Drug Delivery from Cardiovascular Stents

In Pursuit of a Non-Polymeric Approach

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Coronary Heart Disease

• Coronary Heart Disease (CHD) is the result of buildup of plaque (cholesterol and fatty acids) on the walls of the coronary arteries.

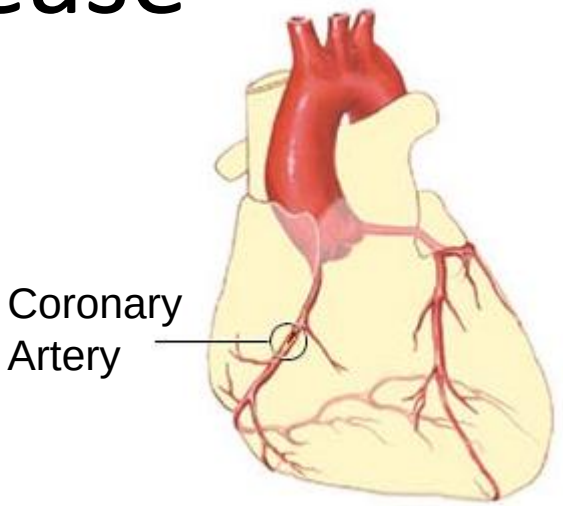
• Plaque buildup can lead to restrictions in blood flow to the heart muscles.

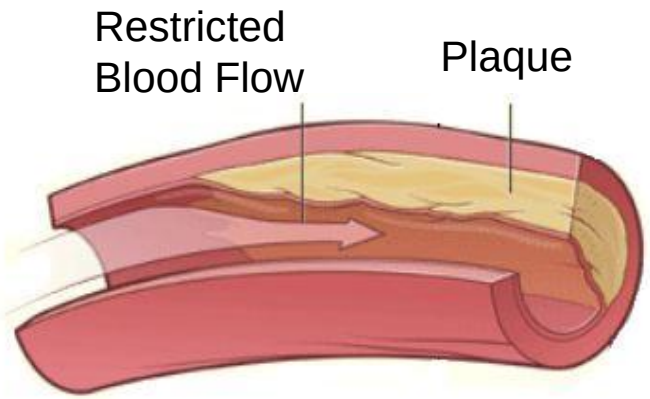
• It can cause angina, irreversible heart damage or a heart attack.

• Lifestyle, diet and genetics all play a role in the occurrence of CHD.

•It is the leading cause of death worldwide.

• Stenosis is the term used to describe narrowing of a blood vessel.





Nhlbi.nih.gov

History of Surgical Treatments of CHD

1960 – Coronary Bypass Surgery

Highly invasive. Emergent procedures reduced by 90% from 1990 to 2007.

1977 – Balloon Angioplasty

Catheter is used to feed a balloon to the problem vessel. The balloon is expanded to break up the plaque. Rarely the only procedure performed now.

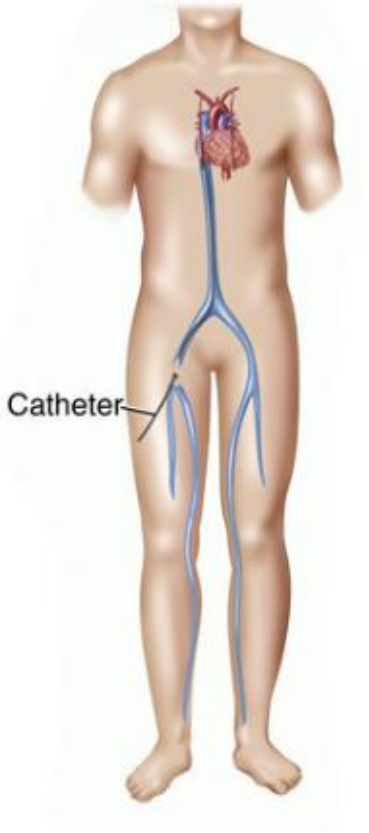
1989 - Angioplasty with stenting

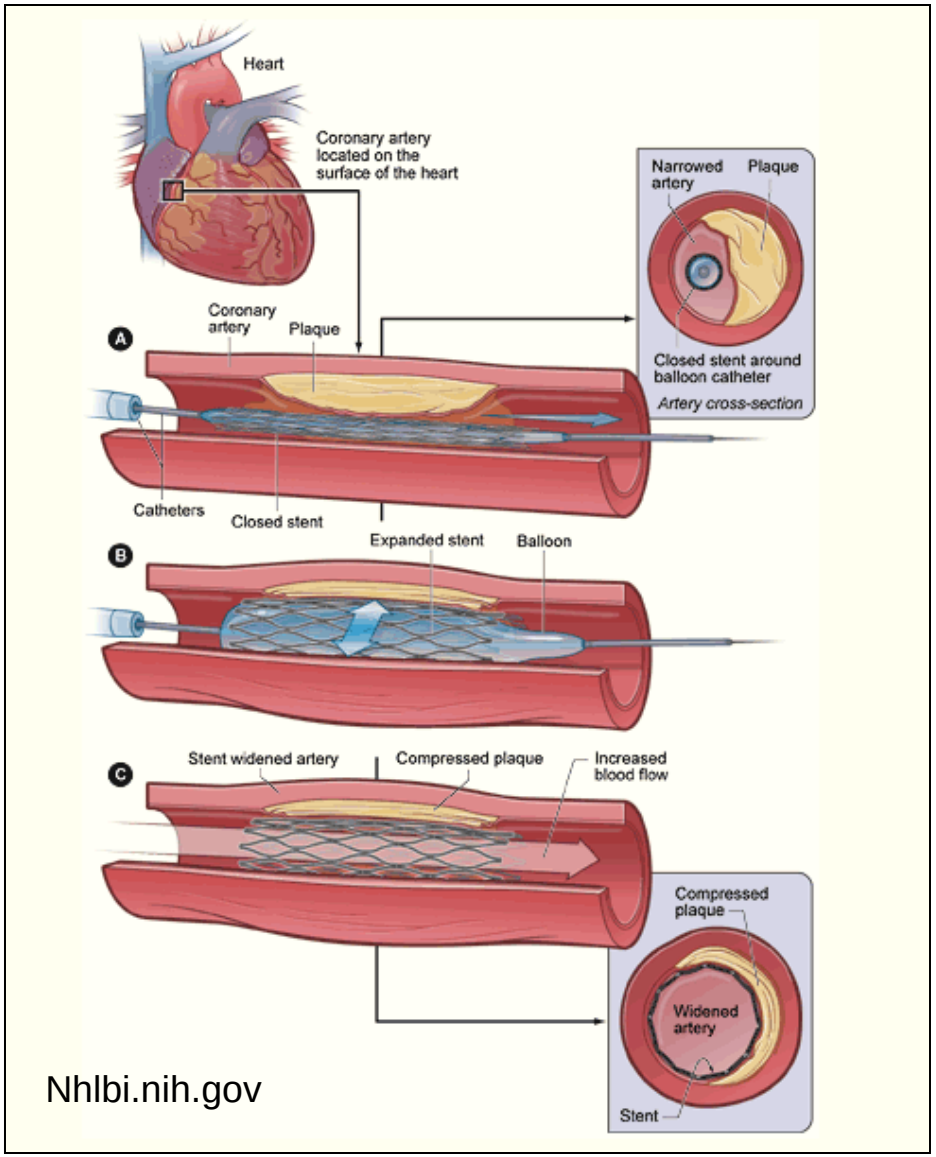
Same procedure as balloon angioplasty except that a small wire mesh tube is left in place to keep the vessel propped open.

CHD Facts (US):

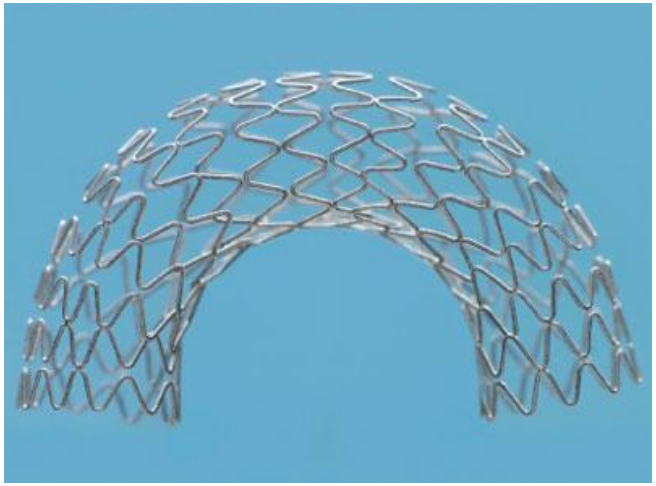
- 425,000 deaths annually
- 17,600,000 people live with CHD

Angioplasty with Stenting

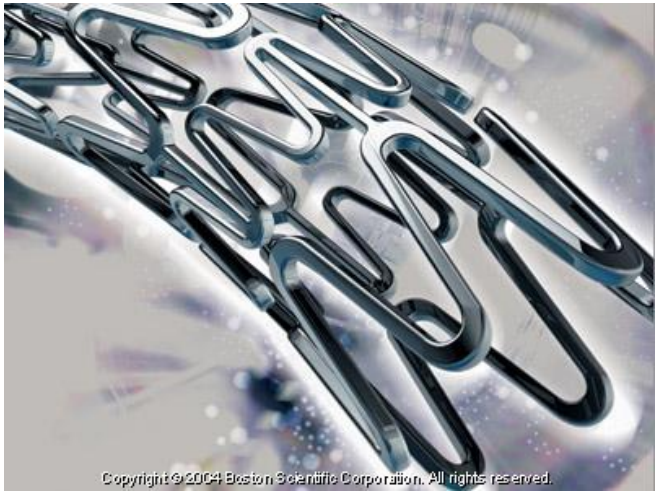




Coronary Stents



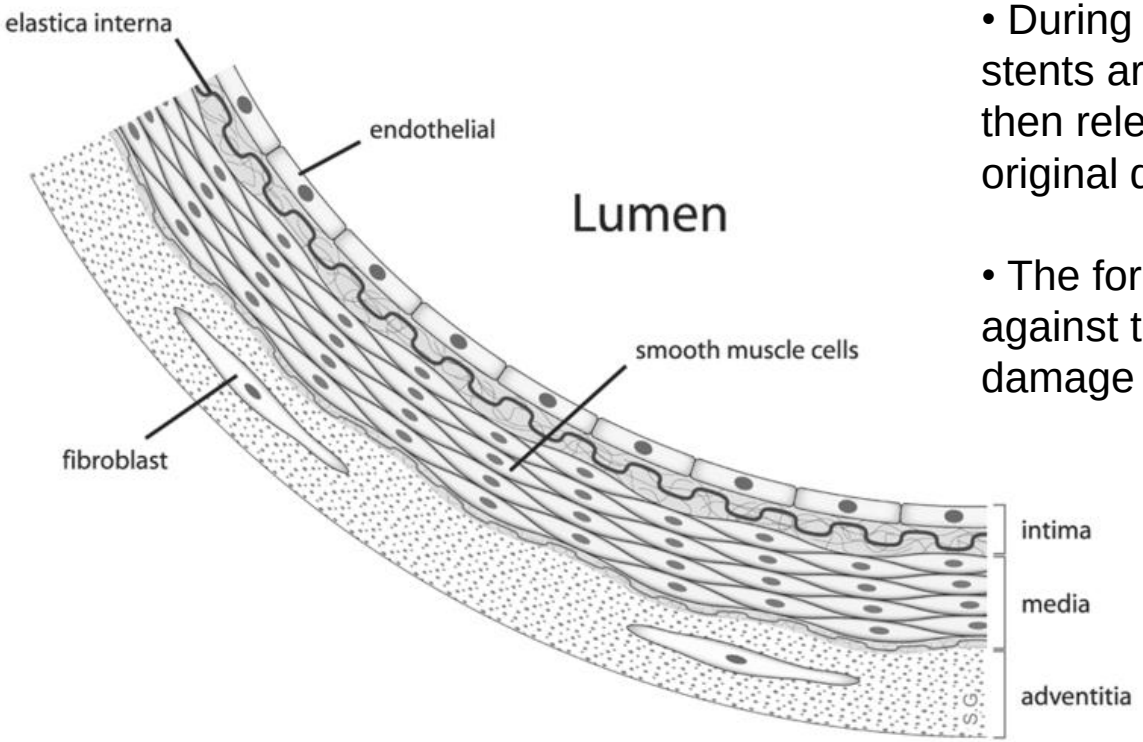
Driver Sprint RX, Medtronic



Taxus Express, Boston Scientific

- length from 8 to 38 mm
- diameter from 2.5 to 4mm
- struts from .003 to .006 in
- 316 SS or L605 CoCr
- laser cut from seamless tubing
- electropolished and then passivated

Stenting Causes Injury

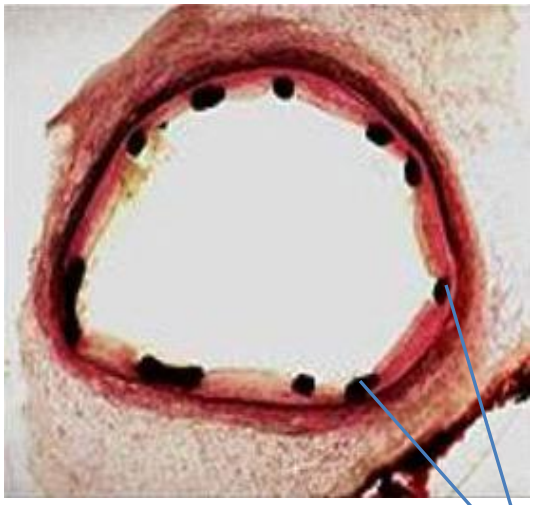


- During implantation, coronary stents are over expanded and then released to shrink to the original diameter of the vessel.
- The forces of the struts against the lumen causes damage (unavoidable).

- Upon injury, the body will attempt to repair itself by growing smooth muscle tissue.
- This “scar” tissue can result in restenosis.

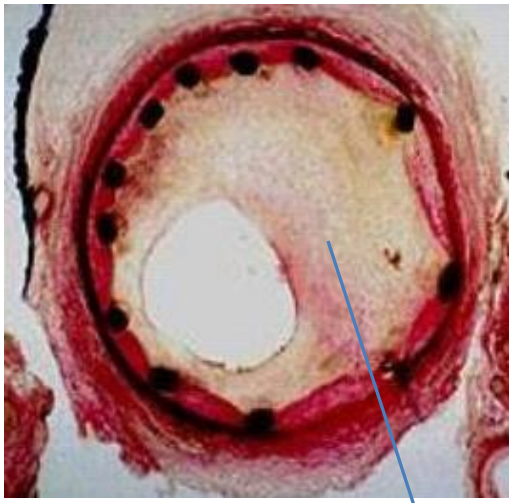
Restenosis

Cross Sections



1 Day

struts



6 Mo

smooth muscle tissue

Bare Metal Stent

Wong, Clinical Cardiology Series

History of Stents

1989 – Bare metal stents (BMS)

- Growth in popularity because it provided pain relief without highly invasive surgery.
- Restenosis rate ~ 30%

In 2006, the worldwide market for coronary stents was $5.1 billion

2002 – Drug Eluting Stents (DES)

- Johnson and Johnson introduced the Cypher stent. Others followed.
- Drugs prevented smooth muscle tissue growth that would normally occur because of injury to the lumen.
- Reduction of restenosis to < 10%.
- **Huge profits for device makers.**

Cypher Stent

Original DES Design

Drugs:

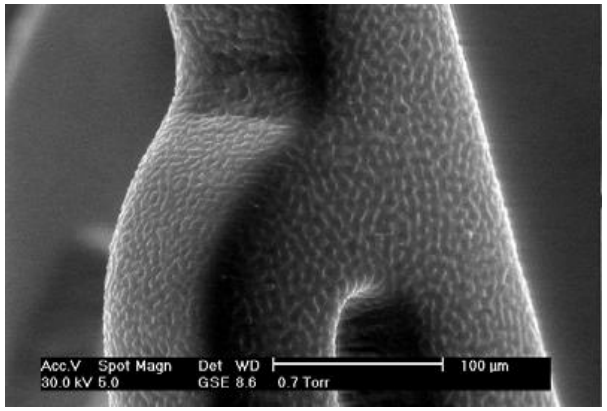
- Sirolimus (MW 914), Paclitaxel (MW 853)
- Both are cytotoxic.

Polymer Coatings:

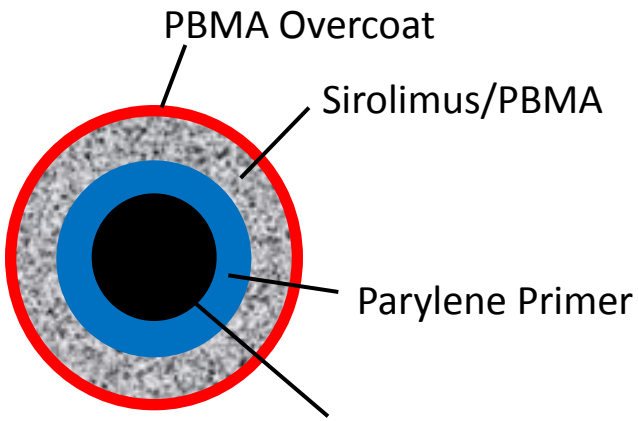
- Drug dissolved in polymer-solvent solution
- Solution used to form coating on stent by spraying or dipping
- 7 to 15 um thick
- Non-biodegradable polymers (PBMA, PEVA)

Polymer Played Many Roles:

- Dissolves drug during processing (up to 40% of the polymer wt)
- Elastic matrix for holding the drug onto the stent (must adhere to stent and not crack under strains of up to 20%)
- Controls release rate (diffusion)
- Must be biocompatible

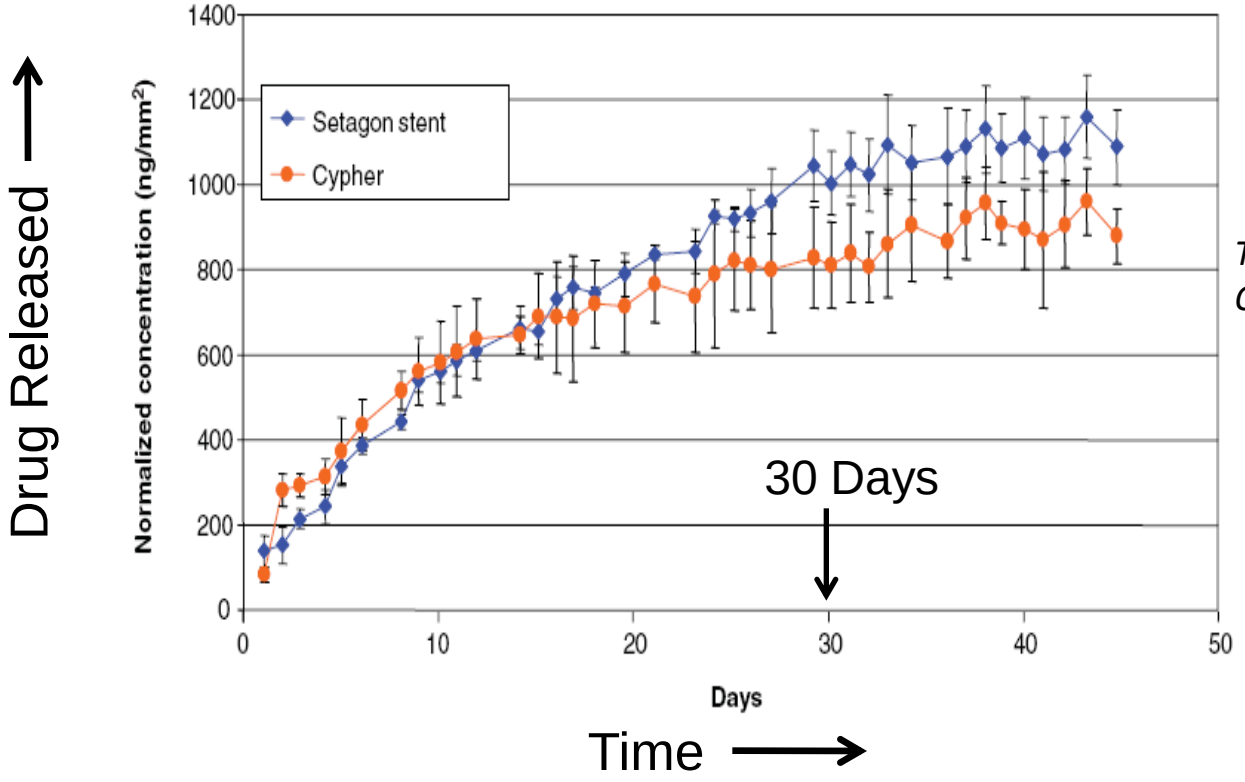


Taxus Stent



Cypher Stent 2002

Drug Release Profile



Tsujino, Expert Opinion, 2007

- Controlled by diffusion through polymer
- Goal was ~ 30 days of drug release

Studies Showed a Problem

- Starting in 2005 studies reported that the original drug eluting stents increased the risk of thrombosis (blood clots) after 30 days.

- Although the frequency was low (< 1%), thrombosis is often fatal.

- In 2007, DES sales dropped by 40%.

- The long term presence of polymers were widely blamed.

- The search was on for alternatives to permanent polymers for controlling drug release from stents.

Current Drug Eluting Stent Research

1. Switch to biodegradable polymers
2. Bioabsorbable stents
3. Micro holes and grooves w/ BDPs

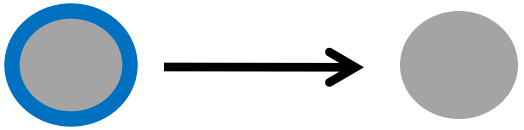
Biodegradable polymer approaches

4. Pure drug coatings w/ and w/o textured surfaces
5. Non-polymeric excipients
6. Nanoporous Coatings

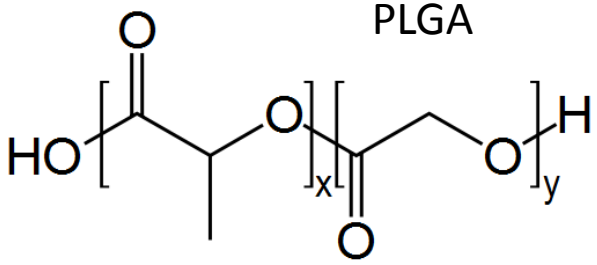
Non-polymeric approaches

Biodegradable Polymers

- Idea is to have a BMS sometime after the drug is gone
- Poly (dl-lactic-co-glycolic acid) (PLGA) is common
- Release profile determined by a combination of diffusion and degradation of the matrix
- There are concerns about biocompatibility and the effect of debris



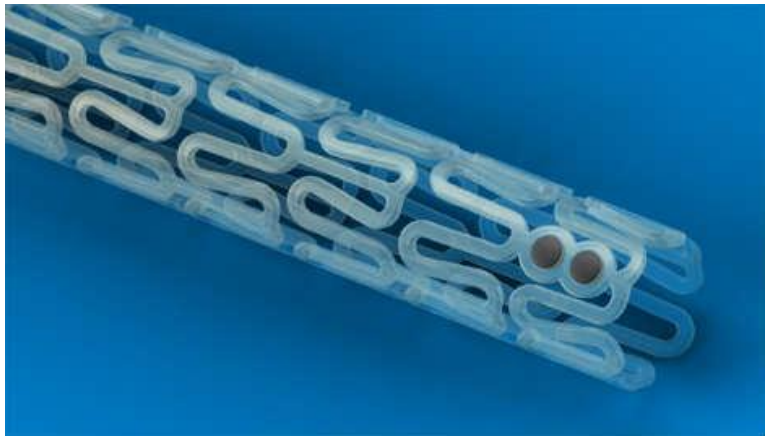
PLGA



Degradation by hydrolysis of ester linkages

Bioabsorbable Stents

- Made entirely of a biodegradable polymer
- Idea is to have the stent disappear completely in about 2 years
- It is hoped that plaque dissolves with increased blood flow to the site
- Polymer loaded with drug to prevent restenosis
- The major concerns have to do with structural integrity and biocompatibility.

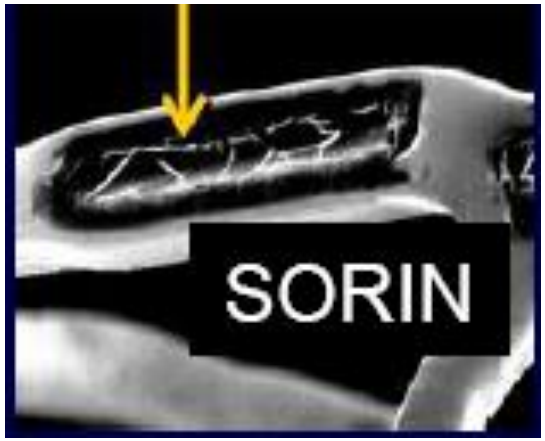


Abbott

Holes and Grooves

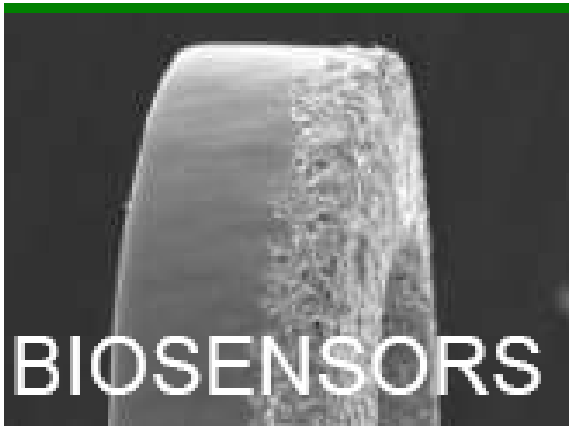
- Idea is to have keep the drug and biodegradable polymers away from direct contact with the tissue.
- Holes and grooves cut into the stent struts (diameter or width ~ 50 um)
- Drugs and polymers loaded into holes using inkjet technology
- Initial clinical studies have been disappointing

Conor Stent by Cordis



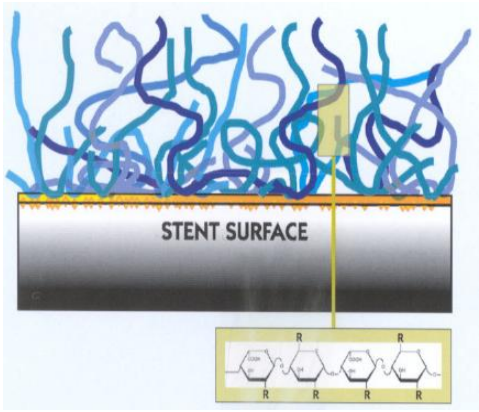
Non-Polymeric Approaches – Pure Drug Coatings

- Drug deposited directly onto stent struts
- Strut surfaces are sometimes etched or bead blasted to improve adhesion
- Dissolution is complete in < 6 hours
- Clinical trials are underway



Non-Polymeric Approaches – Non-Polymeric Excipients

- Excipient is used as a binder for the drug
- Excipient is often chosen to be a biomimetic material
- Biosensors Axxion uses a synthetic form of glycocalyx – a slime found on the surfaces of endothelial cells (commercial success unknown)
- Ziscoat uses triglycerides (pre-clinical)



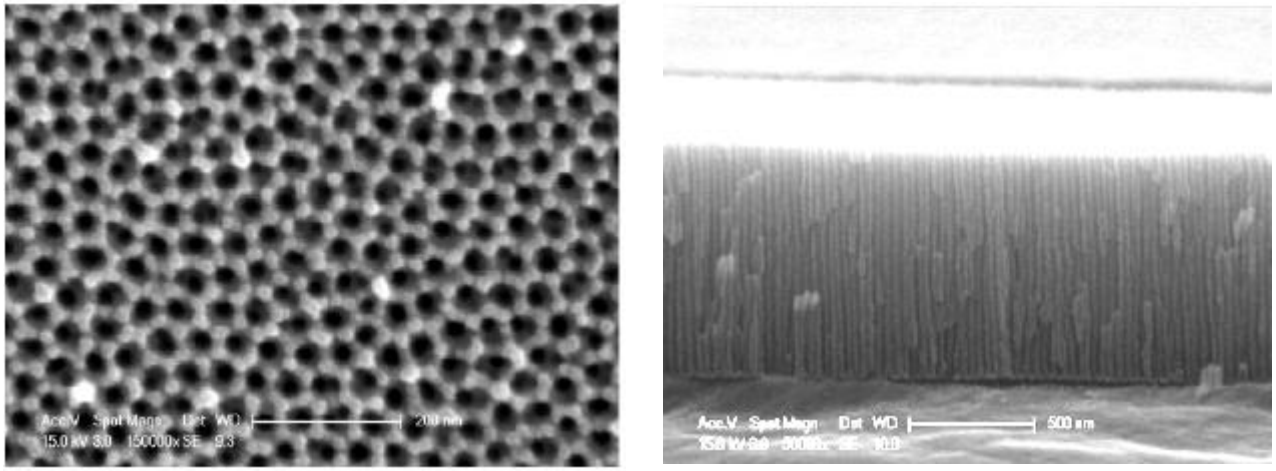
Biosensors Axxion

Non-Polymeric Approaches – Nanoporous Coatings I

Can nanoscale pores be used to control drug release?

Anodic oxide films

- Pore diameter can range from 15 to 200 nm
- Porosity ~ 50%
- Drug released in < 2 days
- Film thickness on flexible substrates limited to 1 – 2 um to avoid cracking and delamination

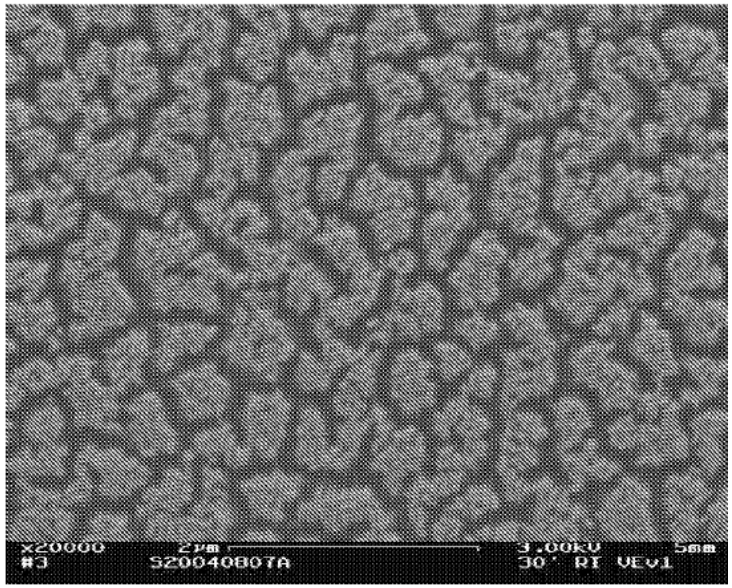


Kang, Controlled drug release using nanoporous anodic aluminum oxide on stent, 2006.

Non-Polymeric Approaches – Nanoporous Coatings II

Dealloyed Coatings

- Sputtered coating containing at least one sacrificial material and at least one structural material is deposited
- The coating is exposed to caustic agents to remove the sacrificial material
- The resulting structure has a “Swiss Cheese” like appearance, ~ 40% porosity, 5 to 25 nm pores
- Release rates uncertain
- Film thickness is limited to ~ 2 um to avoid cracking
- Not commercialized

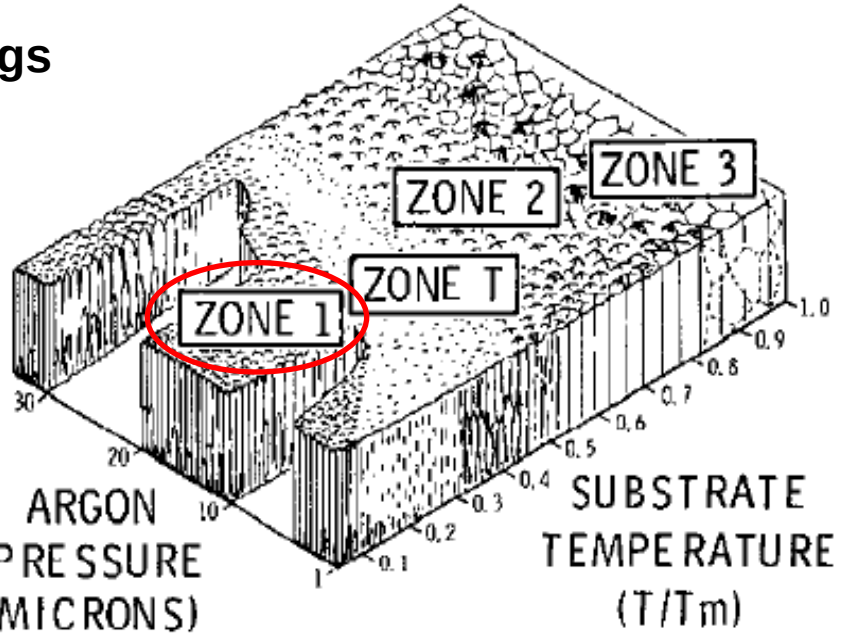


US Patent Application US20080086198

Non-Polymeric Approaches – Nanoporous Coatings III

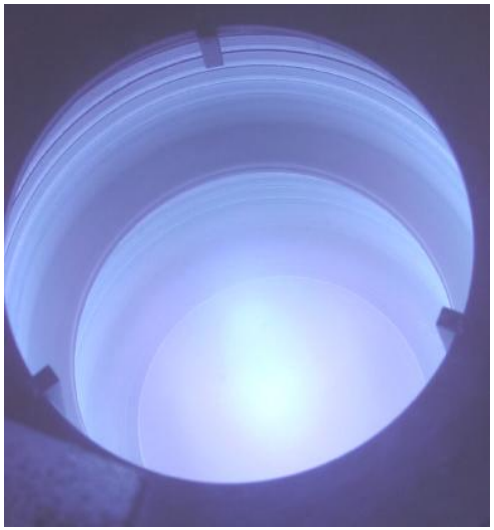
Sputtered Porous Columnar Coatings

- Low homologous temperature
- Low energy (< 1 eV) or oblique angle deposition
- Cylindrical magnetron cathode



Thornton, High Rate Thick Film Growth, Ann. Rev. Mater. Sci, 1977

Isoflux ICM10



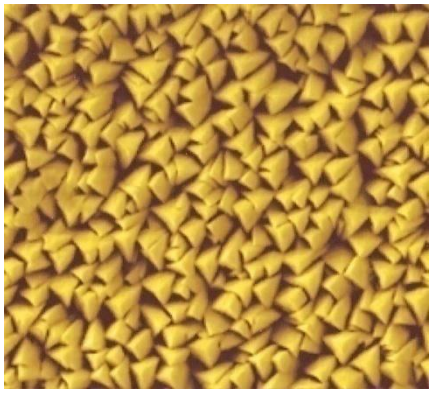
➢ Zone 1 Porous Columnar Structure

Porous Columnar Features

- Coating structure determined by materials and process conditions
- Columns are ~ uniform top to bottom
- Pore sizes range from 5 to 30 nm in width
- ~ 20% porosity for Ta and Cr coatings

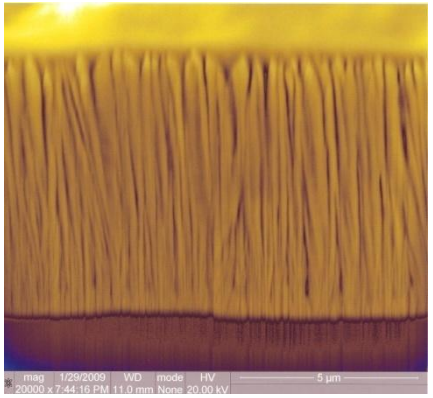
- ➢ Surprising result of excellent adhesion of columns to stent
- ➢ Discrete columns do not transmit stress laterally when coating is flexed (film thickness not limited by risk of fracture)
- ➢ Pore space can be used to deliver drugs

10 um Thick Ta



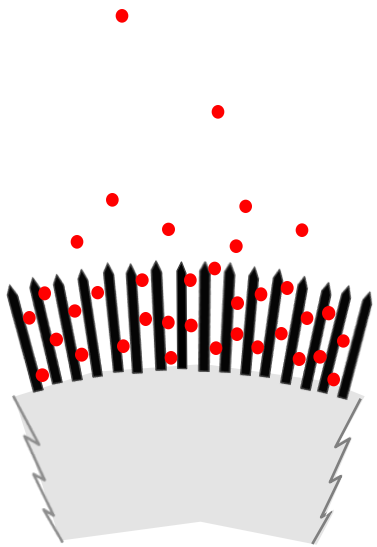
9 μm

7.5 um Thick Ta



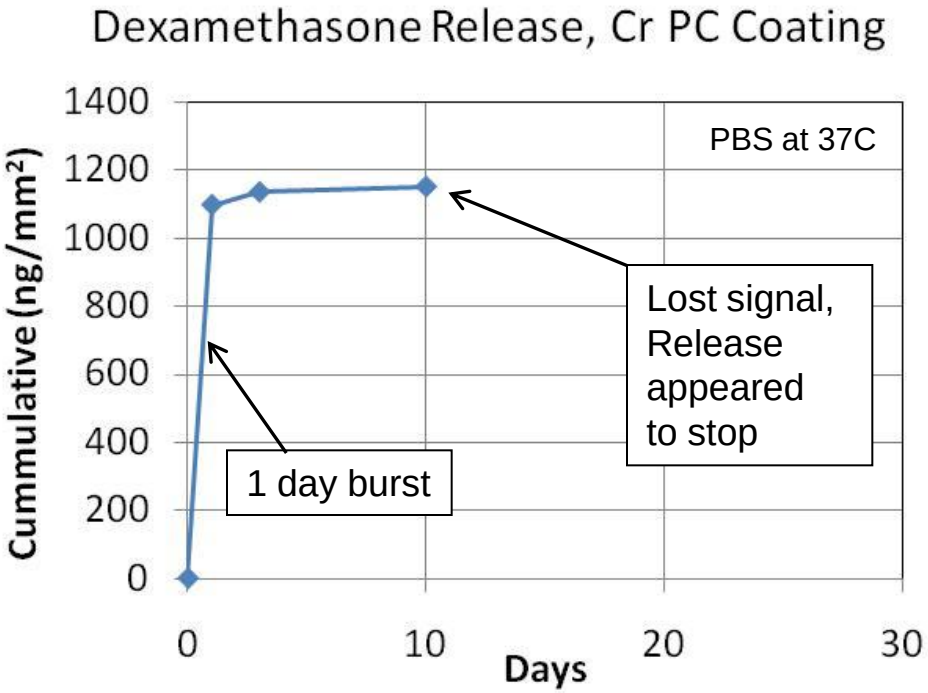
12 μm

First Look at Non-polymeric PC Drug Release



Stent placed in PBS at 37 C

Drug concentration measured by UV Spec

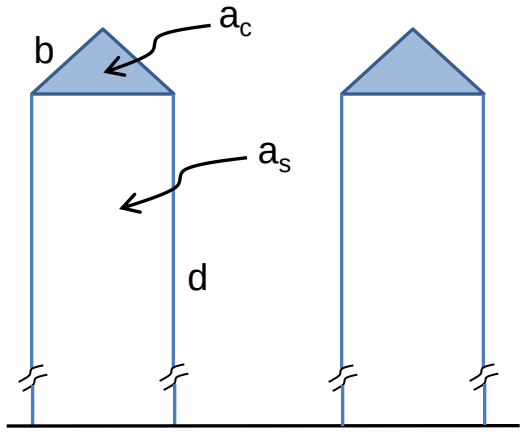


- High drug load but short elution time
- Nanopores did not offer enough diffusional resistance
- **Not all of the drug is released**

Porous Columnar Coating Relationships

$$n_c = \frac{(1-p)}{a_c}$$

Not all independent



Estimated Values

	p	b (nm)	n_c (μm^{-2})
Cr	.18	150	84.2
Ta	.21	200	45.6

Increase in Surface Area

$$\frac{A^*}{A} = 1 + n_c\, a_s$$

n_c = column number density

a_s = column sidewall area

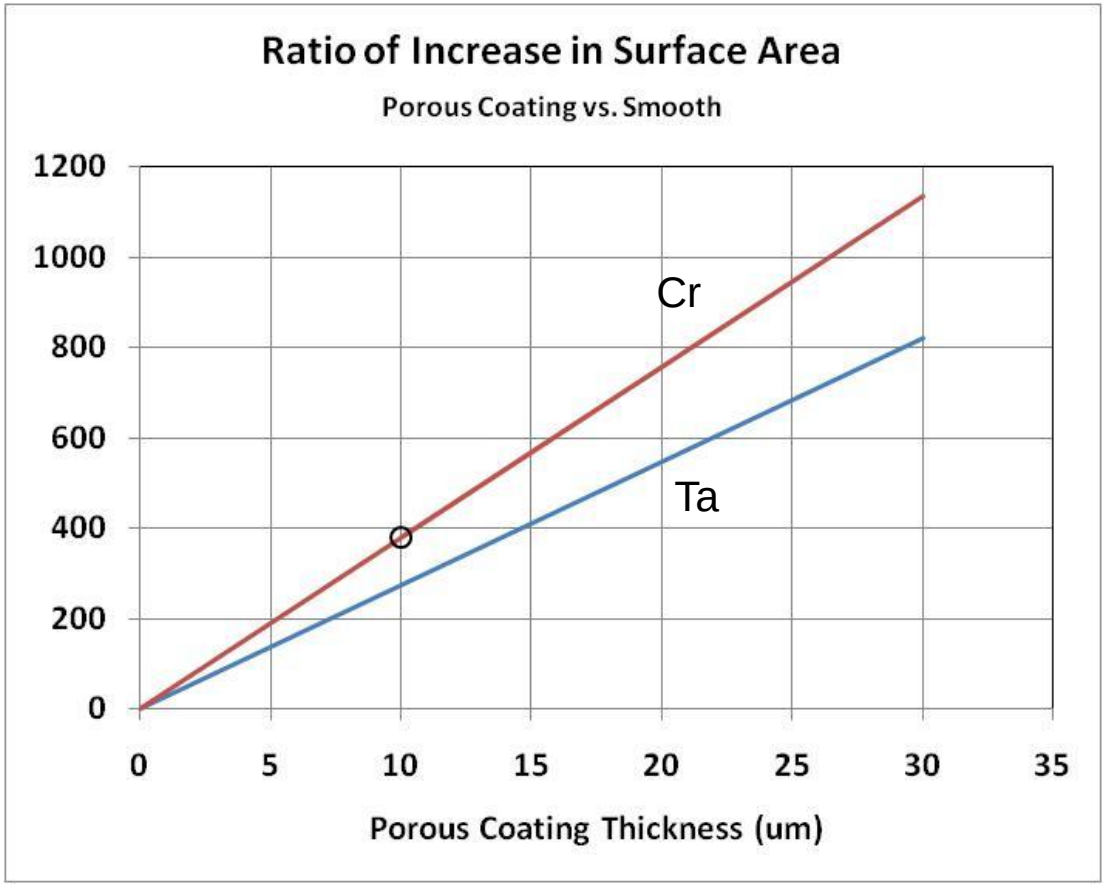
a_c = column top area

b = column side length

d = column height

p = porosity

Surface Area Increase of PC Coatings



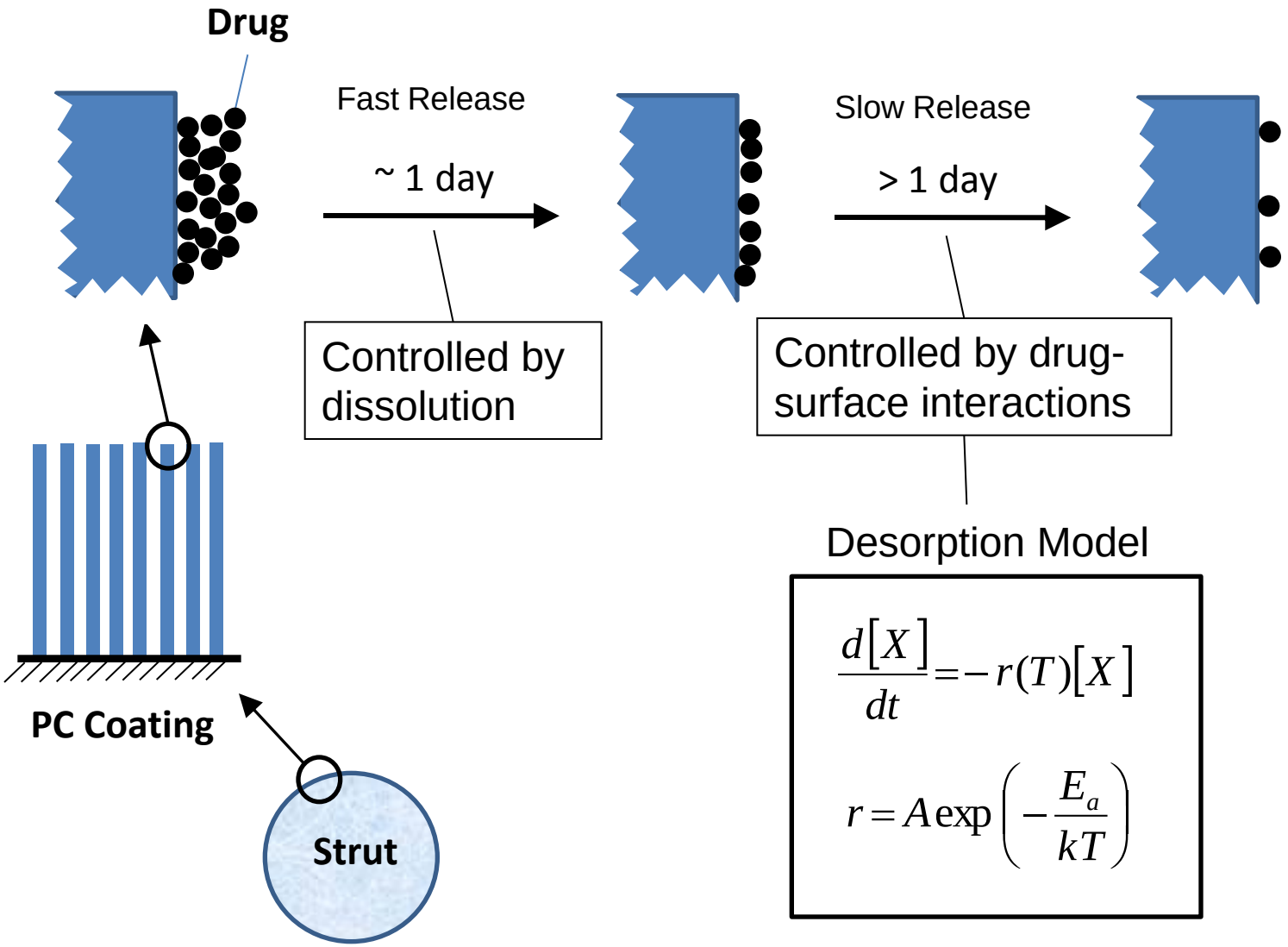
- Medically significant amounts of drug in one monolayer

- 10 um Cr: 1 monolayer ~ 3.5 μg/mm of stent length

- Typical range: 1 – 10 μg/mm

- A monolayer of drug spread out over the high surface area of the PC coating is the same as the amount of drug remaining after the elution step.

Non-Polymeric PC Drug Release Model

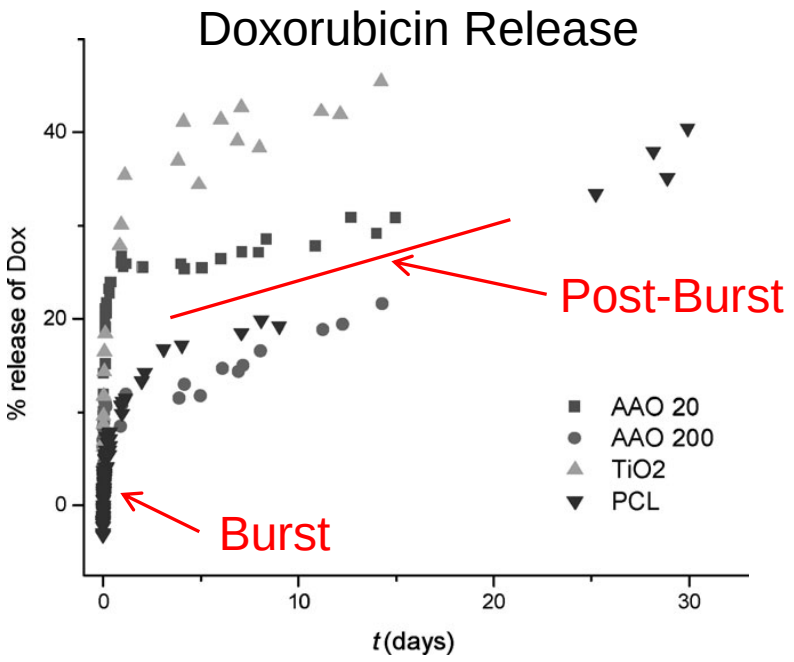


Observations From Others

1. Kang (2006) noted that Drug Release ~ (Film Thickness) $^{-1}$ for anodic aluminum oxide nanoporous films

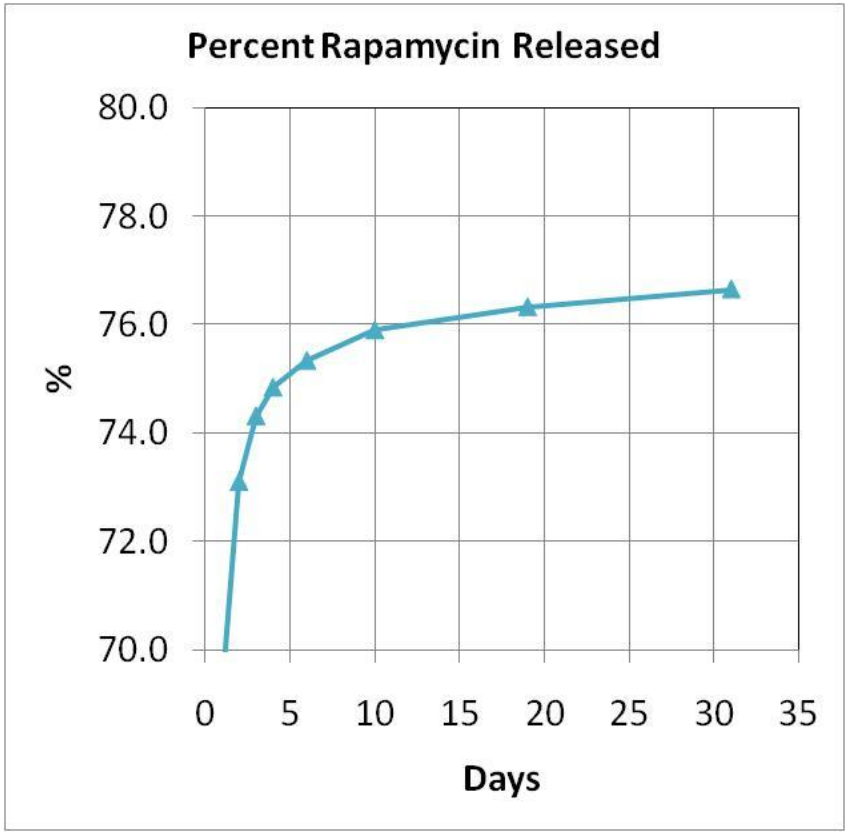
2. Brohede (2009) saw that different drugs had different release rates from nanoporous hydroxyapatite coatings

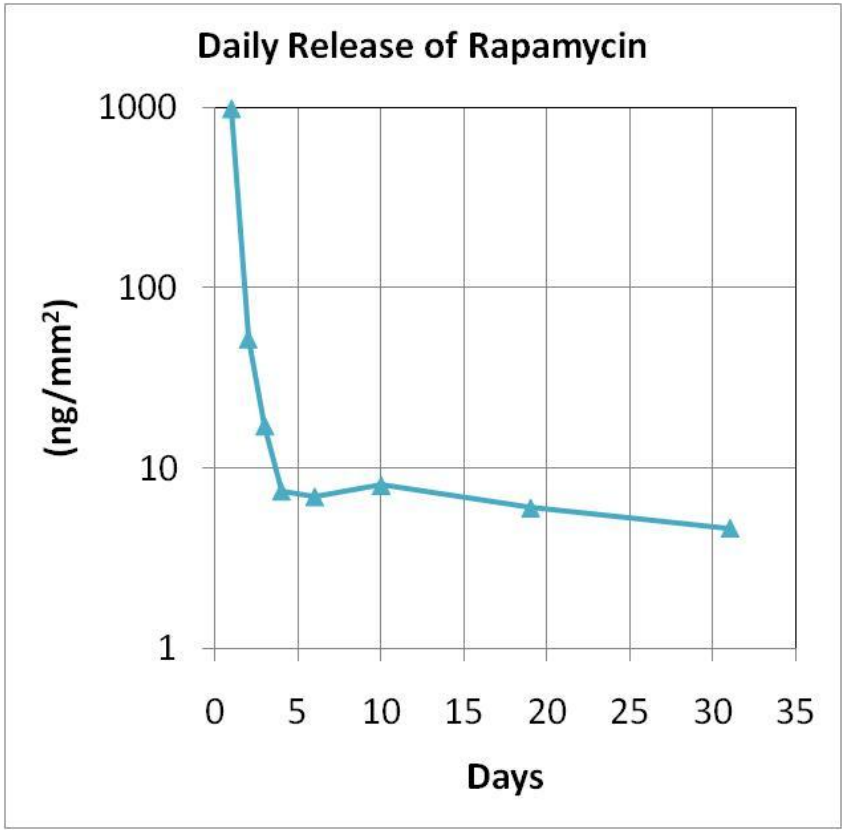
3. Sridar (2010):
   - was the first to cite the high surface area of nanoporous coatings as an advantage in drug delivery
   - showed slow long term post-burst drug release from anodic oxide films



2nd Isoflux Study of Post-Burst Elution Rates

- 13x increase in resolution
- 20 μm nanoporous Cr on SS
- Shows drug is indeed released after the burst period is over





What If The Post Burst Release Rates Are Not What We Want?

The post-burst release of drug from nanoporous columnar coatings loaded with pure drug depends on the drug-coating combination.

Modification of the Method

1. Modification of the Porous Coating Surface

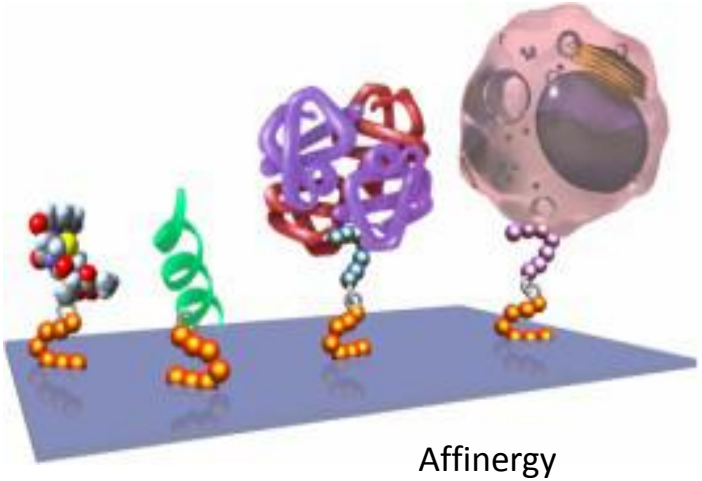
   Can primer coatings or surface modification (e.g. plasma discharge) be used to control drug release?

2. Non-Polymeric Excipients

   Excipients on the porous material would alter the effect of drug-drug interactions and could provide control of the release rate.

3. Chemical Linkers

   Peptide linkers that can be cleaved by enzymes to release drugs or other compounds.



Affinergy

Conclusions

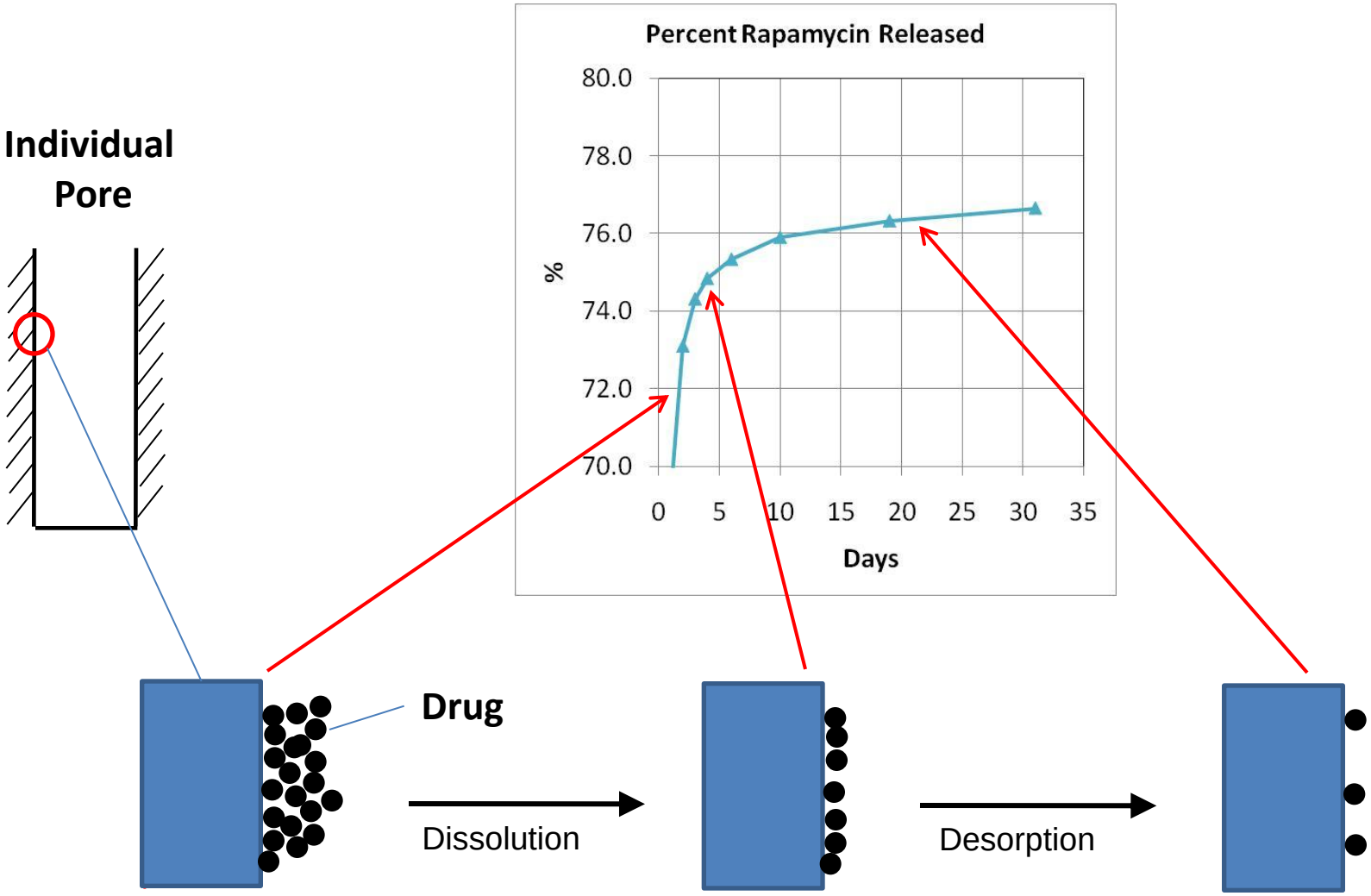
High Surface Area Is Still the Key

Only nanoporous structures offer this advantage

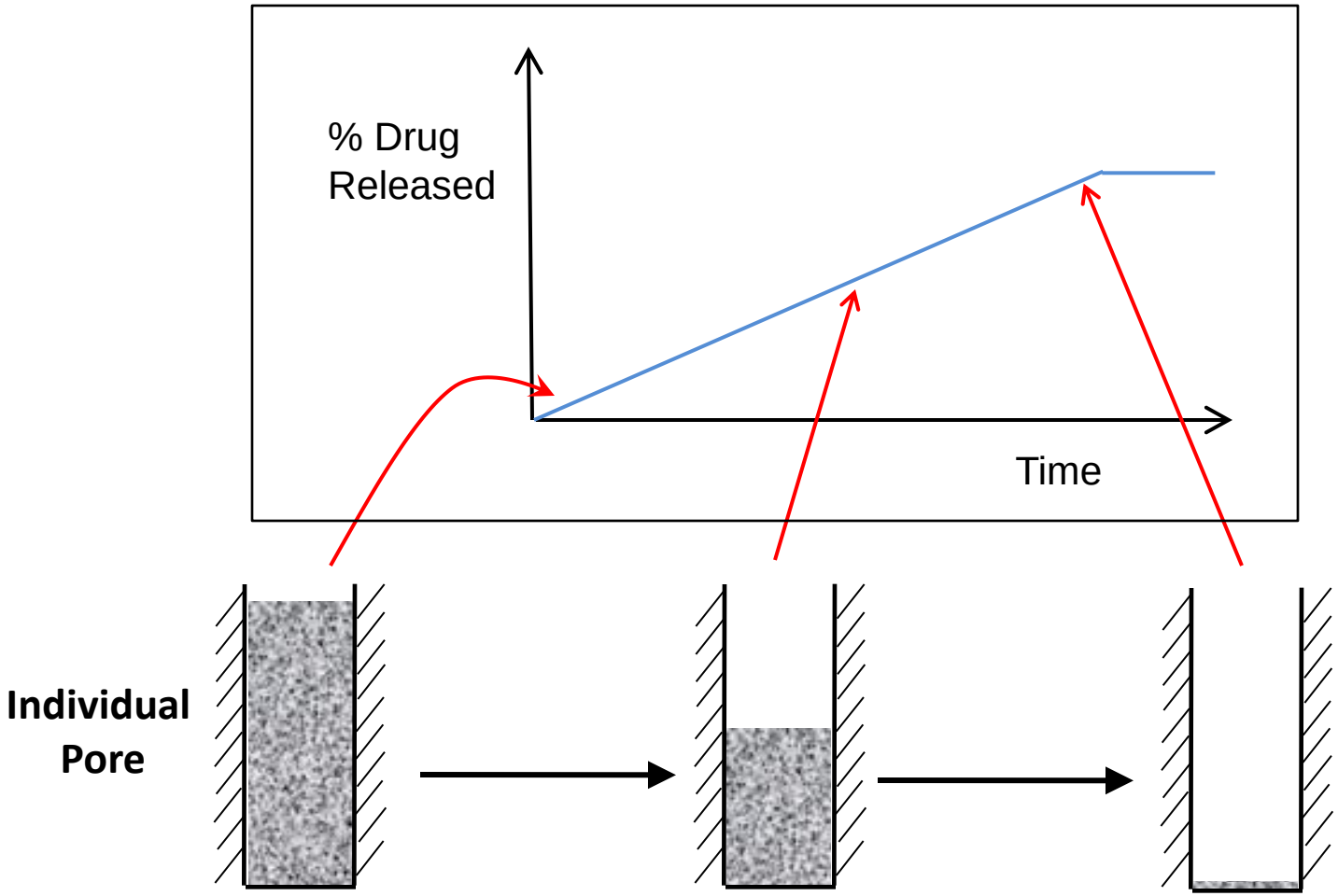
Sputtered Porous Columnar Coatings Offer:

- Excellent adhesion to device
- Film thickness not limited by cracking
- Greater than 200x the surface area of the original surface
- Medically significant drug loads in one monolayer
- Long term release of drug as a result of drug-surface forces

Loading by Dipping Produces a Surface Coating and Two Phase Release Kinetics



Loading by Spraying Fills the Pores
Drug is released by dissolution but only from the top



PC Coating Drug Load Capacity: Pores Filled, No Excess