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# MECHANISM OF CONTROLLED RELEASE KINETICS FROM MEDICAL DEVICES

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**Abstract -** Utilization of biodegradable polymers for controlled drug delivery has gained immense attention in the pharmaceutical and medical device industry to administer various drugs, proteins and other bio-molecules both systematically and locally to cure several diseases. The efficacy and toxicity of this local therapeutics depends upon drug release kinetics, which will further decide drug deposition, distribution, and retention at the target site. Drug Eluting Stent (DES) presently possesses clinical importance as an alternative to Coronary Artery Bypass Grafting due to the ease of the procedure and comparable safety and efficacy. Many models have been developed to describe the drug delivery from polymeric carriers based on the different mechanisms which control the release phenomenon from DES. Advanced characterization techniques facilitate an understanding of the complexities behind design and related drug release behavior of drug eluting stents, which aids in the development of improved future drug eluting systems. This review discusses different drug release mechanisms, engineering principles, mathematical models and current trends that are proposed for drug-polymer coated medical devices such as cardiovascular stents and different analytical methods currently utilized to probe diverse characteristics of drug eluting devices.
*Keywords*: Drug release kinetics; Polymers; Stent.

## INTRODUCTION

The development of polymeric controlled release systems introduced a new concept in drug administration to treat numerous diseases.The purpose of controlled release systems is to maintain an adequate drug concentration in the blood or in target tissues at a desired value as long as possible and, for this, they are able to control drug release rate (Grassi, 1996; Langer and Wise, 1984; Pillai et al., 2001). These systems are less complicated with high stability. Biodegradable polymers have been used in controlled drug delivery for many years as a means of prolonging the action of therapeutic agents in the body, without the need to remove the device after treatment (Domb et al., 2003; Langer, 1990). The significant feature of current biodegradable devices and coatings is that they provide a continuous drug release over an extended period of time. Optimized pharmacokinetic-pharmacodynamic effects of drugs is a prerequisite for a given extended drug release device to achieve favorable biological response. The drug release profile can be programmed to meet specific requirements by optimizing the composition of formulations, processing parameters such as coating level, drug-polymer ratio and type and amount of polymer-plasticizer utilized (Frohoff-Hülsmann et al., 1999; Okarter and Singla 2000; Shao et al., 2002). The ideal goal for any drug eluting device is to deliver the therapeutic agent of high efficacy at the right time to the desired location with a concentration high enough over a sufficiently long period. The challenges of designing optimized drug delivery systems are similar to those of the

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work carried out routinely by chemical engineers, i.e., device design and process design. The principles, theories and devices in chemical engineering can be modified and further developed to meet the challenges in the design of drug delivery systems. Therefore, controlled drug delivery can become a major possibility for chemical engineering to make significant contributions to human health care.

The concept of combination devices, such as drug eluting components together with functional prosthetic implants, represent a multipurpose, emerging clinical technology that promises to provide functional enhancement to implant devices in various clinical applications. The latest generations of coatings have become indispensable in boosting the capabilities of medical devices and implants by improving biocompatibility, hemocompatibility and lubricity. Without these coatings, many medical devices would never reach their true potential to cure the ailment for the intended application. Such coatings for medical devices are also being utilized extensively to carry out specific local drug release and make medical implants more visible to imaging systems. With targeted controlled drug delivery, combination products have already found applications in various areas of cardiovascular disease, diabetes, orthopaedics and cancer (Dubin, 2004). Using novel controlled release formulations, drug eluting stents (DES) were developed to target post angioplasty complications. They revolutionized the field of interventional cardiology by proving safety and efficacy in prevention of restenosis of coronary arteries using local drug delivery in many clinical trials (Colombo et al., 2003; Moussa et al., 2004). FDA approval of the drug-eluting coronary stent (Cypher™ from Cordis) in 2003 opened the gate for broadly adapting similar technology to combine the device and pharma worlds that have remained largely separate to date. In this article, we review drug delivery through coronary stents in different parts. The first part summarizes the importance of drug release kinetics on the overall performance of stent's safety and efficacy. The second part discusses mechanisms of drug release for controlled drug delivery systems and coronary stents, factors affecting drug elution, significance and updates on computational modeling for understanding and prediction of release kinetics, and the importance of advanced analytical methods for characterization-evaluation of essential attributes of DES. Novel surface analysis methods such as atomic force microscopy, confocal Raman microscopy and scanning tunneling microscopy enable us to investigate surface parameters and factors like physical properties, chemical composition and spatial distribution of molecules that play the vital role in determination of overall device biocompatibility and performance. The third part covers the comparison of key performance parameters of clinically investigated major drug eluting stents and factors to consider when designing future stent base drug delivery systems. The concept of combination devices that integrate drug releasing components with various medical devices, especially cardiac stents, represents emerging technology in the treatment of coronary artery diseases. Here we have attempted to compile and discuss almost all essential design parameters that affect the drug releasing characteristics of DES, the significance of different mathematical models and sophisticated analytical techniques to investigate the underlying facts of DES. Essential technical information on clinically acclaimed DES is discussed in order to utilize such information in the development of optimized drug releasing properties of DES with the use of novel biomaterials.

## IMPORTANCE OF CONTROLLED DRUG ELUTION FOR DES

Controlled release (CR) of drugs can be achieved by incorporating them either in dissolved or dispersed form in polymers (Wise, 2000). Depending on the final desired elution profile, these systems can be tailored to deliver the drug at a constant rate, in pulsatile manner, in the form of extended release and in other forms. Stent based delivery systems require a supply of anti-proliferative, anti-inflammatory, anti-thrombotic or pro-healing drugs at a programmable rate to maintain sufficient arterial drug concentrations to avoid excess cell growth with no toxic effects. Therefore, out of many controlled release methods, only a few of them can practically be put into practice to accomplish the objectives set for cardiovascular applications.

Designing a stent based drug delivery system demands an adequate understanding of the pathophysiology of the restenotic mechanisms that initiate after stent implantation. Targeting each of the individual mechanism is the rational approach to prevent adverse events. This can be done by maintaining a sufficient drug concentration, within the range of the safe and effective dosage of the drug

utilized. The rate-controlling system ensures drug retention during stent deployment and modulates drug-elution kinetics. The optimal release profile should be such that the concentration of drug is at any time sufficient to inhibit the proliferation of smooth muscle cells without influencing the re-endothelialization process of the endothelial wall (Deconinck et al., 2008). While it is evident that a DES manages to suppress neointimal growth, it can also provoke inflammatory response and local toxicity by interfering with cellular activities. All drugs work in limited therapeutic windows where an increase/decrease or major variation in the amount of drug exposed to the procedural segment can lead to serious conditions like thrombosis and inadequate healing; hence, arterial drug dose and release kinetics are critical parameters that should be studied thoroughly to ensure device safety and efficacy (Balakrishnan et al., 2007; Prabhu and Hossainy, 2006). The key to ideal procedural success requires optimization of drug dose and modulation of release kinetics which inhibit excess smooth muscle cell growth and does not affect the normal arterial endothelization process.

Moreover, the eventual biological response is greatly influenced by diffusive and convective forces that govern drug transport, penetration, distribution and retention in the arterial wall (Hwang et al., 2001; Lovich et al., 1998), which are dependent on drug content and elution kinetics. Drug properties (mainly hydrophobicity), arterial architecture and local pharmacology exert their own influence on drug release from devices and drug uptake at the stent-artery interface (Hwang et al., 2003, Lovich et al., 2001). Thus, due to the high dependency of the drug release rate on many factors such as drug dose density, drug carrier, processing parameters or physiological transport forces, determination of elution kinetics is very necessary. Since the implantation of drug eluting stents is the major treatment currently utilized to reduce restenosis, major effort is currently being made to improve this device technology with the aim of further reducing restenosis after its deployment.

## DRUG RELEASE MECHANISMS

While investigating novel drug delivery systems, formulations or experimental verification, it is essential to understand the drug release mechanism by applying transport equations and time dependent kinetic expressions. Although a large number of clinical products based on controlled release is available, there are limited mechanisms to explain them. Mechanisms of controlled drug release can be broadly classified based on release of active agents from delivery systems, namely: diffusion, degradation, swelling followed by diffusion and active efflux. All these mechanisms employ physical transformation of constituents involved in the system when they are put into a biological environment. Although there are feasible chemically driven drug delivery systems, they involve chemical modifications with active agents and carrier vehicles for which regulatory approval and adequate toxicology and safety profiles are needed before reaching final application. For such reasons, simpler systems with approved active agents and excipients are often utilized in the preparation of the controlled drug delivery systems used for medical applications.

With various applications and the continual development of controlled release systems, it is rather complicated to classify and describe each system with its mechanism, so here emphasis is given only to the systems related to drug eluting stents and discussed in detail with its rate controlling mechanism.

### Mechanisms of Drug Release Kinetics for Coronary Stents

At the core of DES technology is a conventional metal stent that props open the vessel while delivering a drug from a polymer coating. The drug is blended within a durable polymer or biodegradable polymer to regulate release rate. This core layer is often covered by a drug free top layer which acts as a barrier to have better control over drug elution. This simple system resembles matrix systems for which drug release is primarily governed by diffusion of the drug to the release media.

Elution kinetics for the majority of the DES currently investigated can be explained by diffusion. These systems can be classified as: (1) Monolithic devices in which the therapeutic agent is dispersed in a polymer matrix and its release is controlled by diffusion through the matrix; and (2) Reservoir systems (membrane controlled devices), in which the active agent is contained in a core that is surrounded by a thin polymer membrane and release to the surrounding environment occurs by diffusion through the rate-controlling membrane. Both of the systems have been utilized practically and DES

based on this scheme have proven their safety and efficacy in many clinical trials (Kamath et al., 2006; Leon et al., 2003).

The Taxus™ stent incorporates poly (styrene-b-isobutylene-b-styrene) triblock copolymer for sustained elution of the anti-proliferative drug paclitaxel (Figure 1b), creating a monolithic system where drug is released to the physiological medium by diffusion through the polymeric matrix (Kamath et al., 2006; Ranade et al., 2005). The Cypher™ stent is an example of a membrane system in which the drug sirolimus is embedded within blends of poly (ethylene-co-vinyl acetate) (PEVA) and poly (n-butyl methacrylate) (PBMA) (Figure 1a). The drug-free top layer acts as a release rate barrier through which drug elutes out under diffusion with an in-vitro release profile of 30 days. After preparation, drug starts to migrate to the drug-free top layer. This results in an initial burst which usually decreases after few days and, thereafter, slow release of the drug occurs for the remaining time period (Leon et al., 2003).

In monolithic systems, the release rate depends on initial drug concentration within the polymeric matrix. If the drug concentration is below the solubility limit in the matrix, then diffusion through the matrix limits the release rate and, if the drug concentration is above the solubility limit in the matrix, then drug dissolution in the polymer matrix limits the release rate. For reservoir systems, the drug release rate remains constant, which results in a zero order drug elution profile at the steady state and deviations in release rate can be recognized as an initial burst or time lag in drug release. The release rate relationship with concentration gradient, time, diffusion coefficients, area and film thickness for both of the systems can be found by using the Higuchi equation as described below (Ratner et al., 1996).

$$\frac{M_t}{A} = \left[ D(2C_0 - C_s)C_s t \right]^{1/2}$$

where $M_t$ (g) is the cumulative amount of drug released at time t (sec); A ($cm^2$) is the surface area of the controlled release device exposed to the release medium, D ($cm^2$/sec) is drug diffusivity, and Co (g/$cm^3$) and Cs (g/$cm^3$) are initial drug concentration and drug solubility, respectively.

While the diffusion controlled release mechanism is adequate for stent systems that incorporate non-biodegradable durable polymers, regulated release profiles can be achieved by using biodegradable polymers. Examples of such polymers are polylactide, polyglycolide, polylactide-co-glycolide, polyhydroxybutyrate, hyaluronic acid, polycaprolactone, polyortho ester (Pan et al., 2006; Raval et al., 2007). The property by which these polymers undergo hydrolytic and enzymatic degradation when exposed to biological fluid makes them potential candidates for controlled drug delivery where polymer can be degraded, absorbed or excreted from a biological environment (Schliecker et al., 2003; Sun et al., 2006). Thus, drug release from these systems can be achieved by: (1) diffusion of drug from the polymeric matrix, (2) dissolution of drug into the release medium; and (3) biodegradation of polymeric chains. By careful optimization of the drug-polymer ratio (Kamath et al., 2006), drug density (Alexis et al., 2004), drug-polymer selection (Finkelstein et al., 2003), physical dimensions of the coated film and process parameters, adequate control over elution rate can be achieved.

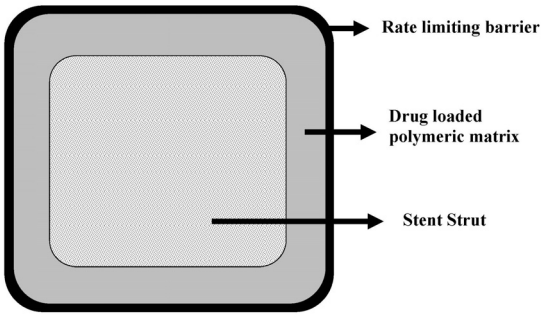


**Figure 1a:** Schematic of diffusion controlled drug coated stent - Reservoir base Cypher™ stent

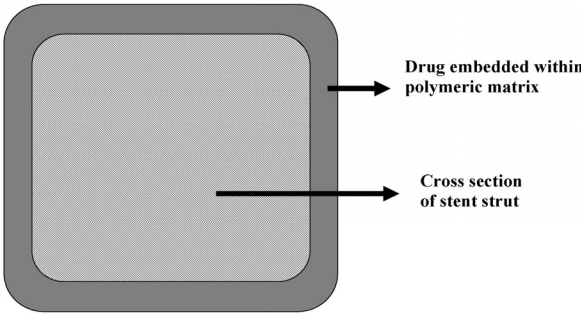


**Figure 1b:** Schematic of diffusion controlled drug coated stent - Matrix base Taxus™ stent

During our studies (Raval et al., 2007) on controlled elution of paclitaxel using a blend of biodegradable polymers from the class of polylactides and co-polymers of polylactide-co-glycolide, it was observed that adequate control over drug release could be attained by coating the stent in multiple layers. Each layer provides a different release rate depending on the composition of the respective layer and properties of the incorporated biodegradable polymers such as degree of crystallinity, hydrophilicity and hydrophobicity, molecular weight and co-polymer stereochemistry. Further research (Kothwala et al., 2006) using similar biodegradable polymers revealed the fact that the initial rate of release was high compared to the later stage of drug release in simulated biological fluid. This initial burst followed by slow release was a result of incorporation of amorphous polymer in the upper layer and inclusion of highly hydrophobic and semi-crystalline polymer in the base layer, respectively. Investigation also revealed that coated thin film was porous when analyzed after incubation and signs of swelling were observed, which were indicative of initial water absorption resulting in an early burst effect due to surface drug dissolution followed by erosion degradation of the polymeric matrix and a slow rate of drug release. Such studies suggest that biodegradable polymeric systems allow drug release modulated by drug diffusion, dissolution, and swelling, followed by degradation of the drug-embedded polymeric film.

Alexis and co-workers (Alexis et al., 2004) experimented with a biodegradable stent (made up of poly-DL-lactide and poly-DL-lactide-co-glycolide) prototypes in which the anti-proliferative drug paclitaxel and the immunosuppressive drug rapamycin were incorporated separately. The release pattern depicted a slow diffusion controlled phase, followed by a rapid degradation controlled phase. No burst effects were observed for either drug and controlled elution kinetics were achieved by judicious selection of the drug-biodegradable polymer combinations and using suitable formulations. In another study (Wang et al., 2006), a multilayer sirolimus-eluting totally biodegradable polylactide-co-glycolide (PLGA) stent was prepared with multiple layers. It was reported that the dependence of the release kinetics of sirolimus from a bilayer Poly-L-Lactide and PLGA coating depends on variables such as different drug loadings, effects of plasticizer in the formulation and the presence of a drug- free top layer for retarding the release rate. Sternberg and co-workers (Sternberg et al., 2006) studied absorbable polymer stent coatings for localized drug delivery based on Poly-L-Lactide. Comparison of the amount of the drug cyclosporine-A (CsA) eluted in buffer and blood plasma revealed that drug release in the latter was higher because of good solubility, as well as more realistic diffusion conditions that resulted from partial binding of the lipophilic cyclic oligopeptide CsA onto the plasma proteins.

## Factors Affecting Drug Release

The controlled release systems used for DES are primarily fabricated as matrix systems or reservoir types, which are simpler to design yet effective and programmable to release the drug at the desirable rate. These systems create high and dynamic concentration gradients across tissues and are hard to identify, characterize and control (Yang and Burt, 2006). The release kinetics for such systems are influenced by all constituents of which the DES is formulated and the process parameters under which it is coated. The principal parameters on which release is dependent are depicted in Table 1 and can govern the drug release rate individually and mutually. Comprehensive study of each factor is necessary when designing and experimenting CR systems as each of them can individually influence release kinetics to a great extent. There are many other biological parameters that should also be considered simultaneously while investigating drug release kinetics for a given system. Transport of drug via diffusion-convection, biological properties of tissue and arterial ultra structure, hydrodynamic conditions at the implantation site and stent design greatly modulate the release rate and the final biological response to drug eluting stents (Yang and Burt, 2006).

## Various Approaches for Drug Delivery from Stents

Current experience with DES and a growing understanding of restenosis mechanisms confirm the short term benefits of DES surface coatings. However, long term complications such as incomplete drug elution, a suboptimal drug elution rate, delayed arterial healing, late stent thrombosis and hypersensitivity to the polymeric coatings remain an issue (Baim, 2007; Finn et al., 2007). The findings have triggered the design and evolution of the next generation of coatings and novel coating strategies.

**Table 1: Factors affecting drug release**

| Parameters | Possible effect | Reference |
|---|---|---|
| **Basic properties of drug** | | |
| Drug hydrophobicity/hydrophilicity | Affects aqueous solubility, protein binding, tissue retention characteristics and local drug concentrations | Creel et al. (2000) |
| Diffusion/dissolution characteristics | Affects release kinetics | Kamath et al. (2006) |
| Solubility in polymer | Affects release kinetics | Venkatraman et al. (2007) |
| Solubility in release media | With higher solubility, higher drug release rate | Ranade et al. (2005) |
| **Properties of rate controlling polymer** | | |
| Thermal properties (Tg, Tm) | Affects degradation, hydrophobicity, drug release and drug solubility in the case of biodegradable polymers, | Jonnalagadda et al. (2000)<br>Frank et al. (2004)<br>Diener et al. (2003) |
| Degree of crystallinity | Affects water penetration and drug solubility in the case of non-erodible polymers<br>Influences degradation and drug release for biodegradable polymers | Grassi (2005)<br>Ranade et al. (2004)<br>Diener et al. (2003)<br>Hurrell et al. (2002)<br>Frank et al. (2004)<br>Diener et al. (2003) |
| For biodegradable polymers – initial molecular weight, co-polymer ratio, absorption rate and time period, pH of dissolution medium | Affects degradation behavior and time | Shameem et al. (1999)<br>Miyajima et al. (1999) |
| **Processing Parameters** | | |
| Selection of coating process (ultrasonic atomization, air brush, dip coating) | Coating film property and drug elution | Sternberg et al. (2007)<br>Acharya and Park (2006)<br>Chen et al. (2005)<br>Pan et al. (2006)<br>Heldman et al. (2001) |
| Properties of solvent (BP, thermal history)<br>Solvent evaporation rate<br>Phase diagram of ternary system (drug-polymer-solvent) | Residual solvent effects, merging of coating layers, thus influencing release kinetics | Saylor (2006) |
| **Coating Design** | | |
| Drug to polymer ratio | Effect on drug carrying capacity of polymer and drug elution rate | Kamath et al. (2006) |
| Coating layer composition and thickness | Affects diffusion of drug through film | Raval et al. (2007)<br>Leon et al., 2003)<br>Prabhu (2004) |
| Drug (initial solid phase) concentration and distribution inside the matrix | Describes initial burst effect and dissolution mechanism | Balakrishnan et al. (2007)<br>Kamath et al. (2006) |
| Microstructure of coating (spatial variation in physical and chemical composition) | Exhibits process conditions and eventual effect on drug delivery kinetics | Prabhu (2004) |
| Top layer (drug free) thickness and hydrophobicity of polymer | Regulates drug kinetics by lowering diffusion phenomena. | Leon et al. (2003) |
| Mechanical properties of coated film | Affects coating integrity during processes like stent crimping and expansion, Improper coating may induce adverse and interrelated effects such as local inflammation and thrombosis and hinder homogeneous drug uptake | Otsuka et al. (2007) |
| Stent design (system geometry) | Affects extent of drug dose differentiation within arterial wall | Balakrishnan et al. (2005)<br>Hara et al. (2006) |

Conor Medsytems has developed a cobalt-chromium stent whose struts are laser drilled and the small holes function as reservoirs that can be filled with drug-polymeric blends to attain programmable drug elution kinetics to cope with restenosis (Figure 2) (Finkelstein et al., 2003). This system allows controlling the direction (luminal, mural, both) of paclitaxel elution by a fully erodible PLGA polymer. The eventual Paclitaxel release is attributed to a combination of polymer erosion and drug diffusion. The Traslumina stent contains no polymers for CR of the drug, but rather the metallic stent surface itself is microporous to accommodate the drug using onsite coating technology (Hausleiter et al., 2005). The high partition coefficient of the lipophilic drug allows long term retention and a biological outcome which indicates that dose-dependent efficacy in restenosis prevention is achievable with this new DES concept. Many naturally occurring substances have already been studied by a multitude of research groups worldwide in regard to their suitability as drug delivery vehicles for stent coating. These materials include phosphorylcholine, chitosan, hydroxyapatite, collagen, fibrin, antibodies, cell

materials like glycocalix, and cellulose (Leon, 2007; Waksman, 2007). An improved alternative coating method, which significantly reduces the amount of polymer used and, consequently, the likelihood of inflammatory reaction due to implanted polymer, is abluminal stent coating, where the surface of the stent adjacent to the artery wall is coated with drug and polymer (Grube and Buellesfeld, 2006). The BioMatrix stent utilizes this arrangement in which the drug Biolimus A9/PLA coating is applied to the outer surface of the stent where it is actually required. This abluminal coating can also be applied by ink jet coating principles where coating is achieved by droplets of polymer and drug on a stent in a precise pattern (Figure 3). The shape and definite area of the droplets provided different elution kinetics from the stent surface. The significantly lower amount of drug and polymer minimizes toxicity issues (Rosenthal, 2007).

With emerging development in bioabsorbable stent technologies, stents with novel biodegradable polymeric formulations and design are currently under preclinical and clinical assessment. With the virtue of incorporating therapeutic agents and controlled release properties, such stents have become interesting in terms of biocompatibility, mechanical strength and drug delivery capabilities (Sharkawi et al., 2007). The future is expected to see active research and development in the DES field and the potential commercialization of exciting new technologies.

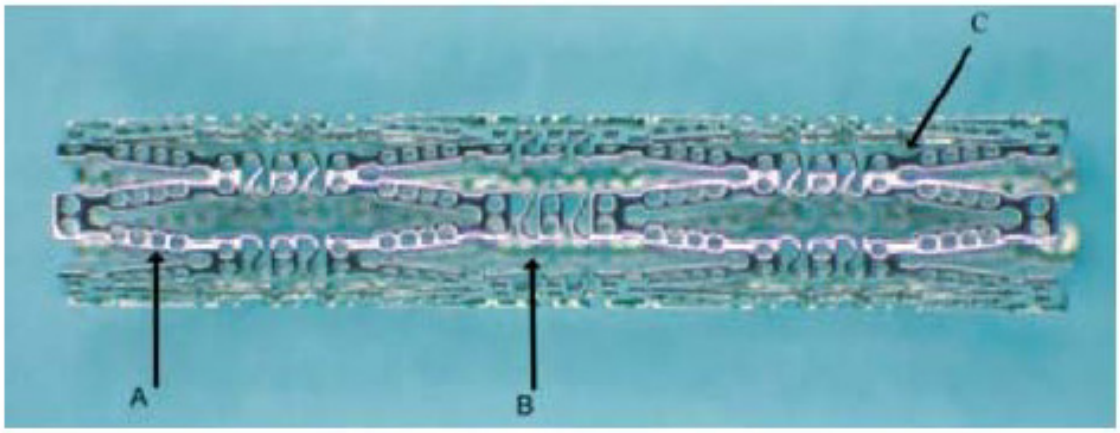


**Figure 2:** Laser drilled Conor stent with drug reservoirs, A-Drug/Polymer wells, B-sinusoidal struts, C-ductile hinges

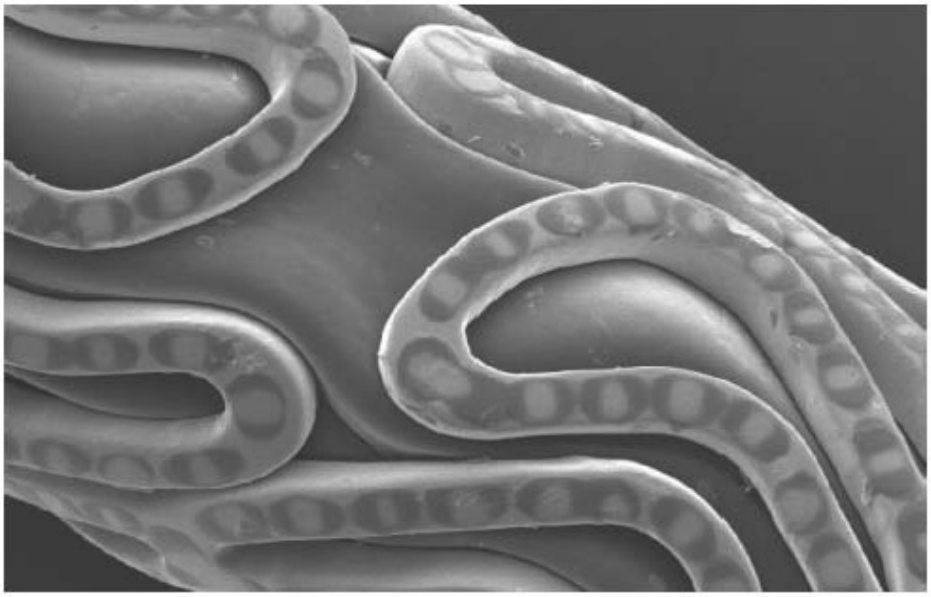

**Figure 3:** Abluminal droplet coating on stents by Labcoat Ltd

## Computational Modeling

Mathematical models and numerical simulation techniques play a relevant role in understanding the most appropriate choices for the optimal design of DES. Several models have been proposed (Table 2) to address fundamental questions of pharmacokinetics, i.e., estimation of drug elution in the tissues over a period of time which helps to assess the biological outcome of released drug. The initial efforts to create a mathematical model were done by Higuchi (Higuchi, 1961; Higuchi, 1963), who studied unidirectional drug release from the polymer matrix assuming constant coefficients. The respective models developed thereafter (Heller and Baker, 1980; Lee, 1980) prior the advent of DES are based on different controlled drug delivery systems but provided basic fundamentals that suggested appropriate mathematical simulations for drug delivery via DES. Recently, Balakrishnan et al. (2007) demonstrated tissue drug uptake resulting from a range of administered drug dose and release kinetics using a 2-dimensional transient diffusion-convection computational model. They found that a simple Fickian diffusion model of drug transport in the coating can approximate the process in which the drug navigates through a complex porous polymeric coating. It was shown that release kinetics and applied drug dose modulate arterial drug deposition, distribution, and retention. In another study (Balakrishnan et al., 2005), drug deposition for single and overlapping DES was studied using coupled computational fluid dynamics and mass transfer reactions. It was proved that drug deposition occurs less via contact between the drug coating and the arterial wall than via flow-mediated deposition of blood-solubilized drug. Prabhu and Hossainy (2006) developed a mathematical model to predict the transport reaction of drug release with simultaneous degradation of the biodegradable polymer PLA. An important feature of this model, which differentiates it from other models, is the compartmentalized approach for polymer degradation, which assumes that a set of oligomers can be identified as one compartment on the basis of a certain molecular weight range for which their diffusion characteristics and degradation kinetics can be considered to be identical. Further, this model takes into account the underlying chemical reactions responsible for degradation in a more detailed manner than the models presented by earlier investigators (Heller and Baker, 1980; Higuchi, 1963; Lee, 1980). It also accounts for the increase in diffusivity with time of various species involved with the degradation of the PLA and the effect of autocatalysis on polymer degradation, facts that are overlooked in most of the earlier models studying polymer degradation. Hose et al. (2004) developed and explored the use of a thermal analogue and the associated three-dimensional convection-diffusion equations to model the spatial and temporal distribution of drug within the vessel wall and applied ANSYS to investigate the dynamics of drug distribution, and to assist in the understanding of the treatment process and in the development of improved delivery systems. Vergara and Zunino (2007) developed a low cost model for depicting drug release dynamics based on mass transfer through a heterogeneous thin layer by the use of an advection-diffusion reaction equation. Their study concluded that, by combining a multiscale model for mass transfer with the proper numerical expression, it is possible to develop a model for coronary stents involving different space scales and dynamics of the system over a long time period. Reis et al. (2007) explained that release properties can be well understood in terms of diffusional transport process and a partition phenomenon. Releasing Vitamin B12, methylene blue, and acid orange 7 from semi-interpenetrating network hydrogels, they proposed a simple mathematical model capable of drug release prediction over 100% range compared to semi-empirical models which predict only the first 60% of released solute. Models discussed here are valuable in isolating and understanding mechanisms for drug delivery, yet idealized models do not account for all possible clinical variables. Various limiting factors force them to apply a simplified approach. These models (Balakrishnan et al., 2005; Balakrishnan et al., 2007; Prabhu and Hossainy, 2006; Vergara and Zunino, 2007) utilized diffusion as a major driving force for drug release, while the other transport force - convection is overlooked, which has a potential impact on transmural drug transport in tissues. Moreover coronary arteries are a dynamic environment with the presence of atherosclerotic calcified lesions, thrombus generating platelets, biological proteins, enzymes and other blood components which eventually influence the programmed drug eluting characteristics of any implant. All these parameters together with 3D flow and drug metabolism and binding properties should also be considered while simulating DES with models. The effect of neointimal growth over the stent strut and deposition of thrombus in the vicinity of the stented region also impacts the functions of DES. Future models are expected to include complexities of the stented region, with simulation of a diseased arterial environment, incorporation of physico-chemical and thermal properties of drug/polymer and 3D fluid dynamics and transmural transport forces to judge the upcoming potential drug eluting stents.

**Table 2: Summary of Major Computational Modeling for DES**

| Sr. No. | Proposed Model/Governing Equation | Remarks | Reference |
|---|---|---|---|
| 1 | $Pe\left(\frac{\partial C_f}{\partial z}+\phi\frac{\partial C_f}{\partial r}\right)=\frac{\partial^2 C_f}{\partial z^2}+\frac{\partial^2 C_f}{\partial r^2}$ | Model simulates luminal drug distribution by coupling the steady state convection diffusion equation with the steady state Navier-Stokes and continuity equation. Some simplification parameters include neglecting drug metabolism and binding, assuming homogenous, healthy tissue composition, assuming negligible arterial drug transport via vasa vasorum, and considering only 2D flow. | Balakrishnan et al. (2005) |
| 2 | $\frac{\partial \bar{C}_L}{\partial \bar{t}}=\gamma_L\frac{\partial^2 \bar{C}_L}{\partial \bar{x}^2}\exp\left[\alpha_L\left(1-\bar{C}_p\right)\right]$ $-\alpha_L\gamma_L\exp\left[\alpha_L\left(1-\bar{C}_p\right)\right]$ $\times\frac{\partial \bar{C}_p}{\partial \bar{x}}\frac{\partial \bar{C}_L}{\partial \bar{x}}+\tau_O^2\bar{C}_O\bar{C}_W\bar{C}_L+\varepsilon\theta_O^2\bar{C}_O\bar{C}_W$ | A simultaneous transport-reaction model used to study the effects of critical parameters like partitioning coefficients, autocatalysis coefficients and structural change on degradation of polymer and drug release from the matrix. | Prabhu and Hossainy (2006) |
| 3 | $\rho\left(\frac{\partial C}{\partial t}+V_x\frac{\partial C}{\partial x}+V_y\frac{\partial C}{\partial y}+V_x\frac{\partial C}{\partial z}\right)$ $=k_x\frac{\partial^2 C}{\partial x^2}+k_y\frac{\partial^2 C}{\partial y^2}+k_z\frac{\partial^2 C}{\partial z^2}+M$ | Model depicts the correlation between the transport of a drug and the transport of heat in a physical system which demonstrate the use of this analogy to perform drug elution analysis | Hose et al. (2004) |
| 4 | $\partial_t a+L_w a+N_w(a,b)=0, in (0,T]x\Omega_w$ $\partial_t b+N_w(a,b)=0, in (0,T]x\Omega_w$ $B_w a=0, on (0,T]x\partial\Omega_w\setminus\Gamma$ $B_a=0, on (0,T]x\Gamma$ | This consist of two $2^{nd}$ order parabolic partial differential equations on adjacent domains coupled by means of the transmission conditions improved for long time scale drug release. | Vergara and Zunino (2007) |

## Characterization Methods for DES

Advanced characterization methods are being employed to understand the different properties of drug eluting stents. DES characterization often tends towards the stent's mechanical performance, analysis of surface morphology and measurement of drug content and elution kinetics (Center for Devices and Radiological Health Guidance, 2008). Mechanical performance can be analyzed at the design stage by finite element modeling and on actual stent prototypes by conducting analyses for radial strength, fatigue, recoil and foreshortening (Migliavacca et al., 2002). Surface properties are of importance as biocompatibility depends mainly on it. The purpose of the surface characterization is to: (1) identify the failure modes of coatings; (2) measure any chemical or physical changes during stability testing; (3) monitor the consistency of coating processes; (4) identify defects and contaminants in coatings; and (5) develop a fundamental understanding of the drug release mechanisms of coatings. Optical microscopy (Pan et al., 2006) and scanning electron microscopy (Otsuka et al., 2007) are commonly utilized to investigate surface properties. Determination of foreign particle quantification and distribution, micro-crack formation and crimping-expansion properties of coated films are examined by such techniques. Atomic force microscopy with phase contrast imaging (Ranade et al., 2004) is utilized to determine different phases and degrees of blending of block copolymers and drug within the coated layer. Also, surface morphology and topographic analysis data are gathered from such analyses (Ranade et al., 2004). Data from AFM can also be utilized to quantify the adhesion forces and cohesive forces with the layers of the drug eluting stent (Wolf et al., 2008). Optical microscopy combined with confocal Raman spectroscopy (Balss et al., 2007) provides spatial distribution of drug and polymer within the DES. This unique spectral analysis has been utilized to identify the solid phase distribution in drug polymer coated stents. Drug estimation is also an important parameter to probe, as well as surface properties. Studies on in-vitro elution kinetics and in-vivo pharmacokinetics require quantification of the drug at different time intervals. Moreover, total drug content measurement is adapted as a crucial quality control parameter in the manufacturing of DES. High

performance liquid chromatography (HPLC) is often utilized to quantify the drug content and drug release from coated stents (Raval et al., 2007). Combined with mass spectroscopy, the limit of detection has reached the nanogram level in physiological media or plasma serum (Streit et al., 1996). Advancement in characterization methods allows detailed investigation of surface morphology and drug elution behavior, as well as the drug-polymer distribution within layers. The resulting data help to understand the actual phenomena behind elution kinetics that affect DES performance in real world application.

### In-Vitro, In-Vivo Drug Release

As the drug eluting stents are widely accepted by regulatory bodies and extensively utilized for the treatment of lesion vascularization, it becomes more important for the medical device industry to produce drug eluting stents that provide consistent performance. Along with mechanical integrity, pharmaceutical aspects are equally important for a drug eluting stent with regards to the uniformity of total drug content and the drug releasing property (Tesfamariam, 2008). Well validated HPLC analytical methods should be employed to investigate the characteristics of drug loading uniformity and drug release across batches. Drug release is studied by using existing drug dissolution methods generally adopted by the pharmaceutical industry with modifications to quantify the drug that is released at different time intervals. In general, stents are subjected to incubation within a release media representing the body conditions. Temperature is controlled throughout the study period. Aliquots are analyzed periodically and sink conditions are maintained to provide a gradient in order to have continuous drug diffusion from the stent coating to the release media (Amidon et al., 1995). The primary goal for developing and validating these release test methods is to analyze the stent for its reproducible drug release characteristics. Moreover, it can be used as a stringent quality control tool to identify manufacturing drifts and formulation variants. Established in-vitro drug release profiles can be correlated with the in-vivo drug release data (Royce et al., 2004). In-vivo release of drug can be estimated after implantation in suitable animal models by measuring the residual drug in explanted stents. Moreover, drug from the surrounding tissue and from blood can be measured at a particular time point to plot precise in-vivo drug release profiles (Vetrovec et al., 2006). This can be extremely useful by which the biological behavior of any drug eluting stent can be predicted based on studying the in-vitro drug release properties.

## COMPOSITION AND CHARACTERISTICS OF SOME DES

Presently there are numerous commercially available DES and others are on the horizon to enter the emerging field of intervention cardiology. Table 3 summarizes the basic DES compositions and characteristics of some clinically investigated stents. The rationale behind selection of these stents is that all stents are US-FDA approved stents except Infinnium™ and they all are well studied by clinical investigators as well as scientists from different fields. They have set major benchmarks in angiographic success and provide vital strategies in the development of the upcoming generation of DES. Out of the 5 stents compared, Cypher™ (Leon et al., 2003), Taxus™ (Kamath et al., 2006) and Xience™V (Xience™ V- PMA # P070015, 2007) utilize non-biodegradable durable polymer for controlled drug delivery. The Endeavor™ (Leon, 2007) stent uses biological PC coating to modulate drug elution. As the first stent with biodegradable polymers acquiring CE certification, the Infinnium™ (Vranckx et al., 2006) stent governs release kinetics with a multiple layer biodegradable polymeric coating. Despite recent safety concerns regarding adverse reactions from the use of bio-stable polymers, the scientific community has accepted the importance of biodegradable polymers that modulate drug elution and are absorbed within the biological environment after a certain time period, leaving behind a bare metal stent. The elution mechanism of all the stents involves diffusion and dissolution forces govern early release of drug, creating an initial burst in some cases. As discussed earlier, the Cypher™ stent manages this event by having a drug-free top layer. Dissolution of drug also contributes to this initial drug release in the Taxus™ stent. Also, the majority of the drug content remains in a non-erodible Translute™ polymer which may contribute to inflammation at later stages. The PC coating of the Endeavor™ stent provides rapid liberation of the active agent, which lasts up to 2 weeks. It is evident from the biodegradable multilayer coating of the Infinnium™ stent that better control over drug release can be acquired by careful formulation of different layers.

**Table 3: Composition and characteristics of some DES**

| | INFINNIUM Vranckx et al. (2006) | TAXUS Kamath et al. (2006) | CYPHER Leon et al. (2003) | ENDEAVOR Leon (2007) | XIENCE V XIENCE™V (2007) |
|---|---|---|---|---|---|
| **Drug** | **Paclitaxel** | **Paclitaxel** | **Sirolimus** | **Zotarolimus** | **Everolimus** |
| Polymer | Biodegradable (Class of Poly lactides, glycolides and their co-polymers) | Translute™ – Non erodible Hydrocarbon base triblock copolymer | Non-resorbable PEVA-PBMA (Poly Ethelyne co-vinyl acetate & Poly n-butyl methacrylate) blend | Phosphorylcholine (PC) polymer | Durable/Non-erodible (Acrylic and fluoro polymer, PVDF-HFP) |
| Base Coat | N.A | N.A | Parylene-C | Phosphorylcholine (PC) polymer | PBMA |
| Drug Release Matrix | Two Layers | Single layer | Single Layer | Single layer | Single Layer |
| Top Coat | Drug free top coat of Polyvinyl pyrrolidone for prevention of premature drug release | N.A | Drug free top coat of PBMA polymer to control drug release | NA | N.A |
| Coating Thickness | 5 - 6 μm | 16 μm | 12 μm | 5-6 μm | 7-8 μm |
| Drug Dose | 1.4 μg/mm$^2$ | 1.0 μg/mm$^2$ | 1.0 μg/mm$^2$ | 1.6 μg/mm$^2$ | 1.0 μg/mm$^2$ |
| Drug Elution profile | 50% drug release after 9 days, 90% after 38 days and 100% after 48 days. | Biphasic Elution Profile: 10% after 10 days, 90% drug remains indefinitely | Release Profile: 50% drug release after 10 days, 90% after 60 days and 100% after 90 days. | 65% in first 2 days, more than 85% in 1st week and total elution by 2nd week | 25% drug release during first 24 hr, 75% drug release during 28 days and 100% release after 120 days. |
| Drug Elution Mechanism | Drug is released from the porous surface regions where diffusion is possible.<br>Initial burst release of surface Paclitaxel followed by sustained elution up to 48 days.<br>Polymers breaks up due to hydrolysis and enzymatic degradation which will eventually excrete from body in form of $CO_2$ and $H_2O$ | 2 days dissolution-mediated burst release of drug.<br>Initial burst followed by slow release of drug through diffusion controlled release.<br>No detectable Paclitaxel release from bulk polymer after 10 -12 days of stent implantation. | Diffusion is the governing drug release mechanism.<br>Release exhibits initial early burst of drug followed by secondary slower release.<br>Non-resorbable polymers does not eliminate by body's natural degradation mechanism. | Endeavor stent exhibits rapid drug release from hydrophilic PC polymer matrix within 14 days.<br>The hydrophilic nature of PC coating enables fast release rate from 3 layer Endeavor stent. | Initial burst release within 24 hr due to the diffusion mechanism.<br>Initial burst followed by slow release of drug through diffusion controlled release.<br>Durable/non-erodible polymers doesn't eliminate by body's natural degradation mechanism. |

## CONCLUSION

Drug eluting stents has emerged as an effective treatment for coronary occlusions. The success of the existing technologies argues for an incremental approach rather than a revolution. Localized drug delivery has proved to be a safe and efficient way to improve the coronary intervention performance by reducing therapeutic side effects. Moreover, DES involves a relationship between chemical engineering, vascular anatomy, pharmacology and polymer chemistry. There are many aspects in which drug eluting technology can be understood and improved based on the arterial pathophysiological requirement. Nonetheless, many questions remain unanswered for engineers, scientists and clinicians to continue to explore and evaluate this technology. Engaging advanced analytical tools to investigate unexplored areas and the elution mechanism for DES will provide important insight for the development of future drug eluting implantable devices.

## NOMENCLATURE

### *Symbols*

| | |
|---|---|
| A | Surface area of the controlled release device exposed to the release medium |
| a | volume averaged concentration of the drug |
| $B_w$ | Linear operators |

| | | |
|---|---|---|
| C | Concentration of drug | |
| $C_f$ | Concentration of drug in fluid | |
| $C_L$ | Concentration of lactic acid | |
| Co | Initial drug concentration | in g/cm$^3$ |
| $C_O$ | Concentration of oligomers | |
| $C_P$ | Concentration of polylactide | |
| Cs | Drug solubility | in g/cm$^3$ |
| $C_W$ | Concentration of water | |
| D | Drug diffusivity | in cm$^2$/sec |
| K | Thermal conductivity | |
| $L_w$ | Linear operators | |
| M | Drug generation rate per unit volume | |
| $M_t$ | Cumulative amount of drug (in g) released at time t | in sec |
| $N_w$ | Non-linear operators | |
| Pe | Peclet number | |
| PLLA | Poly-L-Lactide | |
| PLGA | Poly-Lactide-co-Glycolide | |
| r | Radial coordinate | |
| V | Convection velocity | |
| Z | Axial coordinate | |

***Greek Letters***

| | |
|---|---|
| $\alpha_L$ | Coefficient for autocatalytic effect |
| $\Gamma$ | Interface with the coating |
| $\gamma_L$ | ratio of diffusivities of lactic acid to water at zero time |
| $\rho$ | Density |
| $\phi$ | Ratio of radial to axial velocities |
| $\Omega_w$ | Computational domain representing arterial wall |

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