Factors Influencing 1st and 2nd Generation Drug-Eluting Stent Performance: Understanding the Basic Pharmaceutical Drug-in-Polymer Formulation Factors Contributing to Stent Thrombosis Do We Really Need to Eliminate the Polymer?

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Received, June 18, 2021; Revised, July 28, 2021; Accepted, August 8, 2021; Published, August 22, 2021

ABSTRACT -- Drug-eluting stents (DES) have a major role in treating cardiovascular disease. The evolution of bare metal stents into 1st generation durable-polymer DES (DP-DES) reduced the rate of in-stent restenosis (ISR) and the need for repeat-revascularization. However, clinical outcomes showed similar rates of late stent thrombosis (ST<1 year) and higher rates of very late stent thrombosis (ST>1 year) necessitating the advent of 2nd generation more biocompatible polymer DES and biodegradable-polymer DES (BP-DES) that reduced ST rates with shorter dual anti-platelet therapy (DAPT). Despite the improvements in drugs and polymer biocompatibility for both durable and biodegradable polymers, stent thrombosis remains an issue. Doubts remain about the safety and efficacy of the more biocompatible 2nd generation durable polymers in respect to vessel inflammatory and thrombogenic response as compared to biodegradable polymers despite clinical trial and meta-analyses evidence indicating that 2nd generation DP-DES are non-inferior to BP-DES for stent thrombosis. A long-term presence of the polymer can cause inflammation and thrombogenesis. However, the cause of stent thrombosis is multi-factorial from a drug-in-polymer formulation perspective; e.g., drug release kinetics, drug physiochemical and pharmacological properties, degradation kinetics; polymer biocompatibility and hemocompatibility and coating properties. It appears that the focus should be on controlling burst release and developing more biocompatible, durable polymers, especially considering the cost of PCI utilizing biodegradable, polymer-free and bioresorbable scaffolds. This may give an insight into certain DP-DES effectiveness as compared to BP-DES for the existing clinical data and improve future stent development.

INTRODUCTION

Drug eluting stents revolutionized the treatment of cardiovascular disease in percutaneous coronary intervention (PCI). Each year, millions of patients are treated with PCI world-wide to relieve symptoms of coronary artery disease [1, 2]. In comparison to bare metal stents which only provide mechanical support following stent expansion at the site of the lesion, DES release an anti-proliferative drug from a polymer matrix coating metallic struts in order to prevent arterial smooth muscle (SM) cell proliferation and neointimal hyperplasia at the site of vessel injury. The presence of anti-proliferative agent in DES, as well as the advent of more biocompatible and biodegradable polymers and thinner/biocompatible scaffolds, reduced the incidence of in-stent restenosis (ISR) to < 10% [3, 4]. However, stent thrombosis remains an issue despite the improvements in drug type, polymer and struts, requiring DAPT medical therapy from 6-12 months for those undergoing PCI, which is especially unfavorable in high-risk bleeding patients [5, 6]. A possible reason for stent thrombosis is delayed endothelial and wound healing, as the therapeutic agents in DES also inhibit endothelial cell (EC) proliferation and migration in addition to inhibiting SM cell proliferation [7-11]. Stent thrombosis is associated with high rates of morbidity and mortality, often leading to major adverse events of cardiac death and myocardial infarction (MI) [12-14].

Durable polymers in 1st generation DES have been shown to contribute to the thrombogenic response in arterial tissues as a result of tissue inflammation, delayed vascular healing and incomplete re-endothelization of the stent [15, 16]. Although 2nd generation durable polymers are more biocompatible and less thrombogenic than 1st generation durable polymers, doubts remained about

their long-term safety and efficacy, leading to the advent of biodegradable polymer systems [17].

There is an ongoing debate about the efficacy of BP-DES in PCI over 2nd generation DP-DES given the cost of the former and existing clinical trial and meta-analyses evidence suggesting 2nd generation DP-DES to be non-inferior to BP-DES for late and very late stent thrombosis outcomes. Up until recently, this has been partly due to the short duration of clinical trials (1-yr) and insufficient data covering patient population with more severe coronary artery disease. Recent clinical data from the 2-yr BIOSTEMI trial showed that the DP-DES (Xience, Abbot) performance was non-inferior to a BP-DES (Orsiro, Biotronik) in ST-segment elevation myocardial infarction patients for very late stent-thrombosis. According to the ISAR-Test 4 trial (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) 2nd generation durable polymer everolimus-eluting stent (Xience, Abbot) was non-inferior to biodegradable polymer sirolimus-eluting stent (Yukon Choice PC) for a 10-year outcome in definite/probable and definite ST in a high-risk cohort (≈40% with ACS, 28% with diabetes mellitus, 86% with multi-vessel coronary disease). The main limitation of the trial was loss to follow-up of ≈17% of the randomized cohort [18]. Ten-year follow-up data showing a lack of late advantage of BP-DES over 2nd generation DP-DES is consistent with results from other studies of medium-term duration of thin-strut DES, which asks the question as to whether paying a higher price for BP-DES (in certain healthcare systems) is justifiable [19, 20]. A prospective systemic review and meta-analysis of nine clinical trials comparing Orsiro BP-SES against biocompatible DP-DES showed no statistically significant difference for stent thrombosis between the two groups [21].

Results from the HOST-REDUCE-POLYTECH-ACS clinical trial comparing durable DES to biodegradable DES in patients with acute coronary syndrome (ACS) showed that durable polymer DES were non-inferior to biodegradable polymer DES for 1-year clinical outcomes post PCI with extremely low rates of late stent thrombosis (ST<1 year) [22]. It was surprising to see a group of BP-DES with Orsiro among them fail to outperform DP-DES for late stent thrombosis. Recent 2-year clinical data from the BIOSTEMI trial comparing DP-DES Xience (Abbot) to BP-DES Orsiro (Biotronik) in STEMI patients also showed that DP-DES Xience performance was non-inferior to BP-DES Orsiro performance for stent-thrombosis [23]. Taking a closer look at drug physiochemical and pharmacological properties, polymer properties and release kinetics associated with burst release linked to stent thrombosis may shed light on clinical outcomes showing 2nd generation DP-DES to be non-inferior to BP-DES for late and very late stent thrombosis. Biodegradable polymer DES have a lower rate of stent thrombosis as compared to 1st generation DES, but not compared to the 2nd generation more biocompatible durable polymer DES. [24]

Late stent thrombosis has been attributed to delayed healing and the presence of uncovered struts due to inhibited re-endothelization of stent metallic scaffold [25, 26]. It is important to note that, more than just the durable as compared to biodegradable nature of the polymer and the characteristic inflammatory response, drug release kinetics characterized by initial burst release have been associated with stent thrombosis. This is a result of delayed arterial healing/impaired re-endothelization and toxic drug levels for higher doses in case of both durable and biodegradable polymer DES [27-32]. A rapid, uncontrolled initial release of drug and rapid release rate may cause tissue toxicity without sustaining efficacious drug therapeutic levels long-term due to systemic loss, leaving the tissue exposed to polymer known to cause inflammation and, thus delaying vascular healing and inhibiting re-endothelization [27, 33]. Also, burst release can subject arterial tissue to more drug than it can absorb and retain [31]. High and extreme drug doses overwhelming tissue receptors can cause augmented fibrin deposition, intra-intimal hemorrhages, mural thrombus, medial necrosis and excessive arterial expansion, all associated with stent thrombosis and exacerbated neointimal tissue [28, 29]. Both durable and biodegradable DES systems are associated with burst release, which may provide an explanation for DP-DES non-inferiority to BP-DES performance for stent thrombosis regardless of the polymer permanently remaining in arterial tissue following stent implantation.

As a result, one of the major challenges in DES performance has been developing an optimal release profile to keep drug concentration at efficacious but sub-toxic levels in the arterial tissue over a sufficiently long enough time period to prevent smooth muscle cell proliferation and subsequent restenosis without inhibiting re-endothelization. At the same time, drug elution profile should be sustained for a long enough time-period to provide anti-restenotic effects, especially until the polymer

degrades in case of biodegradable polymers. It is also important to note that some durable polymers have proven to be extremely biocompatible and hemocompatible and are not associated with pH changes to the biological environment resulting from polymer degradation that can lead to local inflammation at acidic pH [34, 35]. Also, drug physiochemical properties play an important role in the dissolution kinetics and drug uptake and retention by the surrounding tissue. Polymer properties, such as hydrophilicity, degree of crystallinity, pore size and pore density, influence drug diffusion through polymer matrix and drug release. Polymer blends, addition of plasticizers and drug load to polymer ratio can change polymer physical, mechanical, and thermal properties and, subsequently, influence drug release kinetics. Understanding formulation components in respect to drug type, release kinetics, factors influencing release kinetics and burst release, certain coating techniques associated with burst release, as well as polymer hemocompatibility can help explain the non-inferiority of more biocompatible durable DES as compared to biodegradable DES for late stent thrombosis.

STENT STRUCTURE AND FUNCTION

A standard durable or biodegradable polymer drug-eluting stent system consists of 3 components: (1) a metallic platform, (2) a drug carrier vehicle in which the pharmacological agent is dissolved or dispersed in reservoir or polymer matrix from which it diffuses into the vascular tissue in a local, site-specific controlled fashion over an extended time period from weeks to months without causing tissue or systemic toxicity and (3) an effective pharmacological agent that reduces SM proliferation and neointimal hyperplasia induced by stent implantation causing injury to the arterial vessel wall [36]. The cross-section of DES structure for both reservoir and polymer matrix can be seen in Figure 1.

The arterial wall is composed of three layers: intima, media and adventitia (Figure 2a). Stent implantation at the site of lesion within the arterial lumen is also shown in Figure 2b. An effective DES system disrupts SM cell cycle and minimizes cell proliferation and migration from media into intima without inhibiting re-endothelization [7-11]. Inhibited re-endothelization has been associated with stent thrombosis [26, 27]. Drug physiochemical properties and drug release kinetics from the polymer formulation should be optimized so that the drug be preferably delivered to the media since smooth muscle cells are predominantly in the media or in the media/intima without depositing in the adventitia. Drug delivery in the adventitia is not as effective in checking neointimal hyperplasia and in-stent restenosis, as paclitaxel DES have demonstrated in comparison to sirolimus-eluting stents [40]. Even though both drugs are lipophilic, paclitaxel deposits preferably in the adventitia as opposed to other arterial layers whereas sirolimus is more evenly distributed throughout the arterial layers [41, 42]. The transmural diffusivity of sirolimus is more than twice as high as that of paclitaxel, and paclitaxel diffusivity is further diminished by the presence of red blood cell count/thrombus adhering to the site of stent-related vascular injury [40, 43]. Also, drug concentration should be minimal at the luminal surface (intima) as this has been associated with delayed wound healing [44].

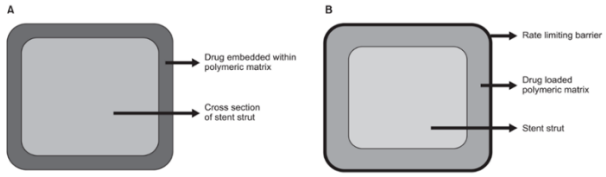

Figure 1. Schematic representation of DES cross-section for drug-loaded polymer matrix and reservoir design [37]. (A) Drug in polymer matrix (Taxus, Boston Scientific); (B) Drug in reservoir (Cypher, Cordis Corporation). With permission.

There are three formulation factors associated with inhibited re-endothelization and subsequent stent thrombosis: drug type (cytotoxic or cytostatic), narrow therapeutic window, drug lipophilicity/physiochemical properties and elution kinetics [7-9, 25, 45-47, 27-33]; durable or remnants of biodegradable polymers beyond drug elution causing a thrombogenic and inflammatory response [15-17, 27]; and burst release, also known as dose dumping [27-33]. Drug concentration in polymer matrix, polymer permeability and thickness, solvent evaporation rate following DES coating, as well as polymer properties governing degradation mechanisms and drug release kinetics are all factors contributing to burst release [44, 48-57]. Initial rapid release of the drug from DES systems should not result in high depletion of the polymer matrix, as

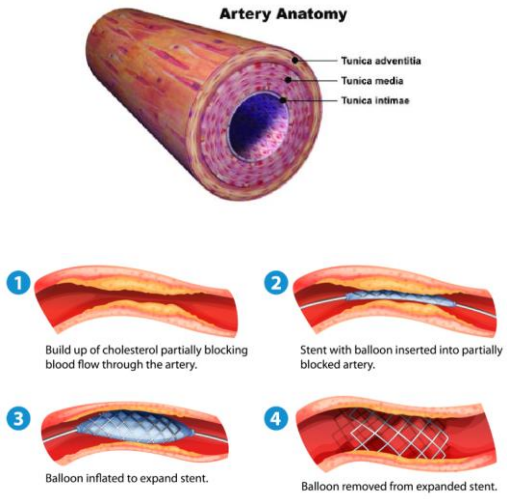

Figure 2. Schematic representation of the arterial wall layers (intima, media, and adventitia) in (top) and stent implantation with balloon angioplasty at the site of occlusion in (bottom). Artery Anatomy: Intima, Media, Adventitia (top) [38]; Stent Implantation at the Lesion Site (bottom) [39]. With permission.

FORMULATION FACTORS CONTRIBUTING TO STENT THROMBOSIS

There are three formulation factors associated with inhibited re-endothelization and subsequent stent thrombosis: drug type (cytotoxic or cytostatic), narrow therapeutic window, drug lipophilicity/physiochemical properties and elution kinetics [7-9, 25, 45-47, 27-33]; durable or remnants of biodegradable polymers beyond drug elution causing a thrombogenic and inflammatory response [15-17, 27]; and burst release, also known as dose dumping [27-33]. Drug concentration in polymer matrix, polymer permeability and thickness, solvent evaporation rate following DES coating, as well as polymer properties governing degradation mechanisms and drug release kinetics are all factors contributing to burst release [44, 48-57]. Initial rapid release of the drug from DES systems should not result in high depletion of the polymer matrix, as drug overwhelming tissue receptors could cause toxicity, increasing the risk of inflammatory and thrombogenic response. High initial burst release would also not allow for longer drug elution profiles at the site of action, necessary to inhibit SMC proliferation and prevent late catch-up restenosis [58, 59]. Table 1 presents drug-eluting stent evolution from 1st to 2nd generation in respect to drug type, type of polymer coating, polymer thickness, strut thickness, drug load and elution kinetics.

As pre-clinical and clinical studies with crystalline sirolimus MiStent (Stentys/Micell Technologies) have shown, drug elution without an initial burst release lasting over 9 months can possibly be associated with lower rates of stent thrombosis and inhibited vessel restenosis, also slowing the progression of late lumen loss (LLL) and preventing target lesion revascularization (TLR) catch-up phenomenon (ISR>1 year) [58, 59, 72].

Table 1. DES Evolution and Characteristics: Carrier Platform, Polymer Thickness, Drug Type and Elution Kinetics

		Strut Thickness	Polymer Thickness	Drug	Drug Dose	Drug Elution Time (days)
1st generation DES						
Cypher (Cordis, Johnson&Johnson Company)	DURABLE POLYMER	140 μm	12.6 μm	Sirolimus	140 μg/cm2	40% in 5 days 85% in 30 days 100% in 90 days [60,61]
Taxus Liberte (Boston Scientific)	DURABLE POLYMER	97 μm	16.9 μm	Paclitaxel	100 μg/cm2	≈10% in 28 days. Rest remains in polymer/not bioavailable [60,61]
Xience: Xience V Sierra Alpine (Abbott)	DURABLE/BIOCOMPATIBLE POLYMER	81 μm	7-8 μm	Everolimus	100 μg/cm2	25% in 24 hrs 75-80% in 28 days 100 % in 120 days [60-62]
Resolute Integrity (Medtronic)	DURABLE/BIOCOMPATIBLE POLYMER	91 μm	4.1 μm	Zotarolimus	160 μg/cm2	50% in 7 days 85% in 60 days 100% in 180 days [60, 63, 64]

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Resolute Onyx (Medtronic)	BIODEGRDABLE POLYMER	81 μm	4.1 μm	Zotarolimus	160 μg/cm2	>85% in 60 days 100% in 180 days [61, 63, 64]
Endeavor (Medtronic)		91 μm	6.0 μm	Zotarolimus	160 μg/cm2	75% in 2 days 95% in 15 days 100% in 28 days [61,62]
Endeavor Resolute (Medtronic)		91 μm	6.0 μm	Zotarolimus	160 μg/cm2	85% in 30 days 100% in 180 days [65, 66]
Promus Premier (Boston Scientific)		81 μm	6.0 μm	Everolimus	100μg/cm2	71% in 28 days 100% in 120 days [60,61]
Synergy (Boston Scientific)		81 μm	4.0 μm	Everolimus	100μg/20mm	50% in 60 days 100% in 90 days [60, 61]
Orsiro (BIOTRONIK)		60 μm	7.5 μm	Sirolimus	140μg/ cm2	50% in 30 days 80% in 90 days [61, 67, 68]
MiStent SES (Micell Technologies Inc)		64 μm	5-15μm	Sirolimus	244μg /cm2	No burst release. 100% in 270 days [62, 69, 70]
Combo (OrbusNeich)		100 um	5.0 μm	Sirolimus	2.5 & 5 μg/mm	100 % in 30-45 days [16, 71]

In DESSOLVE I and II clinical trials with up to five-year follow-up, the MiStent SES has continued to demonstrate low rates of TLR with 0.0% in DESSOLVE I and 3.4 % in DESSOLVE II. No ST was reported with the MiStent in the DESSOLVE I trial up to five-years. DESSOLVE II demonstrated that definite or probable ST was 0.0% with MiStent and 1.7% with Endeavor (Medtronic) [73]. DESSOLVE III trial comparing MiStent to Xience proven to be superior for stent thrombosis outcomes, showed that the rate of definite or probable stent thrombosis was infrequent and similar between the two arms up to 3 years (1.2% for MiStent versus 1.5% for Xience; P=0.64). Similarly, the two devices did not differ significantly in their performance in respect to repeat TLR (5.2% versus 6.5%; P=0.30) [74].

DRUGS PROPERTIES:

Paclitaxel versus Sirolimus

First generation durable polymer DES, Taxus (Boston Scientific) and Cypher (Cordis Corporation), used paclitaxel and sirolimus as anti-proliferative agents, respectively. Paclitaxel is a cytotoxic molecule causing cell death [40, 75, 76] whereas sirolimus (rapamycin) is a cytostatic molecule inhibiting smooth muscle cell proliferation and the immune response to injury [40, 76]. Sirolimus and its derivatives cross cell membranes to bind to the FKBP12 binding protein, which subsequently binds to mammalian TOR receptor (m-TOR), blocking cell cycle mainly of the smooth cell between G1 and S phases to inhibit SMC proliferation [8, 77-79]. Paclitaxel, on the other hand, has a different mechanism of action compared to -limus drugs. It stabilizes the microtubule making them dysfunctional and inhibiting SMC proliferation and migration by causing cell cycle arrest in the G2/M phase [8, 45]. In other words, one of the main differences between paclitaxel and -limus drugs is that sirolimus and its derivatives are cytostatic, leaving the cell viable whereas paclitaxel causes cell death [8, 75, 80]. As mentioned earlier, both drugs also inhibit EC proliferation and migration at nanomolar concentrations [7-11, 81].

Paclitaxel is a highly lipophilic drug with a narrow therapeutic window and a lower transmural diffusivity as compared to sirolimus, so it is strongly retained and accumulated in the arterial wall, especially in the adventitia [40-43], and can cause tissue toxicity and inhibit re-endothelization through delayed healing at elevated concentrations through its cytotoxic mode of action [8, 44, 25]. Even though paclitaxel is cytostatic at lower concentrations [17], at which its antiproliferative and antimigratory properties are not associated with cell death [81], it is so strongly retained in the arterial wall that this can

lead to high drug tissue content and subsequent negative adverse effects associated with cytotoxicity. This means that an initial burst release of paclitaxel can play a major role in delayed healing/inhibited re-endothelization and subsequent stent thrombosis. As mentioned earlier, its transmural diffusivity in the arterial wall is approximately twice as low as that of sirolimus, resulting in an uneven distribution in the arterial wall as compared to the more homogenous distribution of sirolimus. Paclitaxel and sirolimus transmural diffusion coefficients, distribution and deposition are not governed solely by drug lipid/water avidity and transport forces as the drug partitions between different arterial layers of more water-rich regions and lipid-rich pools or elastic lamina [43]. Sirolimus transmural diffusivity surpassing that of paclitaxel has been attributed to the different distribution of the tissue-specific protein binding sites and binding site availability for the two drugs more so than just paclitaxel and sirolimus lipophilicity (LogP 3.66 and 4.3, respectively) and their poor aqueous solubility (0.25-1 ug/ml and 2.6 ug/ml, respectively) [43, 82-85]. Furthermore, sirolimus is an immunosuppressant with better kinetics and wider therapeutic index as compared to paclitaxel, which also explains the anti-restenotic efficacy of sirolimus-eluting stents as compared to paclitaxel-eluting stents [86, 87] Also, the ability of sirolimus to arrest the cell cycle is not associated with cell death even at higher concentrations [88-90].

-Limus Family of Drugs-A Better Choice in Therapeutic Agents for DES Formulations

The evolution in therapeutic agents from first to second generation DES introduced sirolimus anti-proliferative analogues, such as zotarolimus (Endeavor, Medtronic) and everolimus (Xience, Abbott) with varying degrees of lipophilicity, but also a wide therapeutic window and cytostatic nature (Figure 3). Zotarolimus is produced by the tetrazole ring substitution of the hydroxyl group at the C42 position, which makes zotarolimus extremely lipophilic, allowing for lower effective concentration at the site of action as compared to sirolimus in terms of reducing the incidence of adverse vascular events associated with restenosis [39, 91, 92]. High degree of lipophilicity and poor water solubility slow down the dissolution profile in the interstitial fluid of arterial tissue, so increasing dissolution kinetics to increase bioavailability should deliver just enough as opposed to too much drug with better permeability through cell membrane. The slow dissolution profile results in less systemic exposure and negligible drug tissue concentrations conductive to re-endothelization [40]. Zotarolimus has a shorter in vivo half-life than sirolimus but the same high-affinity binding to the immunophilin FKBP12 along with comparable inhibition of t-cell proliferation in vitro [93]. Everolimus is a relatively polar immunosuppressant macrolide with a 2-hydroxyethyl chain at the C40 position of sirolimus, resulting in lower tissue concentration and cell uptake [40]. As compared to sirolimus, everolimus has a much higher interaction with mechanistic target of rapamycin complex 2, shorter half-life and better bioavailability [17]. Everolimus also reduces vascular inflammation [94] and the everolimus-eluting stents like Xience has shown more rapid endothelization [95]. This should not only be attributed to the drug itself considering that success of a DES formulation is a multifactorial phenomenon as described earlier.

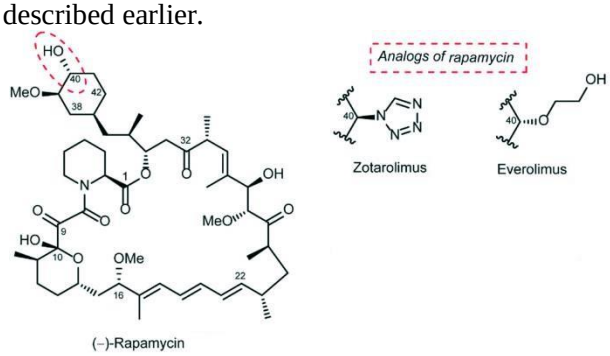

Figure 3. Sirolimus and its -limus Derivatives Chemical Structure: Sirolimus, Everolimus and Zotarolimus. modified from source: [80]. Modified from source. With permission.

The pKa value/presence of ionizable groups at physiological pH (7.37-7.43) and degree of hydrophobicity determine drug ionizability in aqueous interstitial fluid and blood plasma allowing for faster dissolution profiles of more polar -limus derivatives from the polymer matrix that can result in burst release. For example, everolimus physiochemical properties allow for a faster dissolution profile as compared to sirolimus and zotarolimus lacking in ionizable groups. As explained earlier, everolimus faster dissolution profile is countered by a slower rate of cell uptake as compared to the more hydrophobic anti-proliferative agents. Also, burst release results from higher drug concentration being dispersed in the outer layers of DES polymer - a limitation of different solvent-based coating techniques as opposed to high drug content

in DES as evident in Table 1 [96-98] An optimal DES formulation itself should have a lower drug content to prevent a high initial burst release. Also, low MW drugs have higher propensities for burst release as a result of osmotic pressure [99]. Paclitaxel and the above mentioned -limus derivatives are relatively small compounds with the following molecular weight: paclitaxel (850 g/mol) [100], sirolimus (915 g/mol) [88], zotarolimus (966 g/ml) [101] and everolimus (958 g/mol) [102]. Drug solubility in DES polymer matrix systems also affects drug release kinetics from the formulation.

It is important to note that sirolimus presents a challenge for in vitro dissolution testing in terms of presenting limitations in obtaining an in vitro release mechanism and release rate that correspond to the release in vivo. As mentioned earlier, sirolimus is particularly insoluble in water (2.6 ug/ml) and contains no functional groups that are ionizable in the 1-10 pH range [84]. It has a logP value of 4.3 [85]. This can be overcome using surfactants, organic solvents, and other additives to increase the solubility of sirolimus and maintain sink conditions necessary for simulating in vivo conditions during in vitro dissolution testing of DES release mechanism and kinetics [103-107]. However, it should be kept in mind that media other than phosphate buffered saline (PBS) pH 7.4 may influence the release rate by improving the wettability of coating [104]. Surfactants lower the interfacial tension between the product and the release medium, allowing for a more rapid and possibly more complete penetration of the release medium into matrix [108]. At high surfactant concentrations, a greater amount of surfactant is incorporated into the matrix, resulting in greater wetting/solubilization of the drug, and consequently increasing the drug release rate from the matrix [109, 110]. The addition of acetonitrile to the dissolution media also increases the drug release rate due to an increment in total porosity of the matrices [104].

Both zotarolimus and everolimus are also highly lipophilic with a LogP value of 5.9. [100, 101] Zotarolimus is practically insoluble in water with no ionizable groups [111]. Given that sirolimus and zotarolimus physiochemical characteristics in particular present a hurdle to IVIVC, it can be postulated that the limitations for in vitro dissolution testing during formulation development can lead to unpredictable results in vivo. In other words, drug hydrophobicity and lack of ionizable groups can hinder successful DES formulation development despite the effective pharmacological properties of the anti-proliferative agent.

Furthermore, sirolimus is subject to hydrolytic degradation at pH 7.4 buffer solutions and degrades fastest at 37 °C [112] with a half-life of 13 hours [113], so these stability issues should be considered when choosing the appropriate dissolution media. Determining the residual amount in the stent coating instead of the amount released into the media [113] or using a mixture (9:1 v/v) of normal saline and 2-propanol as release media [114] are some ways to overcome the problem of sirolimus instability during in vitro dissolution testing.

The use of hydrophilic drugs in DES is limited as heparin studies showed due to lack of affinity for cell membrane lipids and a greater partitioning into the interstitial fluid and blood, which results in fast clearance [115]. As mentioned earlier in case of paclitaxel and sirolimus, drug distribution, retention and transport in the arterial tissue are not only determined by drug physiochemical properties, such as lipophilicity, drug molecular weight and charge, but are also highly dependent on arterial tissue geometry, composition, and protein binding [43, 116]. In other words, it is not sufficient to only consider the lipophilicity, water solubility and MW of anti-proliferative agents in respect to their cell uptake and transport through the arterial wall when choosing the appropriate drug for a DES formulation. Moreover, drug specific and non-specific biding to tissue and intracellular proteins must be studied along with the distribution of those intracellular protein targets within the arterial wall.

Drug-eluting stents containing crystalline form of the drug may provide better control over drug delivery. Crystalline drug particles may be favored over the conventional approach of spraying amorphous form in polymer solutions onto metallic struts especially when combined with biodegradable polymers and an anti-inflammatory agent like sirolimus that can counter any tissue reaction arising from presence of polymer degradation products. Amorphous drug elution profile from DES is dependent on diffusion along a concentration gradient, and thus associated with a rapid, uncontrolled drug burst upon initial release. On the contrary, crystalline drug elution is dependent on dissociation/dissolution reaction from the crystalline lattice associated with a high activation energy barrier, eliminating the initial burst release characteristic of diffusion-controlled mechanisms, and resulting in a more consistent and gradual drug release rate throughout polymer absorption regardless of the amount of drug remaining in the coating [27, 117]. Published theoretical analyses

[118] predict that dissolution-controlled release of crystalline drugs should display zero order kinetics elution after a negligibly small initial burst, remaining relatively constant over time. As mentioned earlier, MiStent containing sirolimus crystals embedded in a biodegradable polymer matrix composed of polylactide-co-glycolic acid (PLGA) showed an improvement in burst release over conventional DES containing amorphous sirolimus drug, as well as a more linear, long-term drug elution profile. Conventional biodegradable DES are characterized by a relatively short, logarithmic-type pattern drug elution profile as compared to MiStent elution profile with an initial burst release, follow by the remaining drug being released from polymer matrix, but falling below therapeutic levels while the polymer remains intact. This increases chances of late catch-up restenosis and stent thrombosis (Figure 4) [27]. Previously it has been shown that crystalline sirolimus elution from MiStent sustains higher drug loads in tissue compared to conformal coated stents with similar drug loads [58].

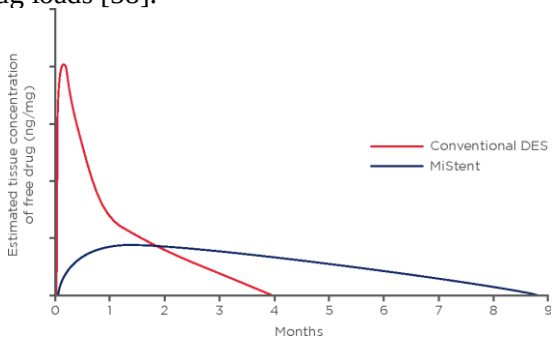

Figure 4. Crystalline sirolimus allows for a gradual, linear, and long-term elution profile [27]. With permission.

As mentioned earlier, DESSOLVE III clinical trial confirmed the safety and efficacy for 3-year clinical outcomes of biodegradable sirolimus MiStent as compared to durable everolimus Xience stent, which has been the standard for very low rates of stent thrombosis. (74) It is important to stress again that drug elution without an initial burst release, or a negligible burst release, lasting over 9 months for the crystalline sirolimus drug released from MiStent can possibly be associated with lower rates of stent thrombosis and inhibited vessel restenosis.

THE TROUBLE WITH CURRENT DES ANTI-PROLIFERATIVE AGENTS

As mentioned earlier, the current anti-proliferative agents not only inhibit smooth muscle cell (SMC) proliferation and migration, but also suppress local regeneration of the natural endothelium [7-11]. As a result, the endothelium may not completely regenerate at the place of implantation stent implantation, which leads to the loss of a key homeostatic feature that regulates the interaction between the vessel wall and the circulating blood components [119]. The loss of this homeostatic feature lacking in case of inhibited re-endothelization has been attributed to causing stent thrombosis, primarily in patients who have discontinued any adjunctive antiplatelet or anticoagulant therapy [15, 16, 120]. Subsequently, alternative agents, such as estradiols and nitric oxide donors, have been investigated as DES anti-proliferative agents that would prevent SMC proliferation and simultaneously enhance endothelial monolayer regeneration, while also reducing the rate of platelet adhesion [121-123]. It is also worth mentioning that sirolimus has been shown to have a stronger inhibitory effect on migration of endothelial cells as compared to zotarolimus [124].

RELEASE MECHANISMS FROM 1st AND 2nd GENERATION DES

Optimal release kinetics from DES are characterized by a prolonged release that can maintain the therapeutic dose for longer periods of time, minimizing both underexposure and the risk of toxicity from overexposure, as well as burst release. The release kinetics of drugs from DES systems depend on the solubility and diffusion coefficient of the drug in the polymer, the drug load, as well as the in vivo degradation rate of the polymer in the case of the biodegradable systems [125]. Mechanisms of drug release from 1st and 2nd generation DES are mainly controlled by a) diffusion and dissolution of drug particles within a coating or within tissue, b) swelling of polymer matrix followed by diffusion and c) polymer bulk degradation and/or surface erosion for biodegradable polymers (Figure 5). (39, 50, 126-128) Drug release profiles usually follow a biphasic or tri-phasic release depending on the durable or biodegradable polymer nature. Elution profiles are characterized with an initial burst release followed by a significant fraction of drug load being eluted in a sustained fashion over weeks or months, broadly classified as zero-order, first order, first

order or Higuchi release kinetics. [36, 47, 129, 130]. Mathematical release models become more complicated with the inclusion of different geometries, processes like swelling/diffusion, drug diffusion/dissolution, polymer degradation and/or surface erosion and biological factors.

Drug release from durable polymer DES systems depends on principles of diffusion and dissolution. In reservoir formulations drug diffusion through the outer polymeric membrane is the rate-limiting step, resulting in zero-order kinetics with constant release at steady state until depletion of the drug load. The release rate is not affected by concentration gradient, but by polymeric membrane thickness and permeability [47, 128, 131]. A top-coat layer can be employed to inhibit burst release of the drug and to have longer elution at the site of action [132]. In matrix (monolithic) durable systems, the release rate is driven by diffusion of drug across a distance through polymer matrix and can be broadly characterized as first order or Higuchi release kinetics depending on the initial drug load and solubility in the matrix, as well as drug dissolution rate in the polymer [36, 47, 130]. Diffusion processes can be either Fickian or non-Fickian [131]. Swelling of polymer systems increases free volume and mesh size and is followed by drug diffusion through the swollen network into the site of injury. Polymer swelling can facilitate diffusion by increasing the aqueous solvent content in the formulation and creating pores though which the drug can diffuse out of the matrix as it partitions between the polymer and the aqueous solvent depending on its polarity/solubility [128, 133].

Release kinetics from biodegradable polymer DES are influenced by a combination of diffusion and/or swelling and bulk degradation and/or surface erosion. [36, 126, 134, 135]. Even though initially drug molecules can be released by diffusion, eventually erosion and/or degradation start to dominate the process, resulting in pore formation that facilitates drug diffusion and drug release [134-136]. For example, PLGA polymer degradation and erosion can facilitate drug molecule diffusion, as molecular weight reduction induces less entanglement of polymer chains in the PLGA bulk, and the mass loss creates pore space for facilitated drug transport and release [134]. Drug release is highly dependent on polymer properties, such as molecular weight, monomer composition, degree of crystallinity, porosity, hydrophilicity, degree of swelling and degree of cross-linking, as these govern drug diffusion and polymer degradation kinetics; polymer degradation is also dependent on temperature and pH [135, 137-139]. Along with properties such as polymer-plasticizer ratio, polymer-drug load ratio and polymer-drug interactions, these factors contribute to changes in polymer glass transition temperature (Tg) and, as a result affect the degree of crystallinity and water uptake, which determines polymer permeability,

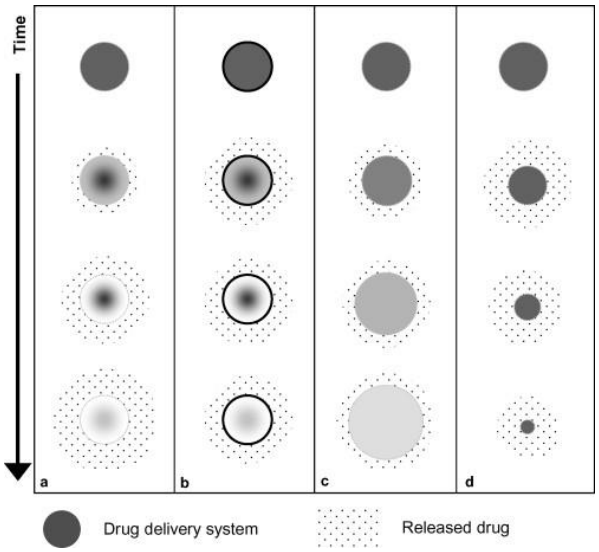

Figure 5. Schematic representation of Drug Release Mechanisms from 1st and 2nd generation DES (Durable and Biodegradable Polymer Systems) [124]. With permission.

subsequent drug diffusion through the matrix, and polymer degradation kinetics. [140-142]. Furthermore, size of the drug delivery system also influences release in that larger particles increase the pH gradient. Particle shape and size also influences drug release, as the ratio of surface area to volume is an important parameter facilitating more water contact [135]. Increasing the surface to volume ratio can accelerate polymer degradation kinetics [143]. Polymer surface morphology is yet another parameter that can be modified to control drug release from polymeric DES systems [144].

POLYMER PROPERTIES

Polymer properties such as Tg, solubility, viscosity, crystallinity, mechanical strength, and degradation rate, are related to the polymer's MW, with low-MW polymers degrading more rapidly [145]. Polymer crystallinity and changes in the degree of crystallinity directly influence drug release kinetics and the rate of polymer degradation, mainly because both drug diffusion and polymer degradation are facilitated by a decrease in Tg and subsequent transition from a glassy to a rubbery state of polymer amorphous regions characterized by more free volume and free movement [140-142]. Crystalline structures represented by a rigid, tightly cross-linked lattice restrict molecular movement and are less affected by solvent penetration whereas semi-crystalline and more amorphous structures have more freedom of movement as the chains are farther apart. Polymer hydrophilicity, pore size and pore density can also contribute to water uptake and increase the degree of swelling, lowering Tg and subsequently allowing for better drug diffusivity given the changes in porosity and improved polymer permeability [131, 135]. Drug polarity, pKa, crystallinity and molecular weight govern its ability to partition between polymer and aqueous regions. In case of biodegradable polymers, pore size and porosity increase as the matrix swells up exposing more polymer backbone to cleavage of ester bonds by hydrolysis, which results in decreased molecular weight and reduced average polymer chain length, accelerating polymer degradation, and releasing more drug from the system [131, 135, 146, 147]. 1st generation DES durable polymers, 2nd generation durable biocompatible DES polymers and biodegradable DES polymers are listed in Table 2.

Durable biocompatible 2nd generation DES polymers like poly vinylidene-flouride hexafluoropropylene copolymer (PVDF-HFP) in Xience stent and BioLinx polymer in Endeavour Resolute [149], Resolute Integrity and Resolute Onyx stents [159] have been associated with favorable clinical outcomes in terms of reduced rates of stent thrombosis [74, 170-172]. Xience combines PVDF-HFP with everolimus anti-proliferative agent, and the Endeavour and Resolute stents combine BioLinx with zotarolimus anti-proliferative agent. The lower rate of stent thrombosis with Xience stent following PCI as compared to other thick or thin strut DES and BMS has strongly been attributed to PVDF-HFP thromboresistance [158]. Ex vivo shunt models and animal studies show less platelet aggregation and less inflammatory cell attachment, as well as earlier endothelization in presence of PVDF-HFP-Everolimus eluting Xience platform [173-175].

The BioLinx polymer is a blend of three different polymers, a hydrophobic C10 polymer, a hydrophilic C19 polymer and a water-soluble polyvinylpyrrolidone (PVP) polymer. This composition gives rise to an amphiphilic molecule with its hydrophilic components on the outer surface, providing better polymer biocompatibility, and a hydrophobic core containing the drug that improves the solubility of the hydrophobic drug zotarolimus and ensures prolonged release [63, 64]. While C10 and C19 polymer provide sustained release, the addition of the water-soluble PVP polymer achieves sufficient, but not high, burst release in the drug elution profile, which can be favorable in inhibiting SMC proliferation upon immediate injury to the vessel [64]. The PVP polymer hydrophilicity also provides good biocompatibility in in-vitro tests such as monocyte adhesion for the BioLinx polymer in that it does not induce activated monocyte adhesion [63, 64]. Monocyte adhesion has been shown to cause local inflammation and promote vascular cell proliferation factors contributing to in stent restenosis [176]. Both (PVDF-HFP) and the BioLinx polymers are an improvement over 1st generation polyethylene-co-vinyl (PEVA), (polybutylmethacrylate), (PMBA) and poly(styrene-b-isobutylene-b-styrene) or SIBBS durable polymers associated with incidences of death or myocardial infarction (MI) after implantation [177], particularly late stent-thrombosis and delayed wound healing, caused by incomplete re-endothelization and the presence of polymer coatings after drug elution [9, 15, 16, 150-153, 178-180].

Commonly used synthetic biodegradable polymers for stent coating include thermoplastic aliphatic poly(esters) such as polylactic acid (PLA),

polyglycolic acid (PGA), and poly (lactic-co-glycolic acid) (PLGA). PLA can be made using two types of monomers: two stereoisomers of lactic acid (D and L). While PLA prepared using D-lactic acid, PDLA, is a crystalline material resulting from its regular chain length, PLA prepared using L-lactic acid, PLLA, has a semi-crystalline structure. PLLA and PDLA polymer blend yields PDLLA, which has amorphous characteristics. PLAs are hydrophobic in nature, as the presence of methyl groups make this polymer more hydrophobic [181]. Therefore, the chirality of the monomer influences the biodegradability and mechanical properties of PLA, and subsequently drug release kinetics. Studies have shown that D and D/L forms of PLA degrade faster than the L form, as the latter is more crystalline in nature [182 -186]. PLA degrades through hydrolysis of the ester bond backbone [187].

One of the major disadvantages of using PLA is its brittleness and rigidness [188]. For this reason, plasticizers are added to the polymer to improve mechanical strength and tensile properties. Addition of plasticizers causes changes in the polymer thermal, physical, and mechanical properties and subsequently, directly influences polymer degree of crystallinity, surface morphology and free surface energy and charge [189, 190]. The plasticizer should be miscible with PLA to create a homogeneous blend. Plasticizers should also not be too volatile because this would cause evaporation at the elevated temperatures used during processing, that could affect polymer physical, thermal, and mechanical characteristics. Evaporation of plasticizer at elevated temperatures during processing could, therefore, result in altered drug release kinetics, as well as worse tensile strength and ductility. Furthermore, the plasticizer should not migrate because migration would cause contamination of the materials in contact with the plasticized PLA, as well as make the polymer-plasticizer blend more brittle [188].

PLGA (Poly (d,l-lactic-co-glycolic acid) is a copolymer of lactic acid and glycolic acid whose physical, thermal and mechanical properties depend on the ratio and type of the monomers used for the blend [160]. PLGA properties can be modified changing the molecular weight and poly glycolic acid (PGA) to poly lactic acid (PLA) copolymer composition to adjust the degree of crystallinity, hydrophilicity, and glass transition temperature (Tg) of the copolymer. Increasing the ratio of lactic to glycolic acid can increase polymer hydrophobicity that in turn reduces the rate of water penetration through the device and subsequent hydrolysis and degradation to allow for a more controlled drug release profile. As a rule, higher glycolic acid content yields faster degradation rates due to PGA hydrophilicity as compared to PLA allowing for higher rates of water uptake and hydrolysis of PLGA ester linkages. The exception to this rule is the 50:50 PGA to PLA ratio which exhibits the fastest degradation rates with increasing PGA content leading to faster polymer degradation kinetics below 50% [161-163]. In other words, PLGA copolymers have high degradation rate that decreases as the content of lactic acid increases from 50 to 100 and that of glycolic acid reduces from 50 to zero. Thus, adjusting the length and ratio of the PLGA polymer backbone can be manipulated to control the rate of degradation in vivo [161-165].

Table 2. 1st and 2nd Generation DES Polymers [148-169] Table modified from source: [158].

Polymer	Polymer Description	Important Characteristics
SIBBS	Thermoplastic elastomer whose physical properties overlap silicone rubber/polyurethane, prone to cracking from stress in organic solvents (poor creep properties) **Ex. Taxus® [148, 149]**	1st generation DES durable polymer associated with inflammation and thrombogenicity (polymer evolution in DES called for more biocompatible polymers) [9, 15, 16, 150-153]
PEVA	Copolymer consistency dependent on % of vinyl acetate with higher percentages resulting in increasingly high durability **Ex. Cypher® contains PEVA, PBMA, PCh [149. 154]**	Coatings made only of PEVA are flexible but less durable and release drugs relatively fast (50% in 24 hrs). As a result PBMA and PEVA polymers are used as a mixture for stent coating given these PEVA characteristics [154] 1st generation DES durable polymer associated with inflammation and thrombogenicity (polymer evolution called for more biocompatible polymers) [9, 15, 16, 150-153]

Table 2 continues …….

PBMA	Transparent liquid with a high degree of hydrophobicity and durability at MW (200 000–320 000 Daltons) [149, 154] **Ex. Promus Premier™ contains both PBMA and PVDF-HFP**	Coating made only of PBMA develops cracks when high drug concentrations are incorporated As a result, PBMA and PEVA polymers are used as a mixture for stent coating given these PBMA characteristics Polymer with slow drug-release kinetics [154] 1st generation DES durable polymer associated with inflammation and thrombogenicity (polymer evolution called for more biocompatible polymers) [9, 15, 16, 150-153]
PCh	Thermoset, water-swellable polymer with 4 monomers as building blocks: ●2-methacryloyloxyethy PC monomer ●lauryl methacrylate; and ●2-hydroxypropyl-methycrylate both reduce hydrophilicity; whereas ●trimethoxysilylproylmethacrylate is a silane crosslinker; it determines PCh polymer mechanical proprieties **Ex. Endeavor ® [149, 155]**	Lower thrombogenicity Biocompatible, Durable [155-157]
PVDF-HFP:	Semicrystalline fluorinated copolymer made from vinylidene fluoride and hexafluoropropylene monomers whose backbone is >50% fluorinated giving rise to polymer hydrophobicity **Ex. Xience V contains PBMA and PVDF-HFP [149, 155]**	Low glass transition temperature (−29°C) and semicrystallinity give rise to high elasticity and fatigue resistance Biocompatible, durable, thromboresistant [155-158]
BioLinx	Mixture of 3 polymers: C10 polymer is mostly comprised of hydrophobic n-butyl methacrylate and is the core containing the drug; C19 polymer is a mixture of hydrophobic n-hexyl methacrylate and hydrophilic N-vinyl pyrrolidone and venyl acetate monomers; Polyvinyl pyrrolidone (PVP) is a medical grade hydrophilic polymer. C19 and PVP hydrophilicity gives rise to better biocompatibility [65, 66] **Ex. Endeavor Resolute®; Resolute Integrity® , Resolute Onyx™ [149, 159]**	Polymers self-orient to yield a substantially hydrophilic surface that is hemocompatible/biocompatible, but retain a substantially hydrophobic core containing the drug Enhanced biocompatibility [63, 64]
PLGA	PGA is highly crystalline and less hydrophobic compared with PLA due to lack of methyl groups on the side chain. PLGA degree of crystallinity and amorphousness depends on the type and ratio of the PLA and PGA monomers [160] **Example: Synergy™ , MiStent SES® [27, 160]**	Biodegradable Crystallinity and amorphousness can be adjusted based on the monomer ratio; e.g. higher content of PGA leads to faster degradation rates with an exception of 50:50 ratio of PLA/PGA (amorphous), which exhibits the fastest degradation; higher PGA/PLA ratio leads to increased degradation interval below 50% Increasing the lactic acid content yields a more crystalline polymer [161-163] Drug release rate is higher in polyesters with a low degree of crystallinity because of higher macromolecular chain mobility [164, 165] However, PLGA degrades by bulk erosion associated with burst release [127, 166-168] Polymer degradation yields acidic products that can alter the pH and cause unfavorable inflammatory responses [34, 35]
PDLLA	PLA has D- or L- stereochemical centers (or R or S, respectively), giving rise to two enantiomeric forms of PDLA or PLLA; PDLLA is completely amorphous [135]	Biodegradable; however, PDLLA degrades by bulk erosion associated with burst release [127]
PLLA	PLA has D- or L- stereochemical centers (or R or S, respectively), giving rise to two enantiomeric forms of PDLA or PLLA; PLLA is highly crystalline [135] **Example: Orsiro ® (PLLA bioabsorption takes 15 months, while drug is eluted in 3 months [169]**	Biodegradable; high MW PLLA undergoes slow degradation and erosion due to its high MW and chemical composition [127]

PEVA: poly (ethylene-co-vinyl acetate); PBMA: poly(n-butylmethacrylate); PCh: phosphorylchlorine polymer; SIBBS Poly (styrene-b-isobutylene-b-styrene); PVDF-HFP:poly(vinylidene-co-hexaflouropropylene); PLGA:Polylactic co-glycolic acid; PLLA: Poly L lactic acid

Biodegradable polymers like PLA, PGA and PLGA, degrade by bulk erosion associated with burst release and subsequent inhibition of re-endothelization associated with stent thrombosis [127, 166-168]. Synthetic PLA, although biocompatible, can take more than a year to degrade and therefore carries a risk of late and very late stent thrombosis [128, 191]. In case of Orsiro (biodegradable DES system), it takes up to 15 months to degrade and is, therefore, present long

after the drug has been eluted in the first three months [169]. Additional problems may arise from poor mechanical performance and generation of acidic products from polymer degradation, which may lead to inflammatory responses and induce neointimal hyperplasia and subsequent restenosis, as well as thrombosis at a lower pH [34, 35]. The acidic by-products of PGA as well as its fast degradation kinetics make it an unfavorable candidate to be used for as a single polymer matrix and can cause inflammation in the local tissue as a degrading component of a PLGA polymeric system [183].

BIODEGRADATION: SURFACE EROSION VERSUS BULK EROSION-IMPLICATIONS FOR BURST RELEASE

Bulk erosion as the mechanism of biodegradable polymer degradation is associated with more burst release and unpredictable drug release profiles as compared to surface erosion. Polymer degrading by surface erosion goes through a heterogeneous process degrading from the surface inward proportional to the surface area, while maintain its bulk integrity. As a result, drug release form surface eroding systems is often correlated with a controllable and reproducible erosion rate with thicker systems having longer erosion times. Polymers degrade quickly at the surface without the penetration of water molecules by hydrolysis [162, 166, 168]. Alternatively, in bulk erosion, the rate at which the water penetrates the device is higher than the rate of erosion, so water penetration rate exceeds the rate at which the smaller polymer constituents are converted into water-soluble materials, resulting in homogenous degradation of the entire matrix with an initial burst release, as the constituents are likely to be hydrolyzed [166, 168]. Bulk erosion is associated with unpredictable release rates as compared to surface erosion and is a suboptimal mechanism for controlled drug delivery [168]. As mentioned earlier, PLA, PGA and PLGA degrade by bulk erosion associated with burst release [127, 166-168].

POLYMER-POLYMER BLENDS AND PLASTICIZERS IN DES: DRUG RELEASE KINETICS AND POLYMER HEMOCOMPATIBILITY

Polymer-polymer and polymer-plasticizer blends are used to control drug release kinetics from DES and improve on the mechanical strength of the polymeric film. In changing the physical, mechanical, and thermal properties of the polymer matrix through their interaction with the polymer, plasticizers can alter drug release kinetics [140-142]. Varying the polymer-to-polymer ratio or polymer to plasticizer ratio can effectively alter polymer film physical, mechanical and thermal properties and, subsequently, change the release kinetics, as well as release mechanisms of the anti-proliferative agent from a polymer blend system [192, 193]. PLGA co-polymer is a common example of polymer properties changing due to a blend of polymers that affect drug release kinetics, as described in the previous section.

Plasticizers, such as polyethylene glycol (PEG), increase the flow and thermoplastic characteristics of a polymer by decreasing the viscosity of the polymer melt, glass transition temperature (Tg), the melting temperature (Tm) and the elastic modulus of the final product [194-198]. Decreasing the blending temperature during heat processing and manufacturing reduces the risk of polymer blend and polymer-plasticizer degradation, as well as the possibility of component separation [188, 199]. Plasticizers can increase the free volume between the polymer chains, allowing the polymer chains to move and rotate more freely and allowing for increased movement of chain segments with respect to each other, which subsequently decreases the polymer Tg and melt viscosity [200, 201]. Therefore, plasticizers can alter polymer morphology and degree of crystallinity to improve flexibility and ductility, which with a reduction in Tg values directly influences drug release kinetics. Selection of the right plasticizer is important in improving polymer mechanical and thermal properties so that it does not come to polymer deformation as in cracking, flaking or peeling during stent insertion and inflation and during high-scale industrial processing and product storage [97]. It is worth mentioning that storage history and processing parameters that can cause polymer blend separation or the partition of plasticizer into one polymer more than the other can result in unfavorable polymer-polymer, polymer-plasticizer and polymer-drug interactions that would affect drug release kinetics from a DES system [32, 199]. Drug release kinetics and polymer degradation are also affected by sterilization process, storage history, annealing and processing parameters [202].

Addition of plasticizers and polymer blends also affects polymer surface free energy and charge, which in turn influence polymer wettability. Testing a favorable plasticizer and creating polymer blends should be associated with a decrease in surface free energy to help improve polymer wettability, which

subsequently reduces the risk of thrombosis, because thrombogenicity of a material surface increases with increasing surface energy [190, 203, 204]. At the same time, the lower surface free energy of more hydrophobic polymers has been associated with lower rates of endothelial cell adhesion, which could further explain the challenge in optimizing polymer properties as being thromboresistant [205]. On the other hand, the presence of polar groups on hydrophilic polymer surfaces has been shown to promote better adhesion, which is not considered to be good hemocompatibility, because platelet adhesion could result in thrombus formation [206, 207]. Hemocompatibility prediction parameters of polymer materials are the energy characteristics of the surfaces of polymer films, the specific surface free energy of the polymer/air boundary and interphase energy of the polymer/liquid interface, all of which influence polymer mechanical strength upon long-term exposure to the blood, as well as polymer adsorption and adhesion properties in respect to blood constituents [207, 208].

Equally as important is an intact surface morphology of the polymer-polymer or polymer-plasticizer blend, as thrombogenicity is generally higher for rougher surfaces [209-211]. Polishing of coronary stents has been shown to result in decreased thrombogenicity and decreased neointimal hyperplasia in different animal models [212, 213].
Water is known to act as a plasticizer in reducing Tg of amorphous polymers and changes their elastic modulus [214]. Depending on the degree of lightly cross-linked amorphous groups present within a polymer matrix and polymer affinity for water, acting as a plasticizer, the matrix can swell in varying degrees, decreasing Tg and subsequently increasing the free volume for facilitated drug diffusivity and improved polymer permeability. Addition of plasticizers to increase polymer elasticity results in disruption of covalent and non-covalent bonds forming the intermolecular cross-linked network. Higher plasticizer to polymer ratio can decrease Tg, resulting in a more amorphous polymer profile, which depending on matrix polarity, can interrupt either hydrogen bonding or van der Waal forces and create more free volume for drug to diffuse, as well as facilitate polymer degradation in case of biodegradable polymers. Low molecular weight polymers have a high elastic module, and the matrix is more deformable, causing pores to expand as a result of osmotic pressure [131]. Water has also been shown to have an anti-plasticizer effect in that it forms stable bridges between polymer chains though hydrogen bonding [215].

DRUG LOAD TO POLYMER RATIO EFFECT ON RELEASE KINETICS FROM DES

Different drug load to polymer ratios can result in differences in polymer film mechanical properties, surface morphologies, thermal properties, and drug distribution [216, 217]. Higher drug load is associated with changes in polymer mechanical properties due to alteration in polymer degree of crystallinity. Higher drug load can lead to polymer-drug interactions where the drug acts as a plasticizer, decreasing Tg and allowing for more free movement, which results in better drug diffusivity and faster polymer degradation kinetics [98]. Higher drug distribution near the surface of the polymer film contributed to high initial burst release [32, 218]. It is worth mentioning that drug-polymer interactions are generally not a problem for hydrocarbon- or fluorocarbon-based matrices due to the stability of C-H and C-F bonds, but that these interactions are more likely to occur when the polymers contain functional groups (such as esters, amides, anhydrides, etc.) that could react with the drug given that the drug has reactive functional groups [32].

DES COATING TECHNIQUES: SOLVENT EVAPORATION RATE AND BURST RELEASE

Coating techniques involving solvent evaporation upon drug deposition onto the polymer/scaffold or scaffold alone can result in burst release. Dip coating involves submerging the stent in a solution of drug and/or polymer in a suitable solvent and then leaving the stent to dry in the air or in an oven, while the solvent evaporates. Spray coating involves spraying polymer and drug solutions using various organic solvents [96]. Complications associated with solvent-based coating techniques include bridging, pooling and lack of uniformity, which is especially the case with coating thickness less than 0.5 mm [219, 220]. Varying concentrations of drug and polymer can result in burst release with an uneven drug distribution such that the outer layers are rich with the active agent in comparison to the rest of the matrix [49, 96-98]. Multiple rounds of spray coating can lead to significant mixing between sequential layers of the polymer matrix [121] and result in higher drug content near the surface [122]. Even though, for example, the Cypher stent was designed

as a reservoir type DES [48], the imaging reveals drug presence in the external rate limiting polymer layer, resulting in diffusion-controlled release for monolithic polymer systems [223].

CONCLUSION

The ambitious goal of biodegradable technology has been to reduce the risk of stent thrombosis and the need for prolonged antiplatelet therapy as compared to earlier DES devices. Even though clinical data shows that BP-DES have superior long-term efficacy and safety as compared to earlier generation DES, current data also suggests that the potential advantages of BP-DES versus second generation durable, biocompatible DES appear less obvious. Considering the present clinical data showing that durable, biocompatible polymer DES are noninferior to biodegradable polymer DES for 1-year clinical outcomes and 2-year clinical outcomes of stent thrombosis, it is important to perhaps take a step back in DES technology geared towards polymer elimination with biodegradable and polymer-free devices. The cost of PCI is higher with BP-DES as compared to DP-DES. BP-DES devices are more complex to develop than DP-DES devices. Biodegradable DES devices are also limited in the range of polymers that can be used as compared to durable polymer devices.

Rather than eliminating the polymer, the focus should perhaps be shifted towards optimization of drug release kinetics and control of the initial burst release associated with delayed would healing, inhibition of re-endothelization and subsequent stent thrombosis. Given that present clinical data shows that BP-DES are not better than DP-DES for stent thrombosis, the focus can perhaps be shifted towards optimal release kinetics, new anti-proliferative agents conducive to re-endothelization, and more biocompatible and hemocompatible durable polymers, especially given the cost of PCI associated with BP-DES. Drug release kinetics from DES are extremely important in DES performance and are influenced by multiple formulation factors. Examining drug-in-polymer formulation properties governing and influencing drug release kinetics can possibly explain the non-inferiority of certain DP-DES devices as compared to BP-DES. Understanding drug physiochemical and pharmacological properties, polymer properties influencing diffusion and dissolution governed elution profiles, polymer properties affecting polymer degradation kinetics, the effect of additives and drug load on drug release, coating techniques in respect to burst release, as well as polymer biocompatibility and hemocompatibility can give an insight into DP-DES non-inferiority as compared to BP-DES for the existing clinical data.

Also, it is important to recognize the limitations of modeling drug release kinetics and polymer degradation kinetics for in vitro-in vivo correlation (IVIVC). Modeling burst release associated with inhibited re-endothelization and subsequent stent thrombosis remains a challenge as there are many physiological parameters and patient-to-patient baseline characteristic variability that cannot be easily incorporated into the mathematical models. However, shifting the focus from biodegradable, polymer-free devices to optimization of durable, biocompatible DES formulation factors that affect burst release and drug release in general could be important in improving current DES technology and cutting down on the cost associated with PCI.

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