform distribution within the coating also enhances its stability and effectiveness [32,33].

Additionally, using hybrid coats allows for incorporating multiple drugs, making it possible to administer combination therapy within a single treatment option. This adaptability supports a potentially personalized and precisely targeted approach to patient care. Despite being at the early phases of adoption in clinical practice, non-crystalline coatings have indicated positive results in initial studies. The enhanced drug release properties and stability offered by these coatings have the potential to revolutionize the field of endovascular interventions, presenting more efficacious treatments for patients suffering from vascular diseases.

5.3. Nano-encapsulation/microcrystalline coating

DCBs employing nanoparticles, which encapsulate SRL in a phospholipid-based nanocarrier, have also been developed. These nanoparticles are designed with a specific diameter linked to a particular drug dosage equivalent to a specific balloon surface area. The nanoparticles are applied as coating via a spraying technique. A vital advantage of the process is the capacity to minimize

drug loss during the delivery, enhance bioavailability, and get more rapid drug uptake. In addition, nanocarriers can improve balloon's biocompatibility, ultimately lowering the likelihood of adverse responses [34]. In the context of an experimental rabbit iliofemoral artery injury model, the SRL-encapsulated nanocrystals within a phospholipid liposome coating maintained their presence in the arterial tissue for two weeks. This prolonged presence significantly reduced neointimal hyperplasia [35]. In different investigations, the performance of non-polyethylene glycol (PEG)-ylated SRL-loaded phospholipid liposomes with a 14 nm size and PEG-ylated SRL-loaded phospholipid liposomes with a size of 90 nm were evaluated for non-endovascular device delivery in a rat carotid injury model. The results indicated that the smaller liposomes successfully prevented restenosis after a 14-day treatment period [36]. Lipid-based nanocarriers, including solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), have been investigated to incorporate SRL. This approach offers sustained drug release and increased drug-loading capabilities [37].

The development of the DCBs was also driven by the challenges associated with the poor solubility of anti-proliferative drugs like SRL. To overcome this, nanoparticle albumin-bound (NAB)-rapamycin was investigated [38]. This formulation uses albumin as a drug carrier and has shown promising results in anti-restenotic therapy [38, 39]. The DCB utilizes bioadhesive polymers that stay localized at the site of the inflated balloon, promoting sustained drug release. Following the specified duration, they degrade without causing any harm to the surrounding tissues [40]. In contrast, a polymer-free coating method was created to address concerns about the potential irritations caused by biodegradable polymers. With this technique, the drug and excipients are coated onto the balloon's surface in separate layers to avoid mixing.

6. Sirolimus drug coated balloons for peripheral arterial disease.

Two main products have been developed for peripheral arterial interventions and used in clinical practice: the Selution SLR™ (MedAlliance CardioVascular SA, CH) and the MagicTouch™ (Concept Medical Inc, US), as shown in Table 3.

6.1. Selution

The Selution SLR™ combines amphipathic lipid cell adherence coating with SRL biodegradable micro-reservoirs to increase drug uptake into the arterial wall—the approximate drug loading on the Selution SLR 1 μg/mm^2. Besides the drug, the coating formulation of the Selution SLR DCBs consists of four excipients intermixed using a specific ratio. The first excipient is a biodegradable polymer polylactic-co-glycolic acid (PLGA). The remaining three excipients constitute a phospholipid blend with previous human vascular use. These phospholipids aim at reducing drug coating wash-off in the bloodstream during insertion, tracking, and lesion crossing, optimizing drug transfer to the tissue during the short-term balloon dilatation, and helping to adhere the micro-reservoirs to the surrounding tissue when the balloon is deflated and removed.

6.2. MagicTouch

The MagicTouch™ (Concept Medical Inc., Tampa, FL, US) employs phospholipid to achieve 100% SRL sub-micron particle coating on its balloon surfaces, allowing controlled drug delivery into the arterial wall. The balloon is homogeneously coated with SRL through spray coating. SRL is encapsulated in a protective lipophilic package, allowing diffusion and penetration into the vessel wall during balloon inflation. The total dose of SRL corresponds to 1.25 mg/mm^2 of the balloon's surface.

6.3. Trials

Choke et al.'s focused on femoropopliteal and below-the-knee (BTK) disease, yielding a 100% success rate in technical and device performance [41]. Additionally, the trial reported a 12-month freedom from clinically driven target lesion revascularization (TLR) of 89.7%, amputation-free survival (AFS) of 81.6%, limb salvage at 92.9%, and wound healing in 84.6% of cases. The Selution SLR study's preliminary findings in femoropopliteal disease are encouraging similarly, showing an 88.4% primary patency, 91.2% freedom from restenosis, and an 85% freedom from TLR at 12 months [42].

The ongoing SELUTION4BTK study assesses the Selution SLR 014 DCBs in BTK atherosclerotic disease treatment among patients with critical limb ischemia [43], complemented by the smaller PRESTIGE study, which also examines BTK disease in such patients [44]. The PRESTIGE study specifically investigates the effects on long tibial occlusive lesions and has reported a 100% technical success rate, 87% freedom from TLR at 24 months, and 75% amputation-free survival.

Building upon the PRESTIGE study, the PRISTINE study evaluates Selution SLR's impact on more complex and longer (>10 cm) infra-inguinal occlusive lesions in femoropopliteal and tibial vessels [45]. Its preliminary results have shown a 72.6% rate of amputation-free survival and complete wound healing in 79.2% of patients. The SIRONA trial aims to establish the non-inferiority of the sirolimus-coated balloon (SCB) compared to paclitaxel-coated balloon (PCB) in femoropopliteal disease and its superiority over plain old balloon angioplasty (POBA) [46]. Success in this trial could substantiate the use of SCB as an effective alternative for femoropopliteal disease treatment. The LIMES study also explores the effectiveness of SCB in

BTK disease and critical limb ischemia (CLI), including comparisons of non-inferiority to POBA [47].

The PREVISION trial is currently evaluating the feasibility of BD SCB in treating femoropopliteal arteries, with initial results expected in November 2025 [48]. Lastly, Todd et al. have undertaken a novel approach to SRL drug delivery by utilizing a liquid form, demonstrating improved drug integration into the arterial medial layer compared to balloons or stents in drug delivery [49].

These studies highlight the potential of SCB as a promising alternative. Various trials show high technical success, favourable patency rates, and promising outcomes in limb salvage and wound healing. The trials that involve SCBs are presented in Tables 4 and 5.

7. Conclusion

The emergence of different generations of drug coatings has marked the evolution of DCB technology. The latest generation of DCBs has harnessed nanotechnology to encapsulate SRL in nanoparticles, ensuring efficient drug distribution, reduced drug loss during delivery, and enhanced biocompatibility. Tissue distribution of drugs in DCBs is critical for therapeutic efficacy. Lipophilic drugs like SRL have demonstrated efficient distribution within arterial walls, contributing to their effectiveness in preventing restenosis.

In summary, the pharmacodynamics of sirolimus-coated balloons (SRL-DCBs), including their drug coatings, excipients, tissue distribution, and preparation processes, have advanced significantly. Preliminary clinical results are encouraging, but pivotal randomized controlled trials with long-term follow-up will be critical to validate their efficacy and safety.

8. Expert opinion

The "leave-nothing-behind" concept has revolutionized how peripheral lesions are treated endovascularly. Operators unanimously recognized the necessity of offering a treatment that would not trigger neointimal hyperplasia, even in complex lesions. The first drug that was used in DCBs was PTX in 2007. The first SCB was marketed in 2016. Both drugs appear to offer a valid outcome in terms of reduction of neointimal hyperplasia, even though there are significant differences between them. PTX stays in the vessel wall for weeks and, in some cases, months, and as previously stated, can exert some cytotoxic effects in the case of over-dosage. This effect has created some concern in the past and, as mentioned in the paper, underwent significant scrutiny and review of all the long-term studies from the involved authorities. The latest on that is that on the 11th of July 2023, the US Food and Drug Administration issued an update on the use of PTX-coated devices in treating peripheral arterial disease, stating that it is "unlikely" that their use increases mortality. The final recommendation was to discuss the risks and benefits of all available treatment options, continue routine monitoring of patients treated with PTX-coated devices, and report any potential adverse events. This re-confirmation of using PTX creates a new dynamic for peripheral intervention. While the international community awaited this verdict, SCBs gained space in clinical practice and produced new evidence.

The following period will undoubtedly lead to a direct comparison of PCBs vs SCBs. This was recently attempted for coronary disease by Ninomiya et al. [50] in a head-to-head randomized, multicenter study enrolling 121 patients with de novo small vessel disease. The study, however, failed to prove the non-inferiority of the MagicTouch (Concept Medical) SCB (1.27 mg/mm^2) vs the SeQuent Please NEO (B. Braun) PCB (3 mg/mm^2) PTX in terms of angiographic net diameter gain at 6 months. Scheller et al. [51] presented more favorable results for SRL with noninferiority in late lumen loss in another similar study. In the peripheral circulation the most interesting data

290 come from the preliminary outcomes of the SIRONA trial that confirm non-inferiority regarding
291 primary patency and primary safety outcome of the MagicTouch SCB vs various PCBs at 12
292 months for femoropopliteal lesions [72]. Furthermore, in the SUCCESS PTA trial, the Selution
293 SLR was on par with Ranger (Boston Scientific), In.Pact Admiral (Medtronic), and Passeo-18
294 (Biotronik), when it came to freedom from clinically driven TLR [70].

295 From the coronary data, the information obtained is that the efficacy of SCBs depends on the
296 design of each device, the drug coating and formulation, the drug transfer, and the drug retention.
297 As shown in a previously published porcine study [52], balloons that retain SRL in the vessel wall
298 due to a highly crystalline coating appear more effective than those with a minimal amount of
299 drug. Therefore, the concept of "micro depots" that offer sustained local drug delivery is
300 paramount for the design of DCBs. Hence, the main technical challenges of SCB are tissue
301 absorption and retention. For tissue absorption to get SRL to enter arterial tissue within 180
302 seconds of balloon dilatation, some "instant glue" is required to transfer the drug from the balloon
303 to the tissue efficiently. For tissue retention, some "time release mechanism" must be employed to
304 maintain therapeutic levels, and SRL is continuously delivered over time. The novel technology is
305 based on converting SRL into sub-micron-sized particles that are then encapsulated into a highly
306 biocompatible phospholipid drug carrier. When the balloon is inflated, the drug carrier with SRL
307 inside gets transferred to the vessel wall following the principle of coefficient diffusion. Upon
308 body pH variation, the drug carrier mimics the body lipids and liberates SRL, and the sub-micron-
309 sized SRL particles penetrate the deepest layer of the vessel. This mechanism is expected to offer
310 drug in the vessel wall for at least 7 days.

While existing evidence suggests non-inferiority, definitive conclusions await pivotal trials. Further studies in this direction with head-to-head comparison will help identify the best treatment for peripheral arterial disease. Nevertheless, the main issues of paclitaxel namely the aneurysmal dilatation of the treated segments and the distal embolization of crystallin amorphous drug, appear resolved with the limus devices. Future directions will include the use of adjunct devices like temporary stent systems that will act in conjunction with sirolimus like in the DEEPER LIMUS study [75], for the treatment of BTK lesions where paclitaxel has been historically rather ineffective.

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Declaration of interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical approval

Not applicable

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None

Figure legends

Figure 1. Limus drugs bind to FK-binding protein 12 and act as signal transduction inhibitors by inhibiting the mammalian target of rapamycin (mTOR), thus arresting the cell cycle in the G1 phase.

Figure 2. Drug delivery and tissue distribution of DCBs.

Table legends

Table 1. The main physicochemical properties of the -limus family of drugs

Table 2. The differences between PTX and SRL

Table 3. List of limus eluting balloons currently on the market and their stated treatment purpose.

Table 4. List of completed SCB studies. *SCB, sirolimus-coated balloon; SLR, sustained limus release; FP, femoropopliteal; BTK, below-the-knee; CD-TLR, clinically-driven target lesion revascularisation, PP, primary patency¨*

Table 5. List of on-going SCB studies. *SCB, sirolimus-coated balloon; SLR, sustained limus release; FP, femoropopliteal; BTK, below-the-knee; CD-TLR, clinically-driven target lesion revascularisation, PP, primary patency*

366 **Table 1.**
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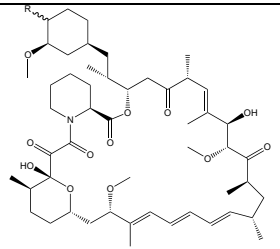
Name	Molecular structure	Physical appearance	Solubility	Stability	Author
Siro limus	 Sirolimus , R = OH Zotarolimus , R = Everolimus , R = HO $C_{51}H_{79}NO_{13}$ MW = 914.19 g/mol	Colourless crystalline solid	▪ Soluble in chloroform (5 mg/ml), methanol (25 mg/ml), DMSO (25 mg/ml), ethanol, ether, acetone, and DMF ▪ Very sparingly soluble in hexane and petroleum ether ▪ Insoluble in water	▪ 10 mg/ml solution in methanol was kept at 2-8 °C for one week with no decomposition. ▪ Unless otherwise indicated, solutions are best prepared fresh and protected from light.	[53–54]
Zotaro limus	$C_{52}H_{79}N_5O_{12}$ MW = 966.23 g/mol	White crystalline powder	▪ Soluble in DMSO and DMF (15 mg/mL), Ethanol (20 mg/mL) ▪ Insoluble in water	Powder ▪ -20°C 3 years ▪ 4°C 2 years In solvent ▪ - 80°C 6 months ▪ - 20°C 1 month	[55]
Evero limus	$C_{53}H_{83}NO_{14}$ MW = 958.24 g/mol	Yellow amorphous powder the active substance is hygroscopic	▪ Soluble in ethanol, methanol, acetone (>10% m/V) with low permeability ▪ Insoluble in water (< 0.01%)	Unstable at temperatures above 25 °C and is sensitive to light, acid, base, and hydrogen peroxide	[56–57]

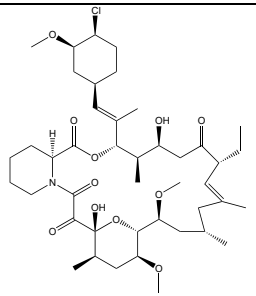
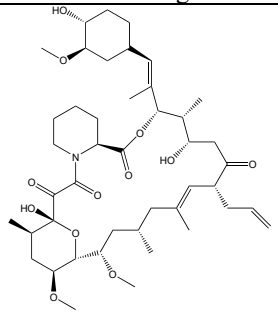
Pimecrolimus	 $C_{43}H_{68}ClNO_{11}$ MW 810.46 g/mol	White crystalline powder	▪ Soluble in methanol and ethanol ▪ Insoluble in water	▪ Stable at 25°C, excursions permitted to 15°C-30°C ▪ Do not freeze	[58]
Tacrolimus	 $C_{44}H_{69}NO_{12}$ MW 804.03 g/mol	Colourless crystalline powder	▪ Soluble in methanol, ethanol, acetone, ethyl acetate, and ether ▪ Insoluble in water	▪ Stable at +4°C or −20°C	[59]

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Table 2.

Author	Topic	PTX	SRL		
			Without protecting coat	With protecting coat	Nanocarrier
[6,60,61]	Lipophilic property	High lipophilic property	▪ Less lipophilic properties than PTX	▪ The design of encapsulating SRL in a protective lipophilic package effectively overcomes SRL's low lipophilicity.	▪ Increase lipophilicity
[6,60]	Drug dissolution	Low drug dissolution	▪ Low drug dissolution	▪ Minimize particulate generation ▪ Resistance to drug loss	▪ Reduce drug loss
[6,60,61]	Drug absorption	Quick absorption	▪ Absorption into the capillary bed and surrounding tissue	▪ The design of encapsulating SRL in a protective lipophilic package allows the drug to diffuse and penetrate the arterial wall effectively during balloon inflation.	▪ Facilitate efficient transfer to the vessel wall and enhance drug uptake without causing embolization
[6,12]	Drug distribution	Favourable tissue uptake	▪ SRL is uniformly distributed throughout the tunica media and adventitia at equilibrium.	▪ Slow to the target site ▪ Low drug transfer rate ▪ Efficient tissue uptake	▪ Increase bioavailability ▪ Leading to faster uptake of tissue
[6]	Sustained therapeutic effect	PTX maintains better tissue retention than SRL	▪ Disease-induced physiological changes in the arterial wall composition affect the distribution of SRL derivatives less than that of PTX.	▪ Promote effective drug retention	▪ Enhance retention
[6,12]	Stability	Stable	▪ Unstable ▪ Need protecting coat	▪ Reducing SRL degradation ▪ Enhancing SRL stability	▪ Increase stability
[6,12,62]	Efficacy	Strong efficacy (an effective antitumor drug)	▪ Affecting efficacy	▪ Amphiphilic excipients, such as polysorbates, can enhance drug coating integrity. ▪ Higher interaction with mechanistic target ▪ More rapid endothelialisation	▪ Improve therapeutic outcome
[6,63,64]	Safety	Cytotoxicity concern	▪ Safer	▪ Safe with acceptable angiographic and clinical outcomes ▪ Confirming the safety and effectiveness of DCBs in complex femoropopliteal lesions at 12 months	▪ Reduce systemic toxicity

374 **Table 3.**

Limus coated balloon	Type of limus	Manufacturer	Treatment purpose
SeQuent SCB	SRL	B. Braun	In-stent-restenosis and de-novo lesions
MagicTouch	SRL	Concept Medical	In-stent restenosis, small vessels, bifurcation lesions, and de-novo lesions
Selution SLR	SRL	Cordis	Peripheral artery disease
Virtue	SRL	Orchestra BioMed	Artery disease, in-stent restenosis
Devoir	SRL	APR Medtech	In-stent restenosis, small vessels where the DESs is not feasible, bifurcating lesions, stenotic portions including total occlusions

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377 **Table 4.**

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Author, year, name of trial	Balloons involved	Segment treated	Study details	FU	Outcomes
Zeller T, et al. [65], 2020, FIM SELUTION	Selution SLR DCB	FP	Prospective, controlled, multi-center, single-arm 50 patients, Rutherford 2-3	6M	PP 88.4%, freedom from angiographic binary restenosis 91.2%, significant improvement over baseline in Rutherford categories and in ABI measurements
Tang TY, et al. [44], 2021 PRESTIGE Study	Selution SLR DCB	BTK	Single-center, prospective, non-randomized, single-arm, 25 patients Rutherford 5	6M	PP 81.5%, freedom from CD-TLR 83.3%, AFS 84.0%, mean Rutherford score improved significantly, wound healing rate was 81.0%
Tang TY, et al. [67], 2024, PRISTINE Registry	Selution SLR DCB	BTK	Single-center, prospective, non-randomized, single arm 75 patients, Rutherford 5- 6	12M	PP 58%, freedom from CD-TLR 74%, mean Rutherford score improved significantly, wound healing rate was 79%
Iida O, et al. [68], 2024, SELUTION SFA Japan	Selution SLR DCB	FP	Multicenter, prospective, single-arm 134 patients, Rutherford 2-4	12M	PP 87.9%, freedom from CD-TLR 97.0%, major adverse event rate was 6.7%, ABI improved significantly from 0.73 ± 0.16 at baseline to 0.96 ± 0.14 at 30 days post-procedure and was sustained through 12 months (0.94 ± 0.13).
Choke ETC, et al. [66], 2024, 3-Year Outcomes of the XTOSI Trial	MagicTouch PTA SCB	FP and BTK	Single-center, prospective, single-arm, 50 patients, Rutherford 5- 6	36M	FP: freedom from CD-TLR 92.9%, freedom from major amputation 93.3%, AFS 70%, and overall survival 70%. BTK: freedom from CD-TLR was 77.8%, freedom from major amputation was 81.0%, AFS was 58.6%, and overall survival 58.6%.

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380 **Table 5.**
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Name of trial	Balloons involved	Segment treated	Study details	Status/ Preliminary results
FUTURE SFA [69] (NCT04511234)	MagicTouch PTA SCB vs POBA	FP	Randomized, double blind, placebo-controlled, multi-center trial, 279 patients, Rutherford 3-6	Recruiting
SUCCESS PTA [70]	SELUTION SLR 018	FP and BTK	Real world, prospective, multicentre, single arm post market surveillance study 723 patients from 27 sites, Rutherford 4-6	Freedom from CD- TLR 91.1%, target lesion amputation rates 2.2% at 12 m
SELUTION SLR™ 014 BTK (NCT05055297) [71]	SELUTION SLR 014 vs POBA	BTK	Prospective, randomized, multicenter, single blinded study 376 patients, Rutherford 4-5	Recruiting
SIRONA (NCT04475783) [46, 72]	MagicTouch PTA SCB vs paclitaxel DCBs	FP	Prospective, multicenter, 482 patients, Rutherford 2-4	At 12 months, PP and primary safety outcome show non-inferiority of the SCB with similar functional outcomes between the two groups
LIMES NCT04772300 [47,]	MagicTouch PTA SCB vs POBA	BTK	Prospective, interventional, multicenter 230 patients, Rutherford 4-6	Recruiting
SirPAD [73]	MagicTouch PTA SCB vs POBA	FP and BTK	Prospective, two-center 1200 patients, Fontaine stage (classes III-IV)	Active, not recruiting

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