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J Control Release. Author manuscript; available in PMC 2009 June 26.

Published in final edited form as:
J Control Release. 2007 November 6; 123(2): 100–108. doi:10.1016/j.jconrel.2007.06.025.

Intravascular Drug Release Kinetics Dictate Arterial Drug Deposition, Retention, and Distribution

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Abstract

Millions of patients worldwide have received drug-eluting stents to reduce their risk for in-stent restenosis. The efficacy and toxicity of these local therapeutics depend upon arterial drug deposition, distribution, and retention. To examine how administered dose and drug release kinetics control arterial drug uptake, a model was created using principles of computational fluid dynamics and transient drug diffusion-convection. The modeling predictions for drug elution were validated using empiric data from stented porcine coronary arteries. Inefficient, minimal arterial drug deposition was predicted when a bolus of drug was released and depleted within seconds. Month-long stent-based drug release efficiently delivered nearly continuous drug levels, but the slow rate of drug presentation limited arterial drug uptake. Uptake was only maximized when the rates of drug release and absorption matched, which occurred for hour-long drug release. Of the two possibly means for increasing the amount of drug on the stent, modulation of drug concentration potently impacts the magnitude of arterial drug deposition, while changes in coating drug mass affect duration of release. We demonstrate the importance of drug release kinetics and administered drug dose in governing arterial drug uptake and suggest novel drug delivery strategies for controlling spatio-temporal arterial drug distribution.

Keywords

Stents; Drug Delivery; Release Kinetics; Arterial Drug Deposition; Restenosis

2. Introduction

Blood flow through atherosclerotic vessels is restored by balloon angioplasty and/or stent implantation, but vessel patency is frequently short-lived. In a process termed intimal hyperplasia, proliferating cells grow radially inward to re-occlude the vessel, which results in a clinical failure phenomena termed restenosis. The burden of restenosis has been alleviated in part by delivering anti-proliferative drugs to the arterial wall. The biologic effect of drug

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therapy is known to be determined by the drug biologic potency[1] and physicochemical properties[2-4]. However, the role of dosage and timing of arterial drug presentation for biologic outcome remains unclear. Clinical studies have hinted toward the importance of exceeding a dose and/or timing threshold to achieve biologic effect. In the O-SIRIS trial, orally delivered sirolimus inhibited intimal hyperplasia only if administered at high doses for 2 days prior to the procedure[5]. In the ELUTES clinical trial[6], paclitaxel delivered from stents significantly reduced the percent diameter stenosis at 6 months only when delivered at the highest applied drug dose. That biologic success could be achieved by vastly different drug delivery modalities, such as oral delivery[5], drug release from coated stents[7, 8] or coated angioplasty balloons[9], suggests that a range of drug dosage and release kinetics is capable of eliciting the desired arterial response.

Based on both clinical and *in vitro* data, our hypothesis was that applied drug dose and release kinetics modulate arterial drug uptake. In turn, drug distribution and retention within the arterial wall likely dictate biologic outcome. In an era in which anti-proliferative outcome must be balanced with the risk of potentially fatal toxic sequelae, such as stent thrombosis, understanding how administered dose and release kinetics impact arterial drug uptake is a critical component to ensuring device safety and efficacy. Thus, we examined tissue drug uptake resulting from a range of administered drug dose and release kinetics using computational models. *In silico* predictions of tissue drug uptake from clinically tested devices were compared with observed *in vivo* biologic effects. Using this method, we have begun to understand the complex relationships between release kinetics, tissue drug levels, and biologic outcome. As advances in local drug delivery technology enable precisely controlled drug release[10-13], choosing an effective drug delivery strategy will rely on our knowledge of how different drug delivery modalities achieve a particular arterial drug uptake, which in part dictates biologic effect.

Computational techniques were ideal for this work because they enable rapid consideration of a range of drug doses and release kinetics followed by precise monitoring of arterial drug deposition, distribution, and retention. We employed an experimentally validated finite volume based computational model in which drug diffused from a drug laden strut to and through the arterial wall with simultaneous diffusive-convective drug washout into flowing blood. The computational model predicted that release kinetics and applied drug dose modulate arterial drug deposition, distribution, and retention. But surprisingly, our predicted variations in arterial drug uptake did not necessarily correspond with a dose dependent biologic response. Biologic response is likely determined by device dependent arterial drug uptake and extrinsic factors such as tissue state.

3. Methods

Mathematical Model

Drug transport was modeled using a 2-dimensional transient model (Fig 1). The luminal diameter (2R), 3 mm, was 3 times greater than the arterial wall thickness (W_{tissue}). The axial distance along the artery was based on the fluid mechanic entry length required to reach fully developed flow[14]. The strut and coating dimensions were based upon representative dimensions of the CYPHER© Bx Velocity drug-eluting stent (Cordis Corporation, a Johnson & Johnson Company).

The blood flow was assumed steady state. This was a necessary simplification, because the pulsatility of blood at 1 Hz would have required a coupled solution of fluid mechanics and mass transfer equations, rather than separate handling of these equations. Such a task would have been computationally prohibitive, because the rapidly changing flow features combined with the long duration of drug release would have increased the computational task by 4 orders

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of magnitude. Thus, for an initial transient analysis, it was concluded that the steady flow approximation would be sufficient to elucidate any potential role of local fluid mechanics in transient drug delivery. Similar steady flow assumptions in coronary arteries have been made in other similar computational studies to facilitate the coupled study of local fluid mechanics and mass transport[15]. Subsequent studies focusing on flow pulsatility may employ a modified computational approach to reduce the computational burden and possibly combine the analysis with parallel experiments.

As in previous work[16], the blood was assumed Newtonian, because blood viscosity becomes shear-independent for shear rates above 100 s^{-1} [17] and Reynolds number above 100 [18], both of which occur in a 3mm diameter coronary artery with steady 100 cc/min blood flow. The fluid mechanics were described using continuity and steady state Navier-Stokes equations (Fig 2, Eq 1-3). The inlet profile, applied at axial position $z = -L_{Proximal}$ (Fig 1), was assumed unidirectional and parabolic (Fig 2, Eq 4). Fully developed flow upstream of the stent strut was verified by comparing the velocity profiles at several axial locations between the inlet and the strut. The outlet, located at axial position $z = L_{Distal}$ (Fig 1), was set to a reference pressure of zero (Fig 2, Eq 6). All components of blood velocity were zero at all solid-fluid interfaces (Fig 2, Eq 5), which reflects the assumed impermeability of the vessel to transmural convective flux and the finite blood viscosity that prevents tangential blood flow at the vessel surfaces. The fluid mechanical blood properties and volumetric flow rate were obtained from standard reference values[19].

Time-dependent drug transport within the coating was assumed to occur solely via transient diffusion of drug (Fig 2, Eq 7), which was reasonable based on the sirolimus-eluting stent (CYPHER© Bx Velocity, Cordis Corporation) coating properties and its application process[20, 21]. This assumption was later validated when predicted release kinetics were compared with *in vivo* measurements of drug release. Drug diffusivity within the coating was calculated based on the desired duration of drug release and the coating thickness, $D_c = L_{coat}^2/t_{release}$ [14]. Drug release ranged from bolus to intra-arterial drug infusion to continuous, 30 day release. Initially, the drug concentration was unity throughout the coating (Fig 2, Eq 18), and all other blood and tissue areas were presumed devoid of drug (Fig 2, Eq 19).

The process of drug diffusion from the coating to the surrounding blood and tissue was handled using a continuity of flux boundary condition at the interfaces between the coating and the tissue/blood (Fig 2, Eqs 16,17). Upon entering the blood, drug transport was described by the transient diffusion and convection equation (Fig 2, Eq 8). The luminal inlet drug concentration was assumed zero (Fig 2, Eq 10)[16], which is valid because in the convection dominated arterial lumen it is virtually impossible for drug to diffuse 5 mm in the direction opposing blood flow, which is approximately 35 times the stent strut width[14]. It is also unlikely that drug would diffuse perpendicular to the direction of blood flow to the opposite arterial wall, a distance equivalent to more than 20 times the stent strut thickness; thus, the tissue wall above the stent strut had a no flux boundary condition (Fig 2, Eq 12). The outlet of the vessel had an open boundary condition (Fig 2, Eq 11), because flowing blood carried solubilized drug downstream. Drug transport between the tissue and blood was enabled using a continuity of flux condition (Fig 2, Eq 13) applied to the tissue-blood interface[16].

Finally, drug transport through the arterial tissue was approximated using the transient diffusion equation (Fig 2, Eq 9). Diffusive drug transport has previously been identified as a dominant transport mechanism in the arterial wall[22]. The perivascular wall ($r = -W_{tissue}$, Fig 1) was assumed to be impenetrable to drug transport (Fig 2, Eq 15). The up- and downstream boundaries of the tissue had symmetry boundary conditions (Fig 2, Eq 14)[16], which allowed drug transport to distal arterial segments. Drug transport parameters in the tissue were based upon experimental measurements of transmural drug diffusivity[23].

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Numerical Methods

Commercially available geometry/mesh generation and computational fluid dynamics software (GAMBIT v2.3.16, FLUENT v6.3.17, Fluent Inc., Hanover, NH) were used to apply the mathematical model. The geometry was discretized into approximately 200,000 rectangular mapped mesh elements. To ensure that the discretized geometry had sufficient resolution to detect changes induced by model parameters, a mesh sensitivity study was performed. Results show that doubling local mesh density resulted in less than 2% change in local and average arterial and coating drug concentrations. The discretized geometry was imported into Fluent, a finite volume based software. Second order discretization schemes were used for all velocities and concentration variables. The momentum and continuity equations were solved iteratively using SIMPLEC algorithm[24] for pressure-velocity coupling; the diffusion-convection equations were handled with upwind differencing.

Experimental Methods

CYPHER© Bx velocity stents (Cordis Corporation) were deployed to a target balloon artery ratio of 1.1:1 into porcine coronary arteries. At the designated time points of 1, 8, 14, 30, 60 and 90 days post-implantation, the stented arteries (n = 6 per time point) were harvested and the stent was carefully separated from the surrounding arterial tissue. Sirolimus was extracted from the stents in 10 ml of HPLC grade methanol and quantified using standard LC/MS/MS methodology.

4. Results

Release Rates are Modulated by Drug Coating Diffusivity and Affect Arterial Drug Deposition and Retention

The validity of the transient 2-dimensional diffusion-convection computational model was confirmed by comparing predicted drug release from stent strut coatings with actual release from devices implanted in porcine coronary arteries. The model accurately predicted *in vivo* fractional drug release over a 90 day interval with a root mean squared error of < 0.1. In both the model and *in vivo* experiment, at 2 weeks post-implantation, the stent had released half of its initial load into the tissue and the surrounding lumenally flowing blood (Fig 3).

Within the model, drug diffusivities modulate drug elution from the coating within the extremes of bolus to continuous drug delivery. At high drug coating diffusivity, e.g. 10^5 um^2/s, drug depletes from the coating within seconds post-implantation, analogous to true bolus drug administration (Fig 4a). If release is prolonged, e.g. with coating drug diffusivity of 1 um^2/s, the timescale for drug elution and depletion extends for hours post-implantation, similar to intravenous bolus drug delivery (Fig 4a). Finally, drug release is lengthened most dramatically to weeks and months post-implantation for coating diffusivity around 10^{-5} um^2/s, which is akin to local stent based drug delivery (Fig 4a). Even within the class of slow stent based drug delivery, release could be made to vary from 10 days to more than 1 month of drug release (Fig 5a).

Arterial drug uptake was predicted to follow drug release. The transient arterial drug concentrations result from a balance between drug availability and the rates of drug release from the coating and tissue uptake. At the extremes of drug diffusivity within the coating, drug is released so rapidly that it exceeds the tissue absorption rate, or so slowly as to limit the amount of drug presented to the artery (Fig 4a-b). The former represents an inefficiency wherein drug is diluted systemically prior to arterial uptake and the latter is an efficient, but release rate-limiting state. True bolus drug administration results in a low peak in arterial drug uptake that is transient and rapidly lost as the model drug does not significantly enter the target tissue and local stent drug concentrations are insufficient to maintain arterial drug delivery (Fig

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4b). If drug is administered over several hours akin to intravascular infusion, peak arterial drug deposition should be maximized, although arterial drug retention will only last for a few days post-implantation (Fig 4b). Without binding, readily diffusible drugs like heparin may achieve high peak arterial drug concentrations that rapidly decay when delivered quickly from the stent. Finally, if drug release is prolonged for weeks and months, the arterial drug uptake is submaximal, but uptake will be more efficient. Continuous, long term drug release enables arterial drug retention which decays more than a month after implantation (Fig 4b). Even increasing drug diffusivity marginally by 3 fold translates into 3 times faster release (Fig 5a), raising peak arterial drug uptake by 70%. This rise subsides two weeks after implantation (Fig 5b). Clearly fluctuations in release rate are responsible for potentially large shifts in the dynamics of arterial drug uptake.

The distribution of drug within the arterial wall also depends on the drug release rate from the coating. Bolus release allows transient drug accumulation within the blood. Subsequently, more drug deposits asymmetrically downstream from the stent strut than upstream in the arterial wall (Fig 4c) within 2 min post-implantation. Conversely, when the release rate is slow, there is limited drug release, minimal luminal drug accumulation, and symmetric arterial drug deposition. In all cases, asymmetric arterial drug deposition should no longer be observed beyond 1 day post-implantation (Fig 4c).

Release Rate Affects Arterial Drug Deposition and Retention Independently of Drug Load

The impact of drug release kinetics on arterial drug uptake was explored by modifying the properties of coated struts while maintaining a fixed initial drug load. Release rates can be modulated independently of drug load not only by changing the drug diffusivity through the coating (Fig 4a), but also by changing the drug concentration with a commensurate and opposite change in coating thickness. Drug release rate from thinner, high concentration coatings is predicted to be fast initially, leading to a rapid decline in coating drug concentration (Fig 6a) as compared to thicker, lower drug concentration coatings. Due to the large fractional drug release for thinner coatings, arterial drug deposition peaks and remains elevated for 20 days post-implantation (Fig 6b). Once the fast releasing thin coatings are nearly depleted, the arterial wall loses drug faster than it receives it from the coating, leading to brief arterial drug retention (Fig 6b). In contrast, thicker coatings possessing a lower drug concentration release their load slowly and relatively steadily, with a gradual decrease in coating drug concentrations (Fig 6a). Slow release reduces the extent of arterial drug deposition in the short term, but by 30 days post-implantation, the continued drug infusion from the thicker coating sustains a more constant level of arterial drug deposition and retention, compared to that occurring from its thinner coated counterpart (Fig 6b).

DES Strut Dimensions and Drug Concentration Impact Initial Drug Load and Arterial Drug Deposition

While release rate can be altered independently of applied drug load, changes in release rate may also result from modifying the drug load. Variable drug loading on stents can be achieved either by increasing the relative amount of drug in the polymer formulation or by increasing both the drug and polymer proportionally on the stent strut. The former was simulated by increasing drug concentration in the coating, and the latter by increasing drug coating thickness on the stent strut. Increasing the coating drug concentration elevates the drug load but not the duration of drug release, which leads to faster drug release (Fig 5a, 6a). In response, arterial drug deposition increases proportionally with the increase in drug concentration (Fig 5b, 6b), such that a 3-fold increase in stent drug concentrations causes a commensurate 3-fold elevation in arterial drug uptake (Fig 5b).

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If drug load is increased by applying thicker drug-laden coatings, release is slow and prolonged due to the longer drug diffusion distance, thus drug levels within the coated stent decline gradually (Fig 7a). Thicker coatings possess a larger initial drug load than thinner coatings and subsequently release more drug within a given interval (Fig 7b). The slower release rate of the thicker coating combined with its larger drug mass should induce 10-20% increase in peak arterial drug deposition that remains elevated over time (Fig 7c). Conversely, thin coatings have smaller drug load (Fig 7b) that release faster (Fig 7a), and lead to lower arterial drug deposition (Fig 7c).

The impact of redistributing the coating thickness from the inner diameter (ID) to outer diameter (OD) of the stent strut was tested with no change in total coating thickness or peri-strut fluid dynamics. If the OD coating is 3-fold thicker than the ID, drug release will be slightly slower and arterial drug uptake will increase minimally; all of which are insignificant changes compared to the effects of increasing total coating thickness (Fig 7a,c). Similar results were obtained with strut dimensions. Strut size is dependent upon stent design and varies dramatically amongst devices, often resulting in different stent drug loads. When struts possessing 5-10% longer width and greater drug mass are examined by simulation, the surface area of the strut contacting the arterial wall increases. The resulting drug release is predicted to be negligibly impacted (Fig 8a), although peak arterial drug deposition should increase 10-20% within 2 days (Fig 8b) due to greater surface area drug exposure. By contrast, a 15% taller strut carrying more drug than the wide struts is not predicted to exhibit any difference in release rate or drug uptake compared to a shorter strut carrying a smaller drug load (Fig 8b). These model findings illustrate that arterial drug uptake is not only determined by total applied drug load but it is sensitive to strut-arterial wall contact area. Specifically, strut-artery contact more significantly altered drug deposition than equivalent changes in strut height.

5. Discussion

Computational models of drug transport and target penetration are only valid if the simulated release kinetics are realistic. In this study, we demonstrate that a simple Fickian diffusion model of drug transport in the coating can approximate the process wherein drug navigates through a complex porous polymeric coating[21]. This was illustrated when predictions of concentration gradient drug diffusion faithfully matched 30 day *in vivo* release (Fig 3a). Although passive diffusion is governed by the effective drug diffusivity and the porosity and tortuosity of the polymer coating[25], these multivariate interactions were treated in aggregate by using a constant effective drug diffusivity to characterize the drug-polymer interaction. This validated model was used to simulate arterial drug uptake resulting from a range of release kinetics.

Drug dose and release kinetics, predicted arterial uptake, and biologic outcome

From the first identification of restenosis after angioplasty, the role of drug dosage and release kinetics in inhibiting intimal hyperplasia has been questioned. The importance of timing and dose of local drug delivery was highlighted by clinical studies. Oral sirolimus reduced angiographic restenosis post-stent implantation only when the drug was ingested at high doses and given at least two days before the procedure[5]. Decreases in intimal hyperplasia have not been limited to a single drug presentation kinetic, as evidenced by the success of vastly different modalities such as: administration of drugs in a sustained fashion over months from the stents themselves[6, 7, 26-28], drug delivery over a few minutes from coated angioplasty balloons[9], intra-coronary injections in the presence of angiographic contrast media[29, 30], and infusion from microporous catheters[1, 31].

Drug delivery systems induce arterial drug exposure in a manner that ranges from short bursts to sustained release. The resultant biologic outcome has been variable for each delivery modality. To correlate differences in arterial drug uptake with biologic outcome, we compared

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the arterial drug levels resulting from transient, slightly prolonged and markedly sustained drug exposure (Fig 4a) with observed clinical results. Arterial drug uptake was predicted to vary significantly for different release kinetics. True bolus release, which releases and clears drug from the local milieu within seconds, should have negligible arterial drug uptake (Fig 4b), and indeed intra-arterial bolus injection of paclitaxel into the femoral artery adds no benefit to balloon angioplasty alone[9]. However, when drug delivery is slightly prolonged, occurring over several minutes to hours, more significant arterial drug levels are expected (Fig 4a-b). This situation is approximated by drug that is mixed with ionic contrast media and injected into the coronary circulation[29, 30, 32]. The mixing of and subsequent binding of drug with contrast media alters the transport of the drug and its tissue interaction. As a result, drug circulation time is likely prolonged beyond the true bolus profile and drug penetration is enhanced. Paclitaxel and contrast media injection reduces hyperplastic stenosis and preserves lumen diameter for days and weeks after stent implantation[29, 30, 32]. Taken together experimental and computational studies to date imply that transient arterial drug exposure can sustain a relatively longer term favorable biological response when initiated shortly after injury. This paradigm is consistent with the reduction in lumen loss and restenosis occurring when paclitaxel coated balloons were expanded within the femoral artery for minutes allowing drug delivery directly from balloon-artery contact [9]. Such a procedure not only affects local injury and healing but also should provide a high magnitude peak arterial drug uptake that only subsides within a day (Fig 4). These findings hint toward the existence of a temporal window for biologic efficacy that begins immediately after procedure induced injury.

In contrast to fast drug release kinetics, polymer matrix-based stent arterial drug delivery is prolonged for weeks and even months. Sustained delivery is expected to produce sustained arterial drug levels (Fig 4a-b), but may result in variable in biologic outcome. In the PISCES clinical trial, paclitaxel was effective when released over 10 or 30, but not 5 days[33]. Tripling the delivered dose did not alter outcome when delivered for 5 or 30 days, and only minimally improved biologic response when delivered over 10 days. Computational predictions show that extending the release of a fixed dose from 10 to 30 days creates a relatively more constant arterial drug infusion (Fig 5a). Delivering three fold more drug by increasing stent drug concentration predicted a 3-fold increase in peak arterial drug uptake, which subsequently declined rapidly (Fig 5). Thus, for the doses and durations considered in the PISCES trial, duration of arterial drug exposure, rather than peak arterial drug concentrations appears to have been the primary determinant of biologic response.

A broad range of drug delivery kinetics has demonstrated potential for inhibiting intimal hyperplasia; abbreviated release likely requires substantially larger arterial drug concentrations to achieve efficacy while sustained release does not. The ability of short and long term drug release modalities to inhibit intimal hyperplasia and the range of outcomes observed from each kinetic indicate that there may exist a mix of arterial drug dose and retention times whose therapeutic potential depends on the arterial tissue state and extent of injury.

Understanding Absence of Dose Response

Despite the range of local and systemic drug delivery modalities, there has yet to be a definitive demonstration of a dose response in animal models or clinical experience[6, 33, 34]; drugs work at some dose and do not below this level. One interpretation of these observations is that the arterial wall is insensitive to differences in the drug delivery modality. However, the many failed attempts to eradicate restenosis make this idea remote[6, 34, 35]. Alternatively, seemingly disparate, successful modes of local drug delivery may actually be biologically indistinguishable. This could occur if the complexities of the arterial drug metabolism and biologic pathways preclude a dose response. In addition, the artery may be capable of eliciting a dose response, but the actual dose/kinetics of drug delivery for various clinical modalities

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may be so similar that they do not adequately stress the system to achieve a varied response. Our findings are consistent with all of these views.

Potential explanations for the absence of a dose response within clinical trials[6, 33, 36, 37] can be formulated by comparing computational predictions of polymer matrix-based stent arterial drug delivery with outcomes from clinical trials. In the 3D study[37], doubling the dose of sirolimus from the Cypher stent did not alter IVUS detected neointimal hyperplasia in diabetics followed for 6 months to 2 years. We predict that a double dose achieved by doubling drug coating thickness prolongs drug release (Fig 7a) but only increases peak arterial drug deposition by 20% (Fig 7b). In this case, the modest increase in arterial drug uptake despite a 2-fold increase in administered drug dose is a result of the slow nature of drug release through the thickened coating. The 20% increased arterial drug uptake is not likely to elicit distinguishable biologic dose effect. In fact, most possible modifications of stent design, such as the possible range of coating distribution around the strut (Fig 7a,c), or strut dimensions (Fig 8a-b) cannot be changed enough to significantly impact release kinetics or arterial drug uptake. Design may dictate arterial wall injury, but does not change release features and subsequent arterial drug uptake within the limits of the formulations considered.

Even trials with potentially significant fluctuations in release kinetics and arterial drug uptake did not produce a dose response, indicating that the arterial wall may regulate either its drug absorption or its response to absorbed drug. The arterial wall may be controlling biologic outcome independently of arterial drug uptake through control of drug binding. Specific and nonspecific tissue binding sites for example, enable arterial control over response to drugs used in eluting-stents[4]. The dose response range could be easily missed if the applied drug concentration exceeds the receptor density and if the receptors have strong binding affinity for the drug. In this case, the receptors would rapidly saturate and display nearly binary biologic response.

The ELUTES trial illustrates how devices with expected large variation in arterial drug exposure do not demonstrate dose response. In the ELUTES trial[6] paclitaxel was precipitated directly onto bare metal stents at four doses spanning a 10-fold range, Only the highest dose had a statistically significant reduction in angiographic restenosis compared to the bare metal stent. Simulations demonstrate that a ten-fold increase drug dose achieved by increasing stent drug concentration resulted in faster drug release and 10-fold increased transient peaks in arterial drug deposition, which gradually tapered (data not shown). Since dramatic fluctuations in arterial drug deposition did not elicit a dose response, one may infer that the range of potential dose response is narrower than the range of stent induced arterial drug uptake kinetics. Tissue-based drug metabolism and clearance may produce an exceedingly narrow dose response range which practically leads to threshold, binary behavior.

6. Conclusions and Future Directions

Drug release kinetics and applied dose are responsible in part for the duration and magnitude of arterial drug uptake. Surprisingly, the clinical data in conjunction with computational predictions suggest that biologic effect exhibits a threshold response despite wide variations in arterial drug uptake. It is likely that the drug delivery modality and arterial wall jointly contribute to the biologic effect of drugs on vascular repair. Thus, a favorable biologic response to locally delivered drug likely requires a balance between arterial drug dose, exposure time, capacity for drug absorption, the extent of injury and subsequent reparative process. It remains for future work to fully characterize the arterial wall and the relationship between drug uptake and biologic outcome.

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Computational models are valuable and expedient tools for understanding the impact of specific physical phenomena on arterial drug delivery, yet they necessarily employ simplifications. In this computational model only diffusive drug transport forces within the arterial wall were considered. In reality, the arterial wall is a heterogeneous complex milieu in which drug diffuses passively, travels via pressure-driven radial flow, and also binds to drug-specific arterial components. It remains for future work to assess the aggregate impact of additional physical phenomena upon arterial drug uptake.

Acknowledgments

The study was supported in part by grants from the NIH (R01 HL-49309) and an unrestricted gift from Cordis Corporation (a Johnson and Johnson Company). We thank Drs. Ajit Mishra, Ramesh Marrey, and Robert Burgermeister (Cordis Corporation) for their assistance in determining representative stent and coating dimensions.

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9. Abbreviations Key

Ω_{Tissue}, Ω_{Blood}, Ω_{Coat}
: Tissue, blood, and coating domains.

W_{Tissue}, L_{Coat}
: Thickness of arterial tissue and coating.

R, 2R
: Arterial lumen radius and diameter

$L_{Proximal}$, L_{Distal}
: Length of vessel upstream and downstream from the strut.

$t_{release}$
: Duration of drug release.

V_C
: Maximum centerline velocity of blood flow.

r, z, t
: Radial and axial axes, and time

v_r, v_z
: Radial and axial component velocities

P
: Dynamic pressure

C_t, C_b, C_c
: Drug concentrations within tissue, blood, and coating

μ, ρ
: Blood properties: dynamic viscosity and density

D_t, D_b, D_c
: Drug diffusivities within tissue, blood, and coating

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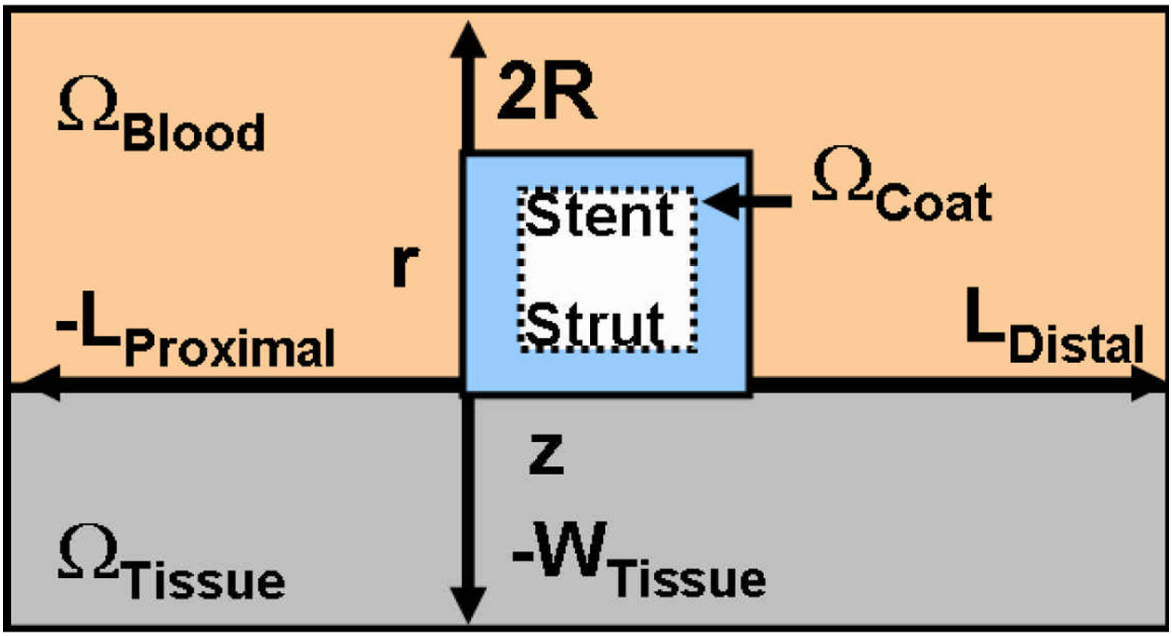

Figure 1.
Schematic representation of an implanted endovascular drug coated stent strut residing in the blood flow field and overlying the arterial wall. Ω_{Tissue}, Ω_{Blood}, Ω_{Coat} represent the tissue (shaded gray), lumen (shaded tan), and drug laden strut coating (shaded blue) regions. Blood flow occurs in the positive z axial direction.

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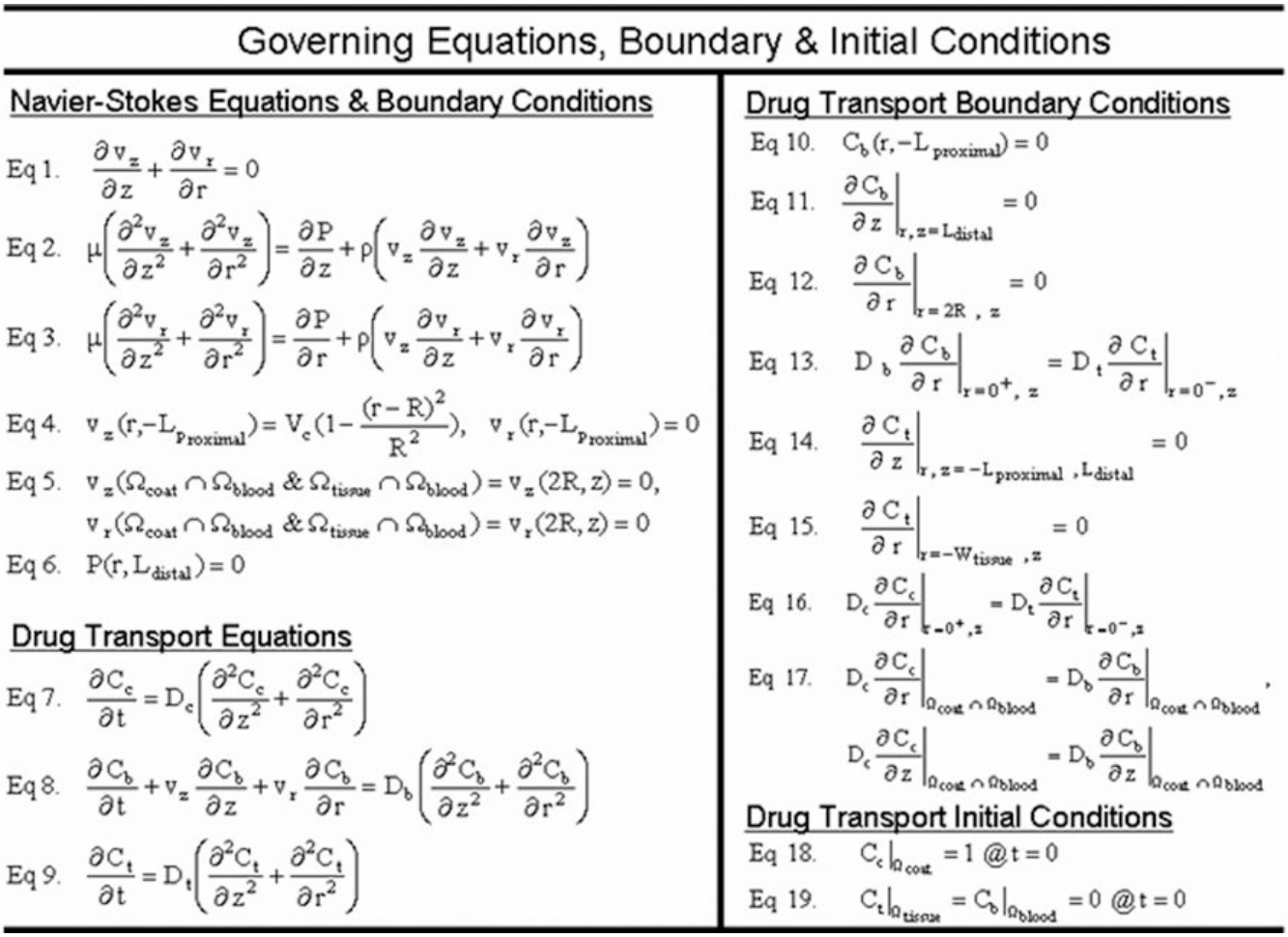

Figure 2.

Governing equations and boundary conditions describing the physics of fluid dynamics and transient drug transport. The arterial luminal radius (R) is 1.5 mm and the arterial wall thickness (W_{tissue}) is 1 mm. The velocity map in the radial and axial directions, v_r and v_z, were calculated based on the inlet parabolic profile with centerline velocity (V_c) of 46 cm/s. Tissue and blood drug concentrations, (C_t and C_b) were normalized to the strut drug concentration, $C_c = 1$. D_b, D_t, D_c are drug diffusion coefficients in blood, 10^{+5} um^2/s, in the arterial wall, 1 um^2/s, and in the coating, ranging from 10^{+5} - 10^{-5} um^2/s.

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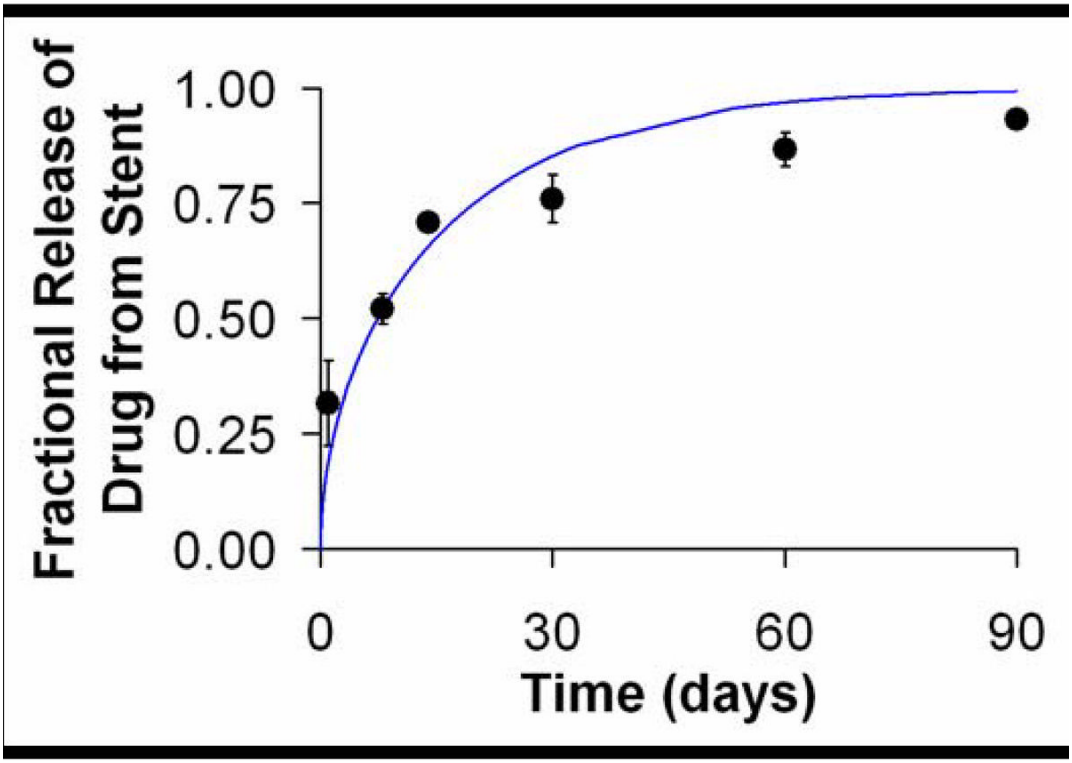

Figure 3.
Experimental validation for computationally predicted fractional drug release from a stent. In vivo data were obtained from analysis of porcine implanted stent drug levels at designated time points of 1, 8, 14, 30, 60, and 90 days post-implantation. Computationally predictions of fractional drug release were obtained using coating drug diffusivity of 1.5×10^{-5} um^2/s.

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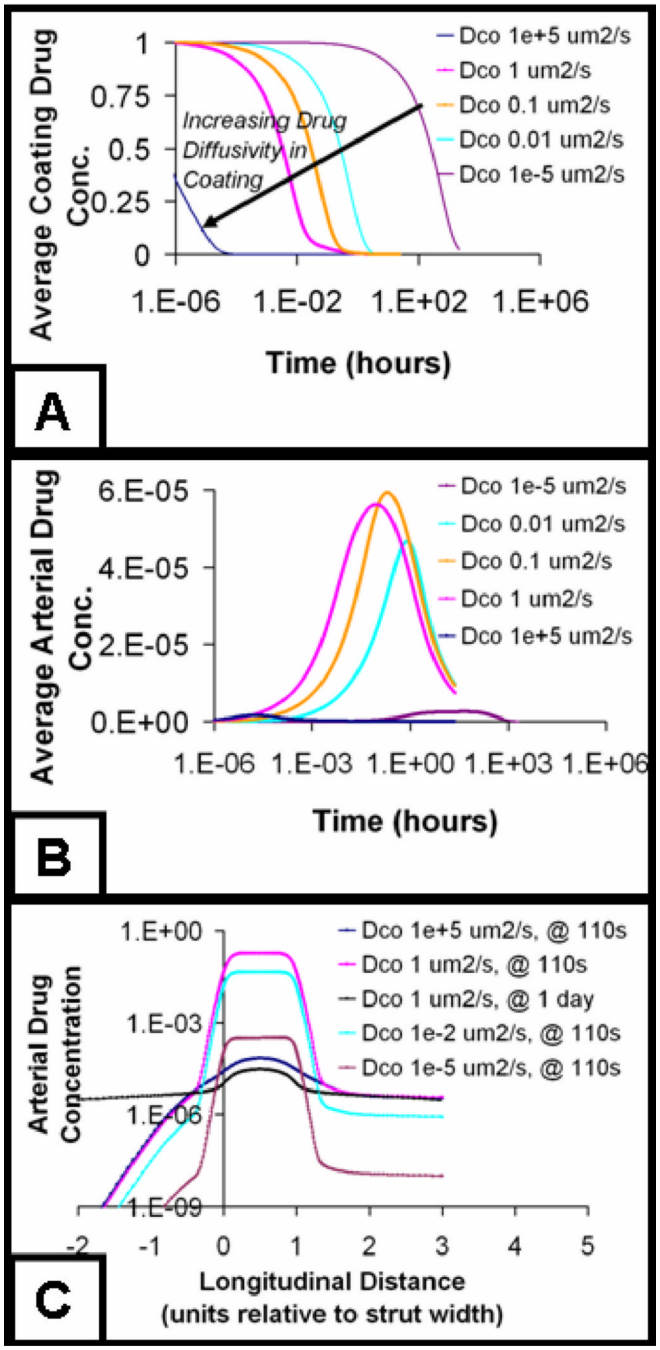

Figure 4.

Impact of varying drug release rate from the coated strut by changing drug diffusivity within the coating within a 10 log range. A. Average coating drug concentration vs. time, B. Average arterial drug deposition vs. time, C. Arterial drug concentration vs. longitudinal position along the arterial wall at a location <1 strut depth within the arterial wall at 110s and 1 day post-implantation. All data were acquired using a transient computational model with equivalent initial drug load conditions.

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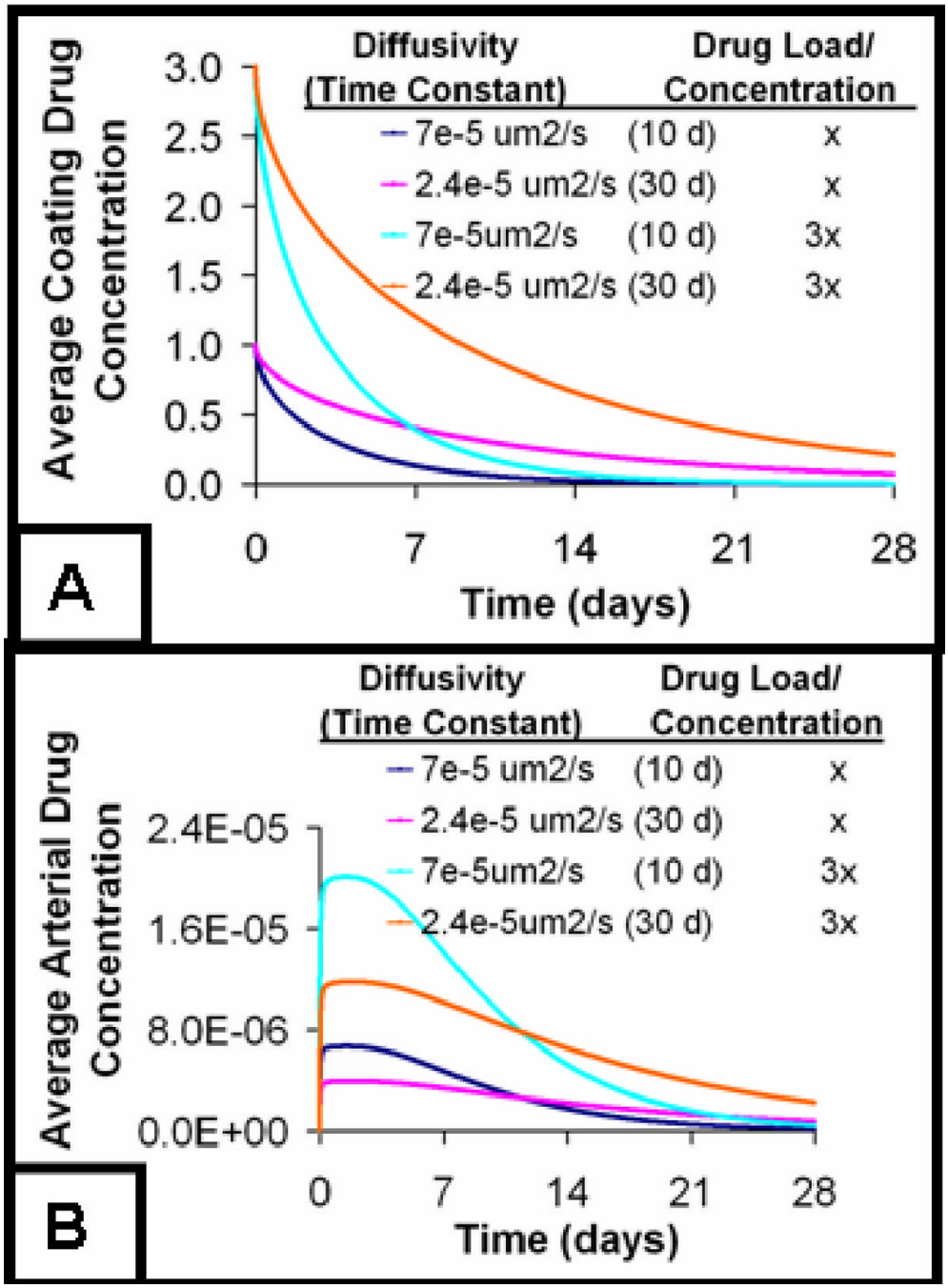

Figure 5.

Impact of modulating release rate by (1) increasing coating drug diffusivity while maintaining constant coating drug load and (2) increasing applied drug concentration and coating drug load while maintaining constant coating drug diffusivity. A. Average coating drug concentration vs. time. B. Average arterial drug concentration vs. time.

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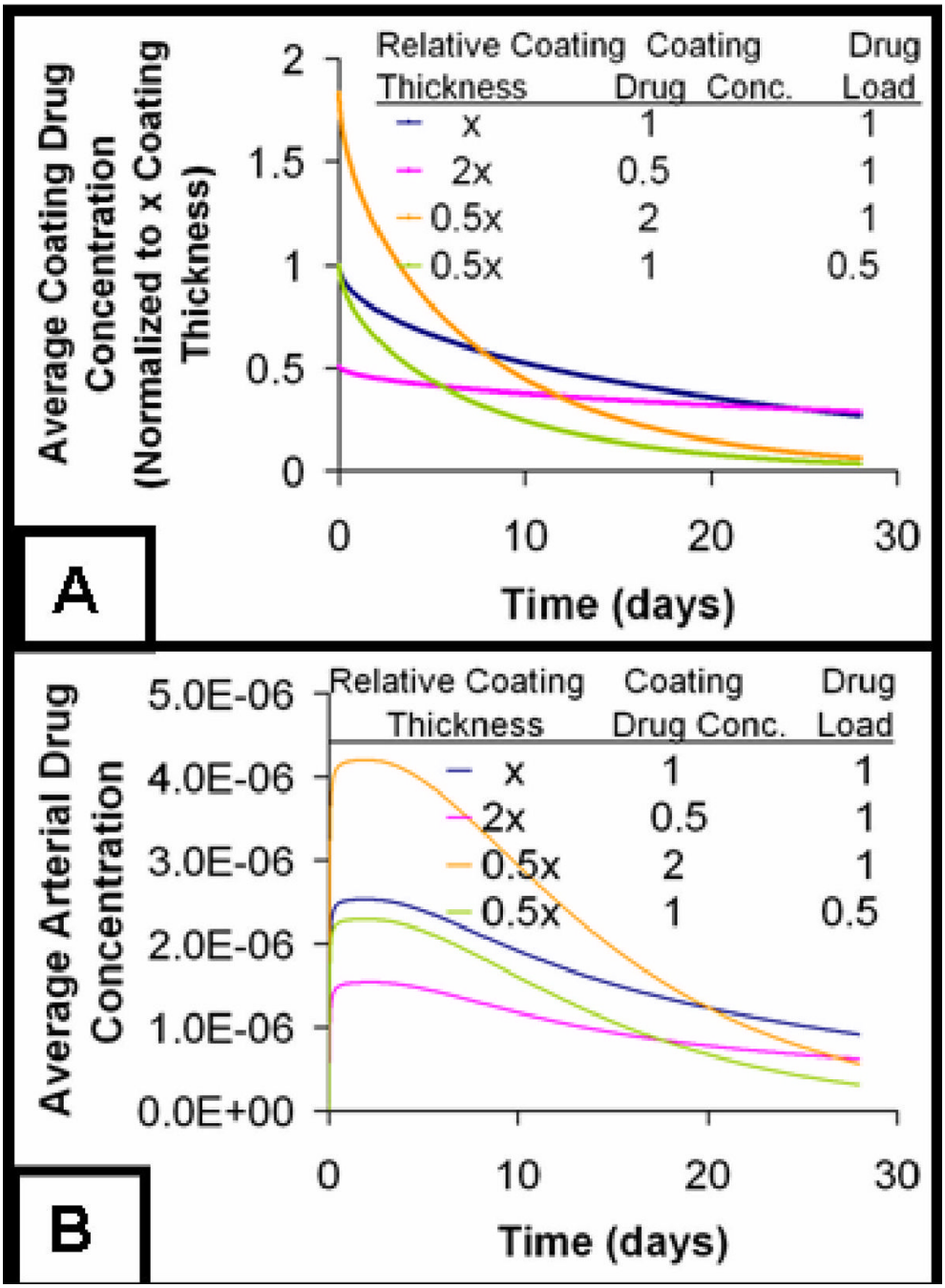

Figure 6.

Impact of altering release rate independently of initial drug load by simultaneous and opposite variations in relative coating thickness and coating drug concentration using a coating drug diffusivity of 10^{-5} um^2/s. A. Average coating drug concentration vs. time. B. Average arterial drug concentration vs. time.

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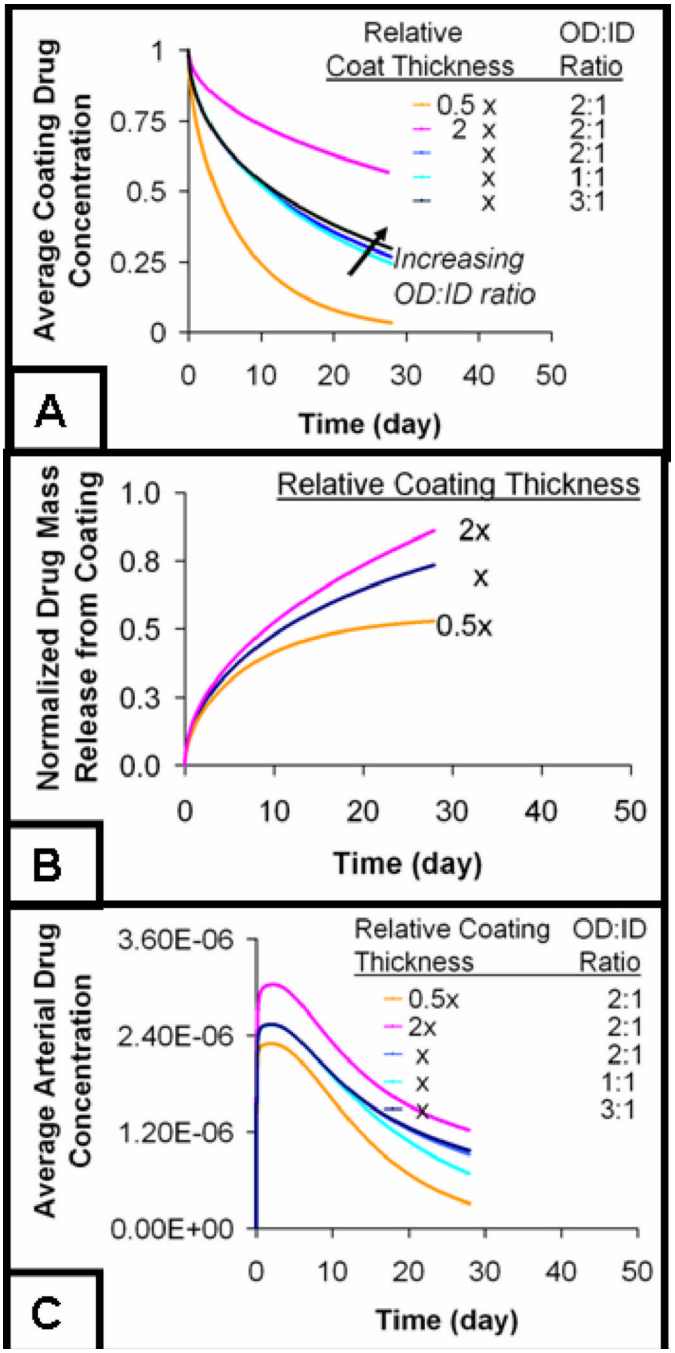

Figure 7.

Impact of altering release rate by changing initial drug load via increased coating thickness using coating drug diffusivity of 10^{-5} um^2/s. A. Average coating drug concentration vs. time for different coating thicknesses and distributions of coating around the strut, B. Drug released from the stent normalized by the initial drug load on the "x" coating thickness strut, C. Average arterial drug concentration vs. time. All initial coating drug concentrations were unity.

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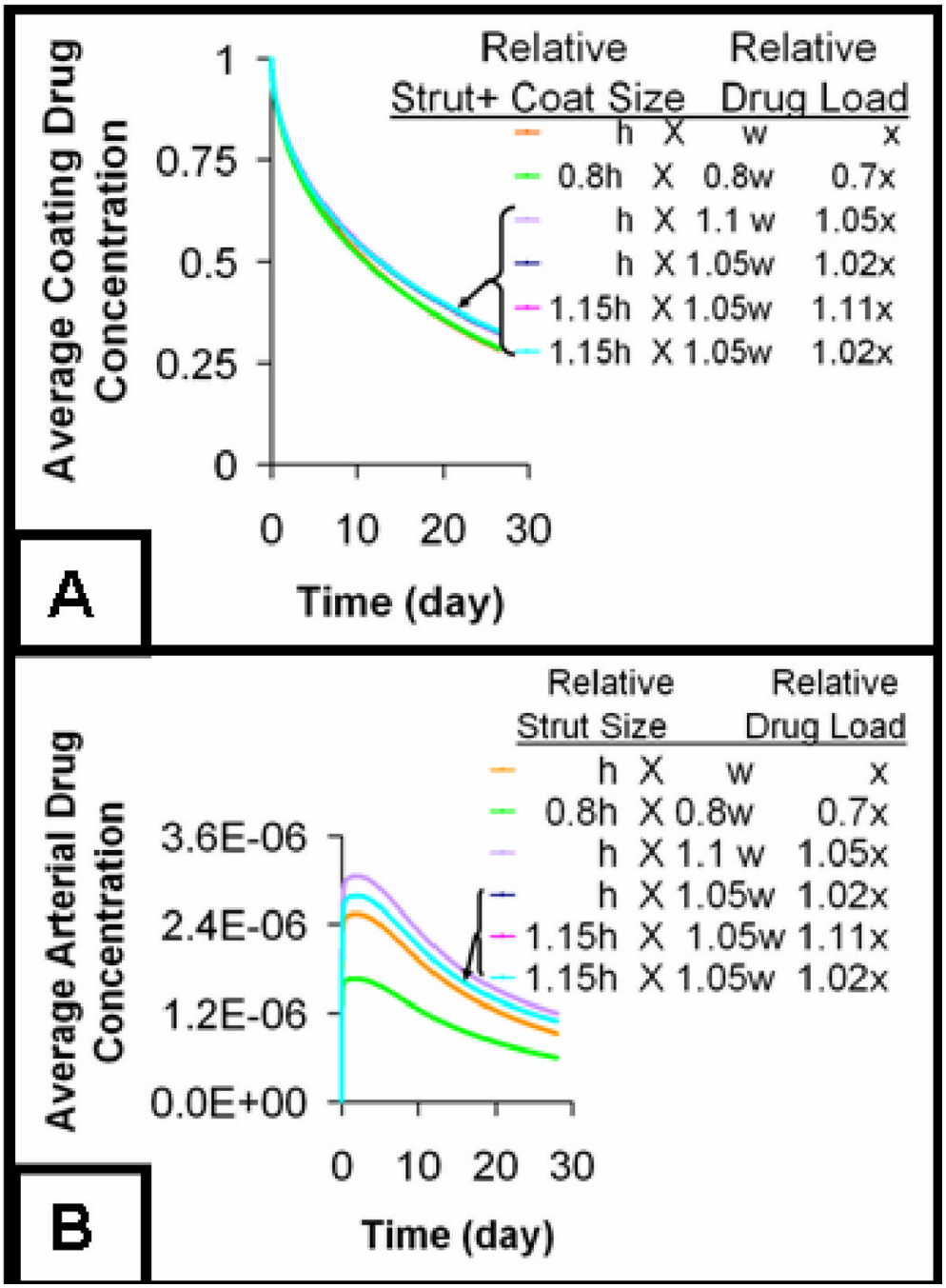

Figure 8.

Impact of variations in coated strut size and coating drug load on drug release kinetics and arterial drug uptake using coating drug diffusivity of 10^{-5} um^2/s. A. Average coating drug concentration vs. time, B. Average arterial drug concentration vs. time for different strut sizes. All coating drug concentrations were initially unity. Brackets around legend entries indicate overlapping curves as designated by arrow.