"A Drug-Eluting Stent Case Study: TAXUS™ Express²™ - From Development to Approval"

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Boston Scientific Corporation

New England Chapter Parenteral Drug Association Workshop
October 1, 2004

Key Considerations for DES*

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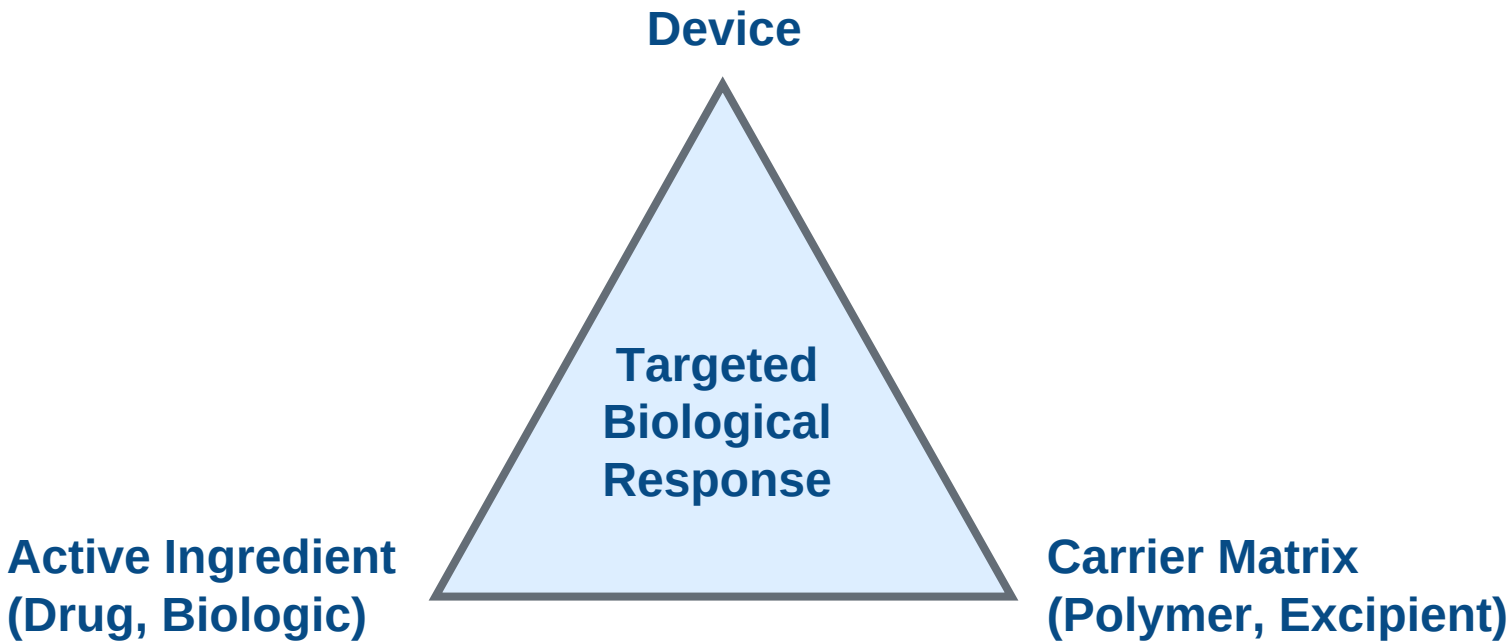
Balance Between Individual Components and the Methods of Combining Them



*DES = Drug Eluting Stent

Key Components of DES Combination Products That Can Impact Biocompatibility, Functionality and Manufacturing

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DEVICE

- **Material**
  - Polymers
  - Metals
- **Design**
  - Geometry
  - Mechanical Function
  - Anatomical location

CARRIER MATRIX

- **Chemistry**
  - Manufacturing residuals
  - Compatibility with drug
- **Compatibility with Device**
  - Mechanical Integrity
  - Material stability
  - Maintain device function

DRUG

- **Pharmacology**
  - Tissue kinetics
  - Toxicity profile
  - Systemic effects
- **Chemistry**
  - Purity
  - Stability
- **Compatibility with Matrix**
  - Chemical interactions
  - Solid state characterization
  - Manufacturing residuals
  - Degradation products
- **Compatibility with device**
  - Maintain device function
  - Compatible with material

Key Components of DES Combination Products That Can Impact Biocompatibility, Functionality and Manufacturing

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Finished Product Analysis (Drug related)

- **Label claim for drug**
  - Drug content per device
- **Drug Release Profile**
  - Sustained versus short term
- **Lot uniformity**
  - Manufacturing variability of drug content from unit to unit
- **Drug degradants**
- **Drug-Carrier adduct formation**
- **Residual processing solvents**
- **Endotoxins**
  - bulk to capture process impact
  - surface to capture final product assembly impact
- **Sterility**
- **Stability (ICH)**
- **Pharmacokinetics of drug**
  - Depot formation in tissue
  - Metabolism

Manufacturing Controls for DES Combination Products Ensure Safety and Biocompatibility

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DEVICE

- Quality Systems Regulations (QSR)
- 21 CFR 820
- ISO
- ASTM

DRUG

- cGMP
- 21 CFR 210
- 21 CFR 211
- Defined Analytical Procedures and Acceptance Criteria
  - International Conference on Harmonization (ICH)
  - FDA CDER or CBER guidances
  - Compendial guidances (U.S. Pharmacopeia)

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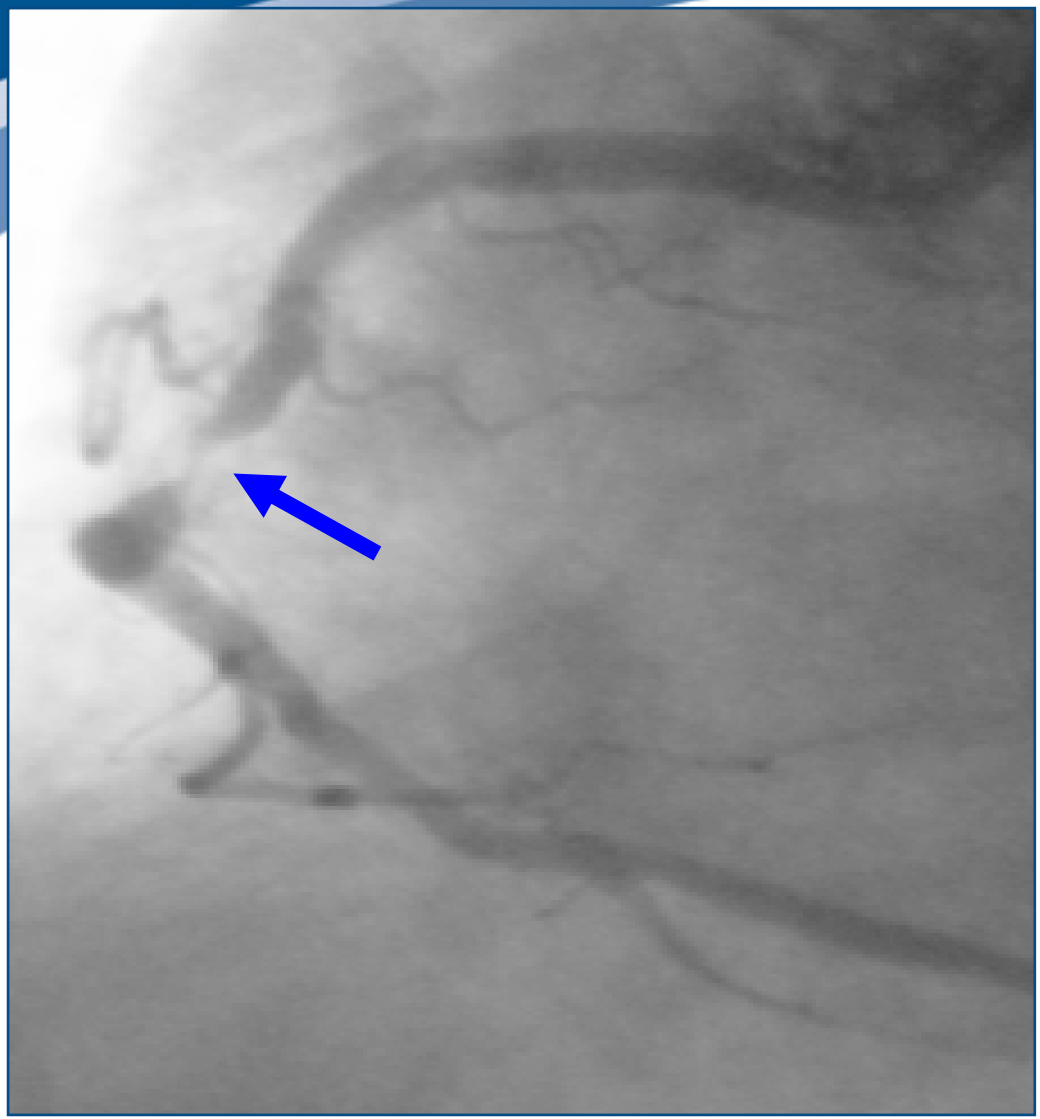
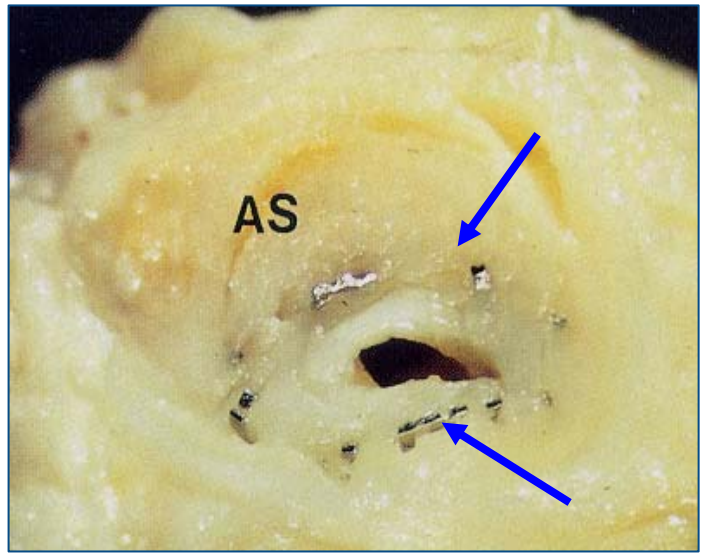
Delivering what's next.™

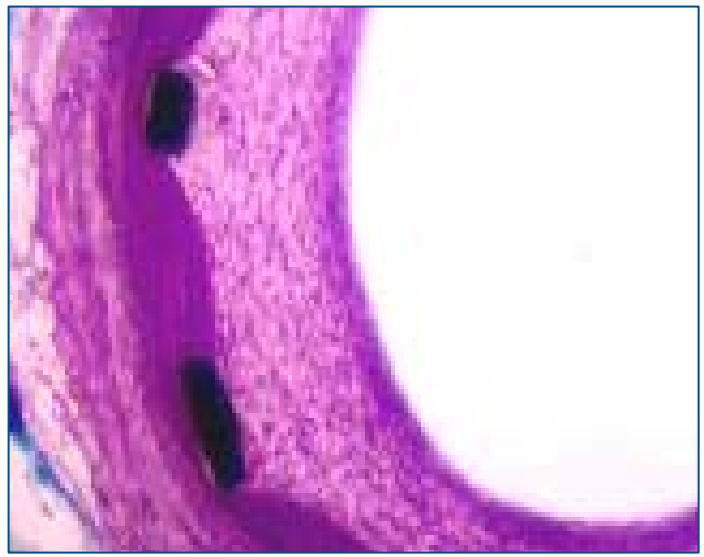
Case Study:

TAXUS ™ Express²™ Paclitaxel Drug-Eluting Stents

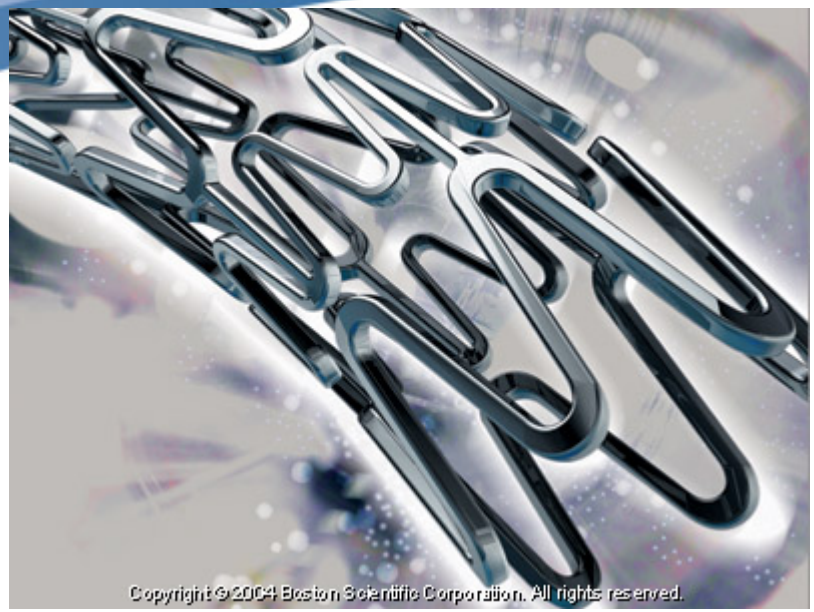
The Problem:
In-stent Restenosis







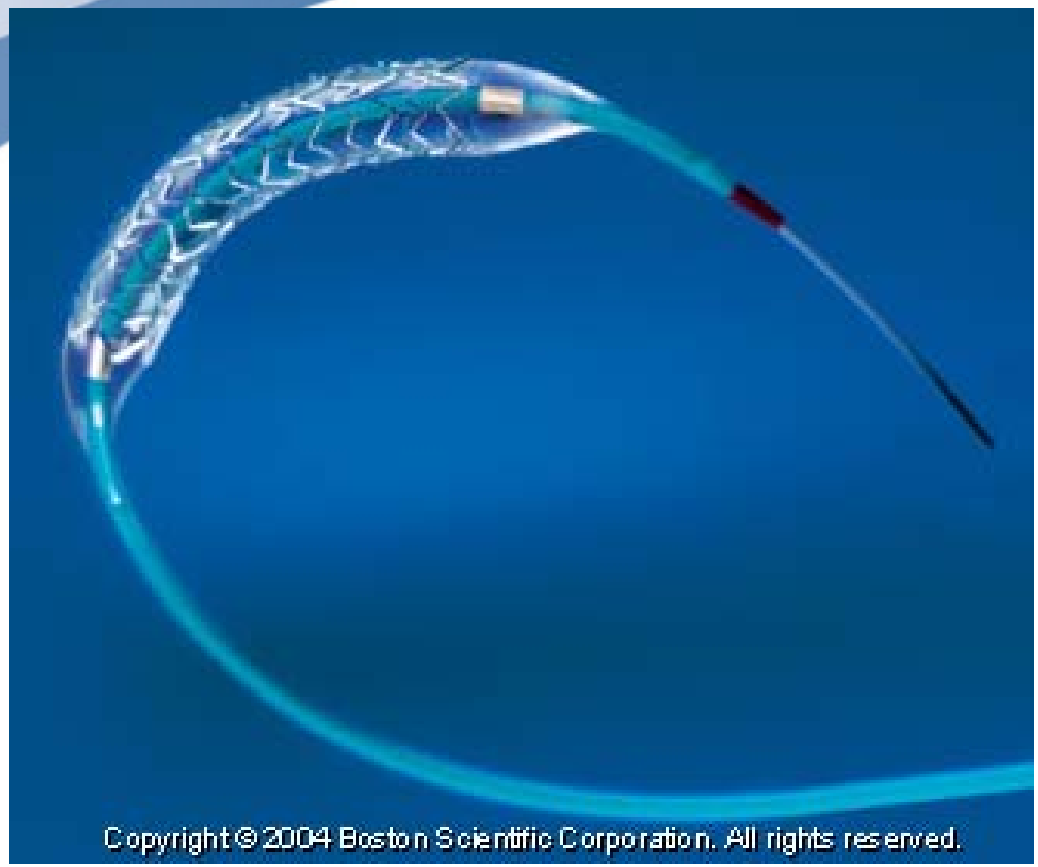
A Solution: Drug-Coated Stents

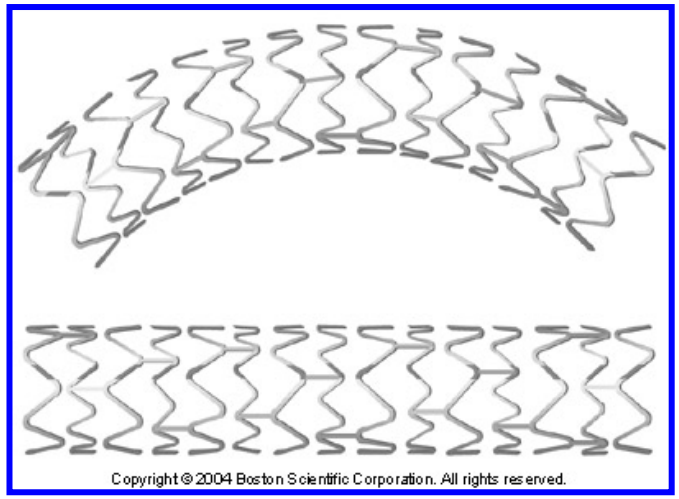


Current Design Components and Functions

- **Stent**
  - Provides a mechanical scaffold to maintain patency of vessel
- **Drug**
  - Pharmacological or biological agent targeting cellular control of restenosis
- **Polymer Carrier**
  - Provides a means to control administration of drug (site, rate and dose)

TAXUS™ Express²™ DES





TAXUS ™ Express²™ Drug Eluting Stent

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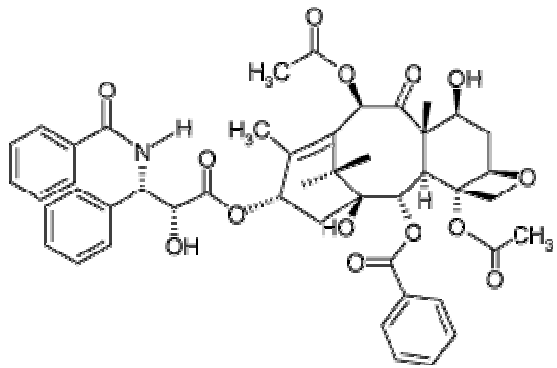
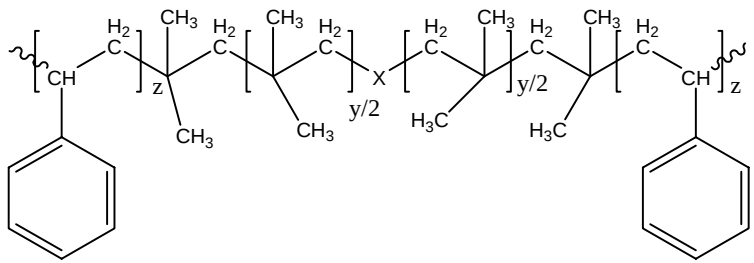
Drug: Paclitaxel (PTx)



Polymer: poly (styrene-b-isobutylene-b-styrene) (SIBS)



An ABA type triblock thermoplastic elastomer that exhibits phase separation as microdomains

Polymer Carriers

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Advantages of Polymer Carriers

- Range of drug loading allows targeting a specific therapeutic response
- Precise control of drug dosage
- Uniform drug distribution on device surfaces
- Prevents loss of drug during handling and deployment
- Versatile
  - One polymer can be used for a portfolio of drugs
  - Can be applied to various device geometries
  - Manufacturing processes are compatible with pharmaceuticals

Regulatory (CMC) issues regarding polymers as excipients

- Residual monomers, catalysts, process solvents in polymer raw materials
- Residual process solvents from stent or device coating process
- Process-induced interactions with drug or device

Examples of Variable Polymer Coating Integrity

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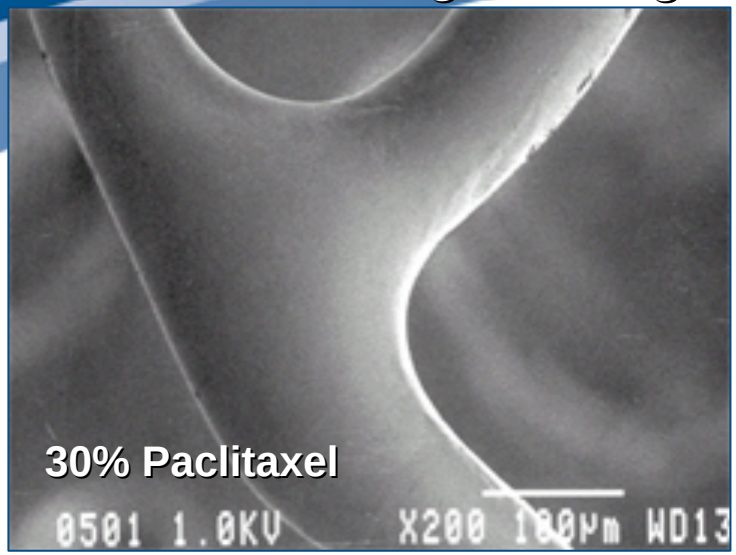
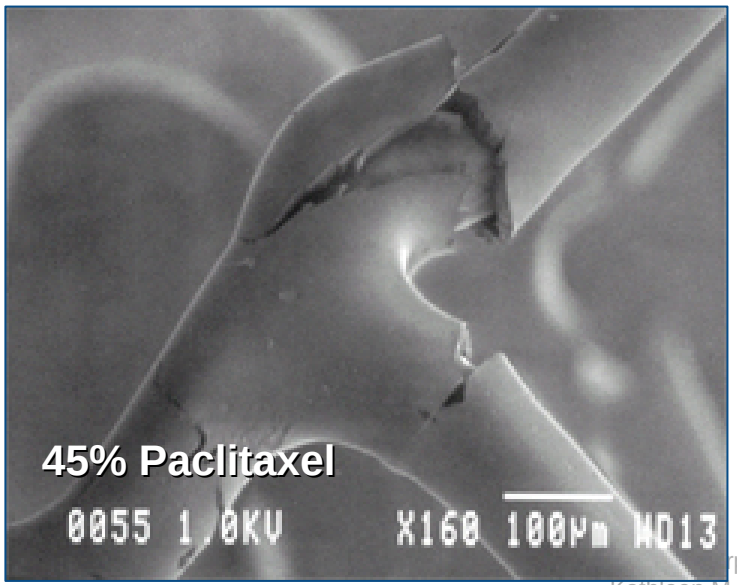
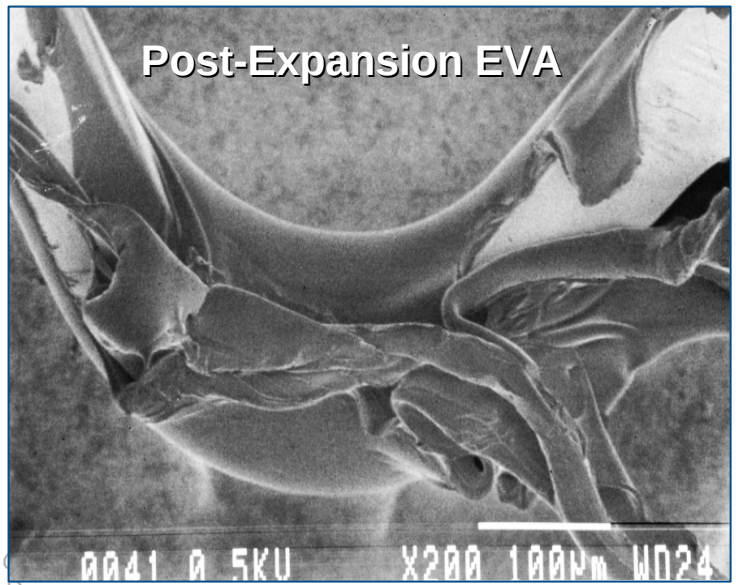
Effects of Drug Loading





Coating Process Incompatibility



Coating Integrity with Translute™ Carrier

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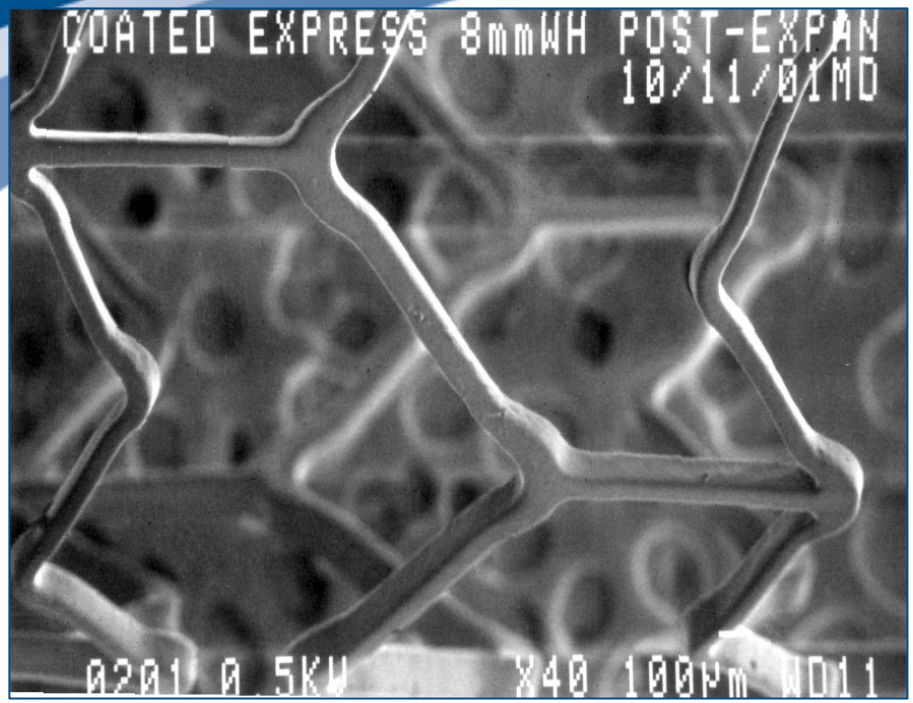

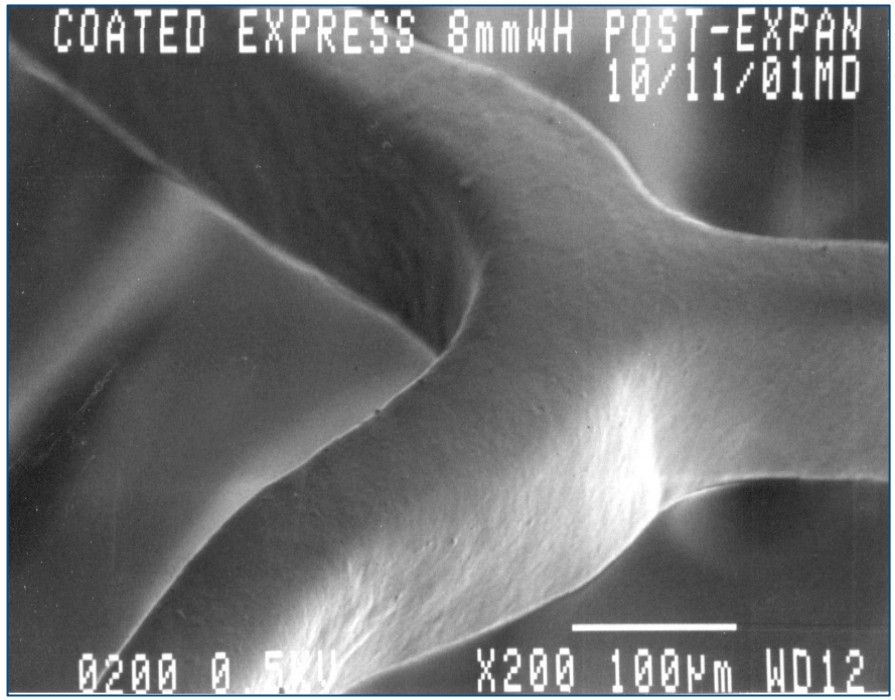

40x **200x**

- **Smooth, Uniform Coverage**
- **No Cracking, Flaking or Delaminating**
- **Post sterilization, post expansion**

Effect of Animal Model and Implant Site on Compatibility Assessment

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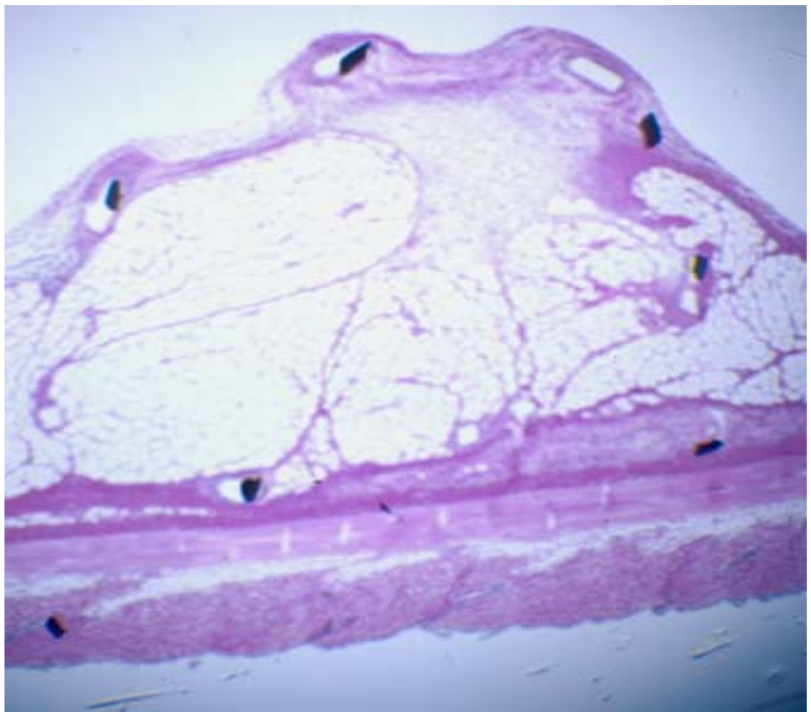
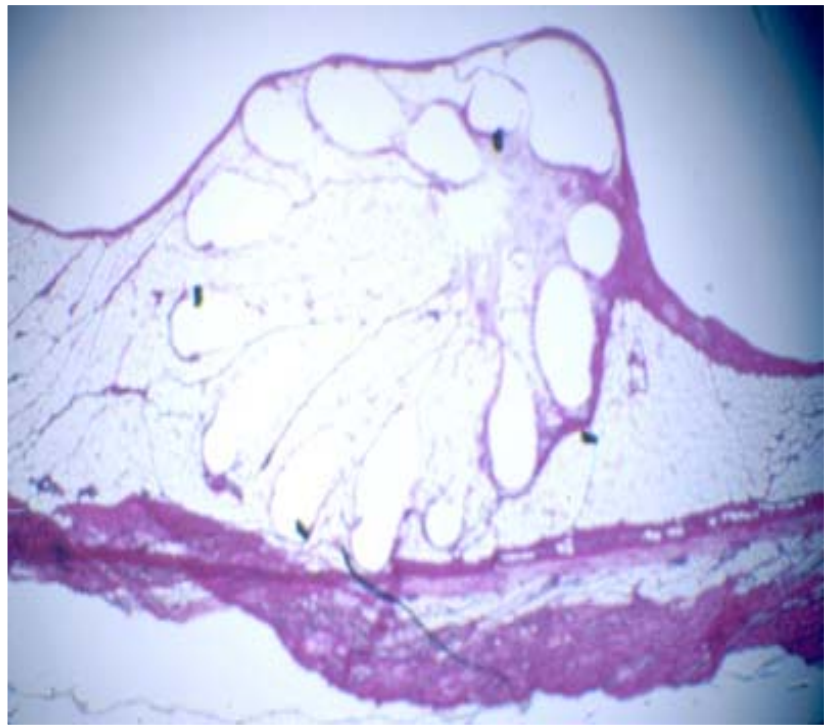
Rat Subcutaneous Implant Model

28 day implant - H&E Staining



Uncoated Metal Stent



Polyurethane-coated Stent

In collaboration with Drs. Anderson and Ziats, CWRU

Effect of Animal Model and Implant Site on Compatibility Assessment

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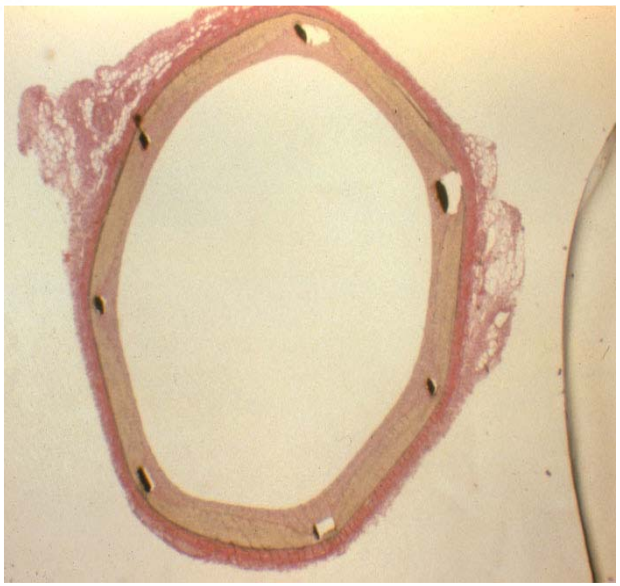
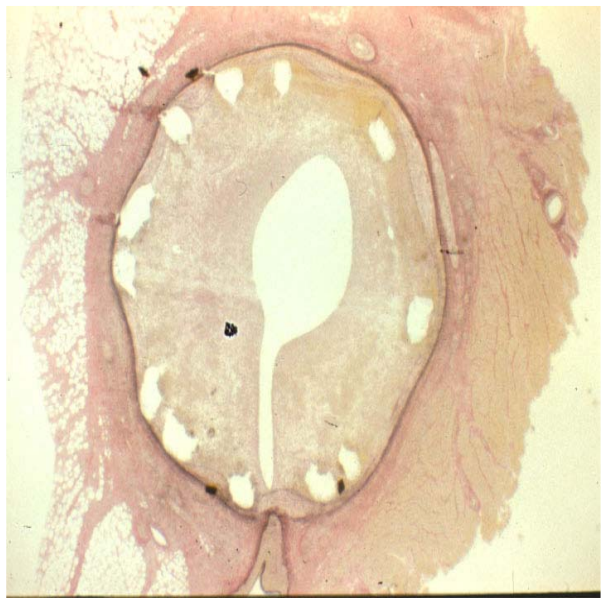
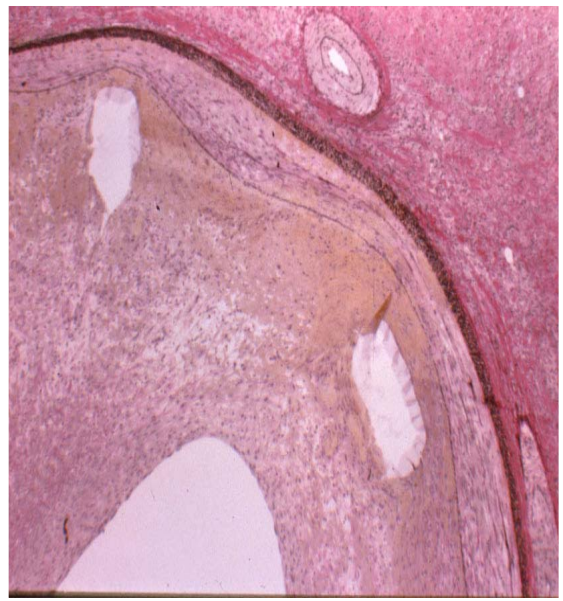
Porcine Coronary Artery Implant Model

28 day implant - H&E Staining







Uncoated Metal Stent ***Polyurethane-coated Stent***

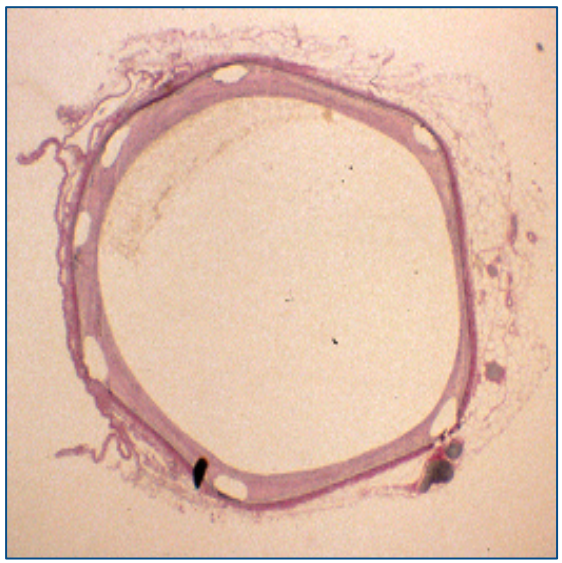
In collaboration with Drs. Rogers and Edelman, MIT

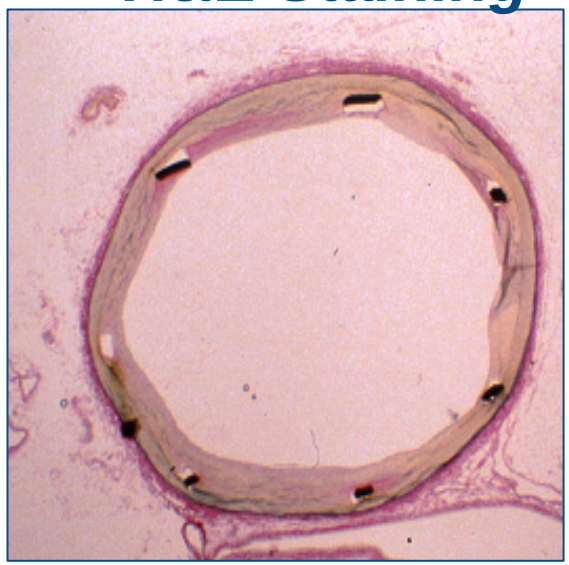
Effect of Animal Model and Implant Site on Compatibility Assessment

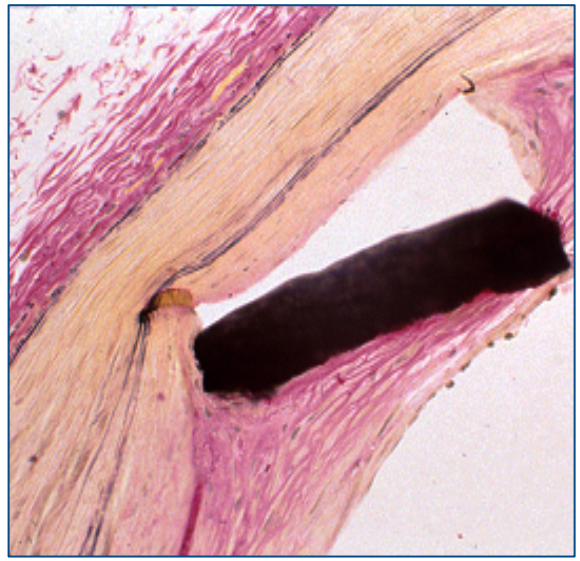
Boston Scientific

Rabbit Iliac Artery Implant Model

H&E Staining







28 day PLA/PCL coated stent

56 day PLA/PCL coated stent

In collaboration with Drs. Rogers and Edelman, MIT

Vascular Compatibility of Translute™ Polymer
Normal Porcine Coronary Artery

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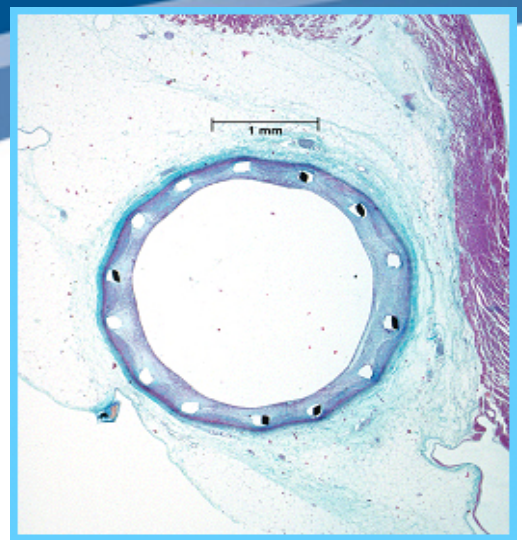
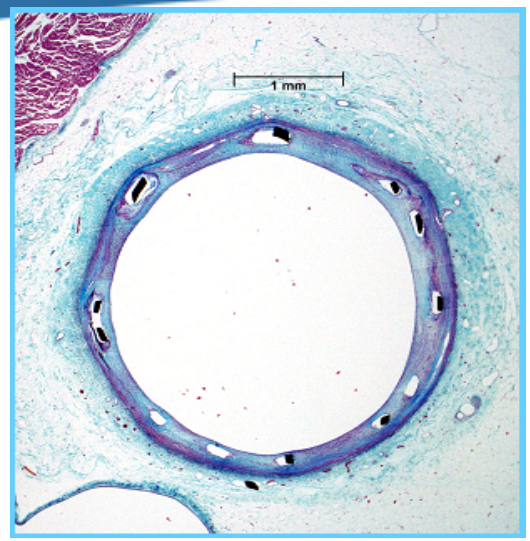
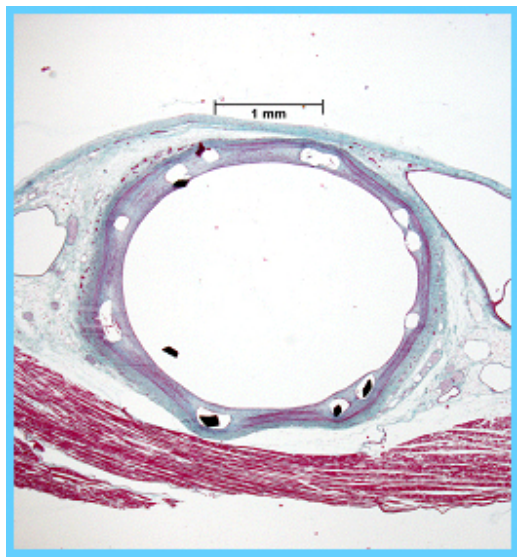
90D Bare Metal Control

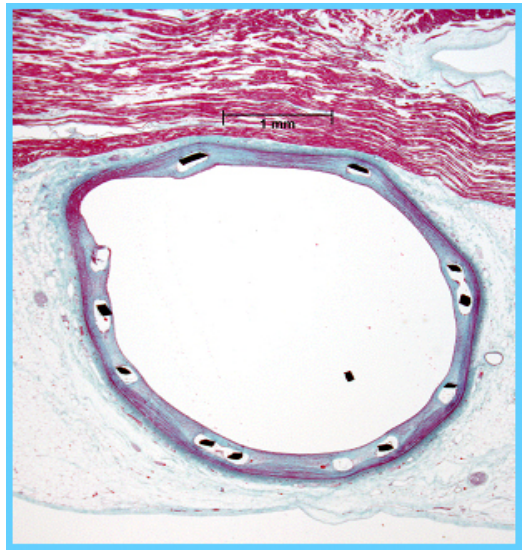




180D Bare Metal Control

90D polymer coated

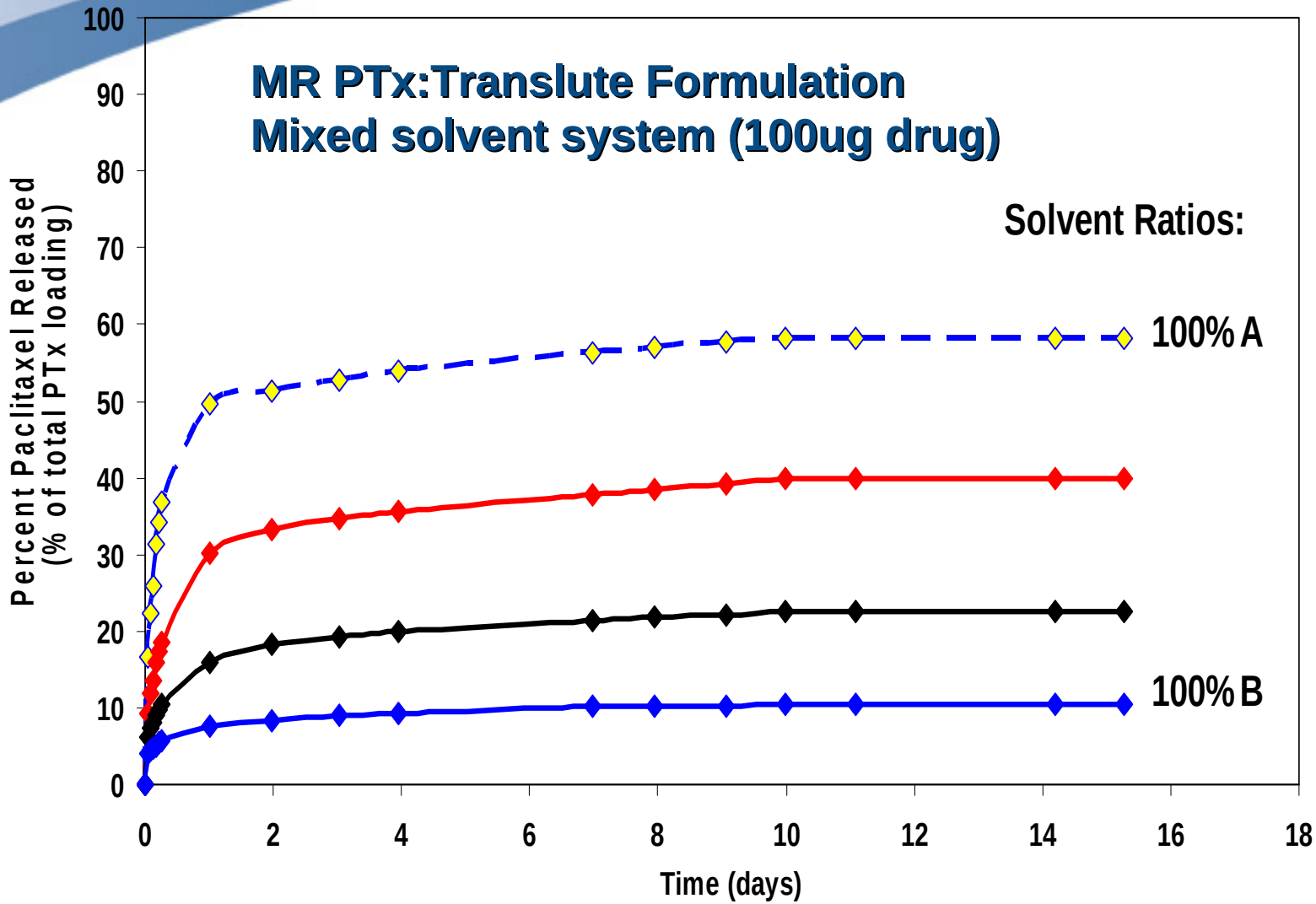




180D polymer coated

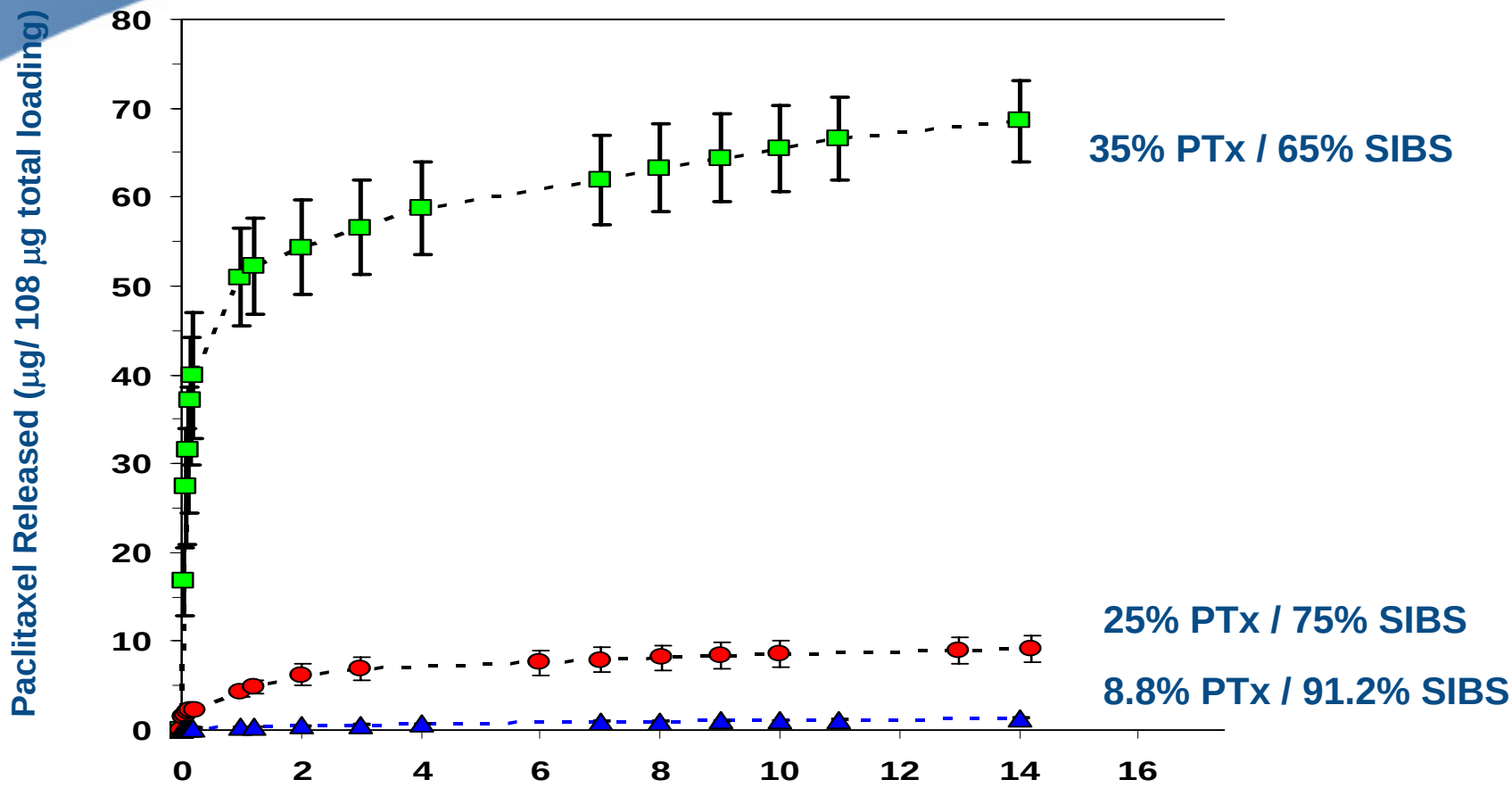
In collaboration with Dr. Rob Schwartz Mayo Clinic and Dr. Greg Wilson Sick Children's-Toronto

Cumulative % Drug Release Can Be Modified By Solvent Properties



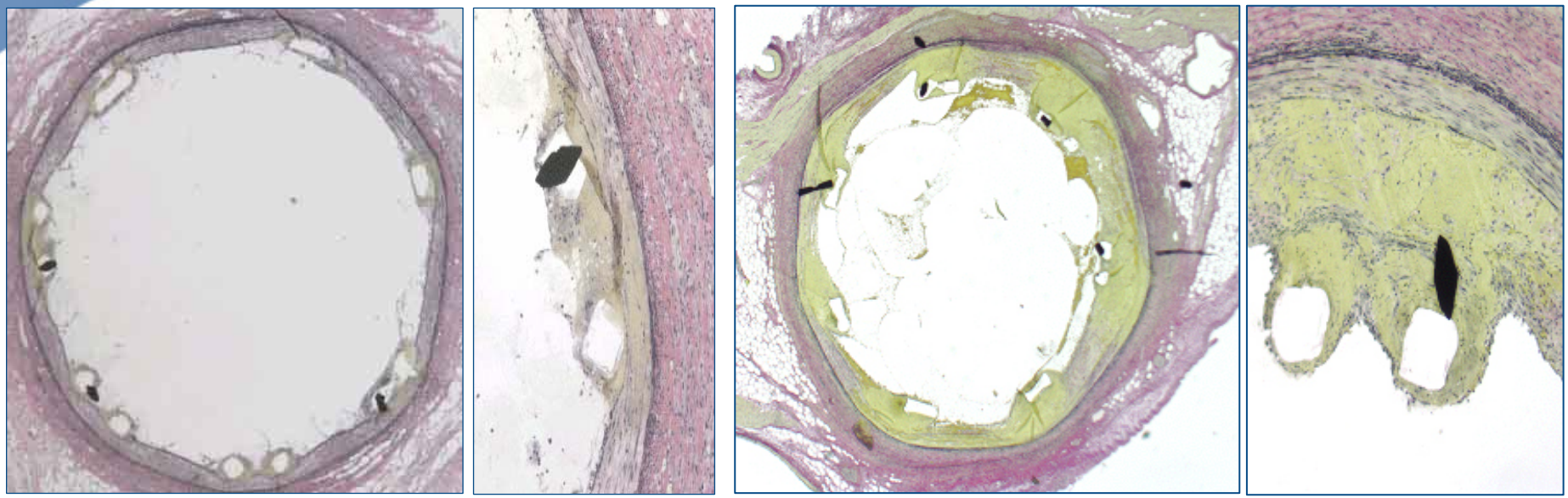
Range of In vitro release profiles

Release Media: PBS-Tween 20 @ 37^{0}C



Vascular Effects of High Dose Paclitaxel over Time

35% Paclitaxel



28 Days

Few Vascular Effects

90 Days

EC absence, medial necrosis,Sub strut fibrin, positive remodeling

In Collaboration w/Drs. Rogers and Edelman, MIT

Wide Dose Range Achievable with Paclitaxel and Translute™ Polymer

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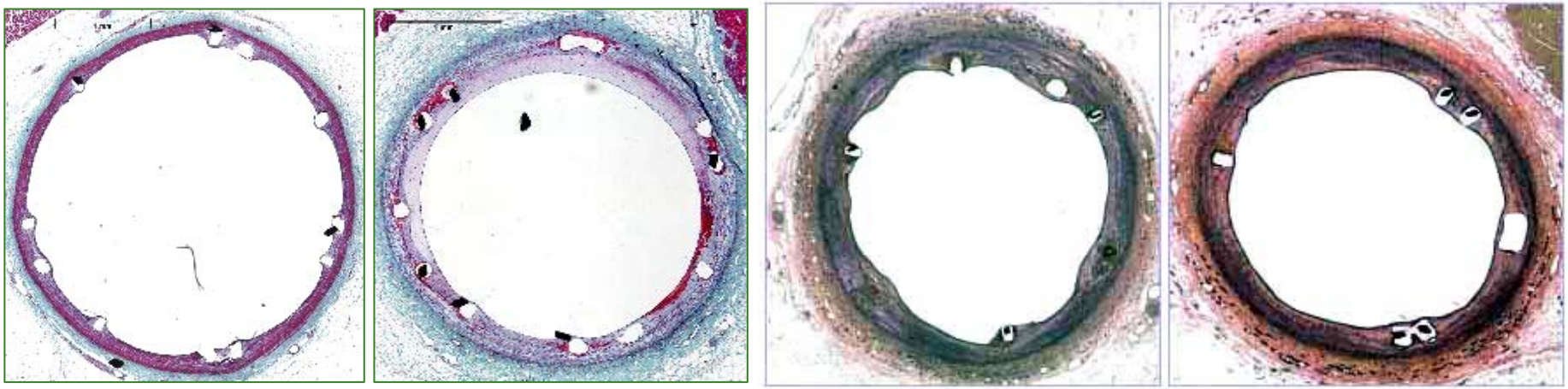
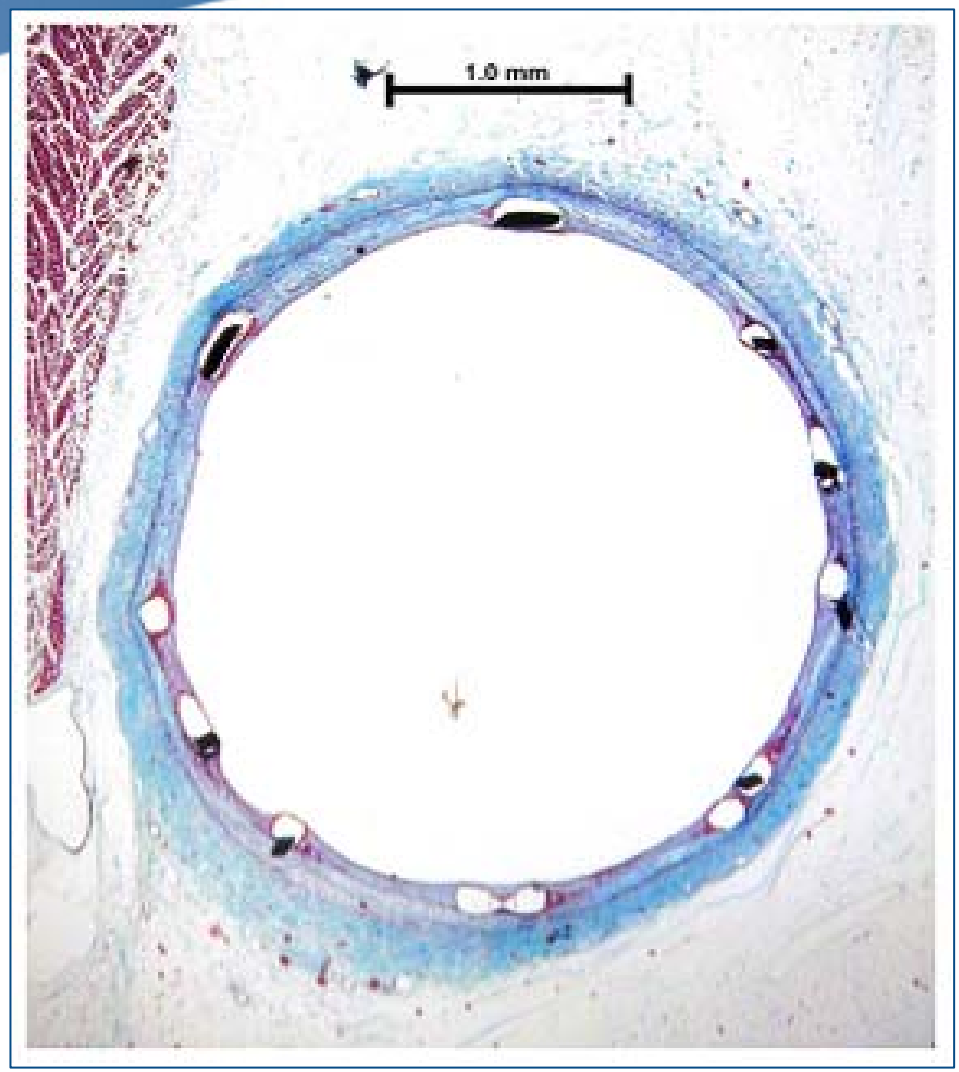
Normal Porcine Coronary Artery Response with Increasing Total Loaded Doses with the Moderate 25%PTx Release Formulation.

Bare | 1μg/mm^2 | 2μg/mm^2 | 4μg/mm^2



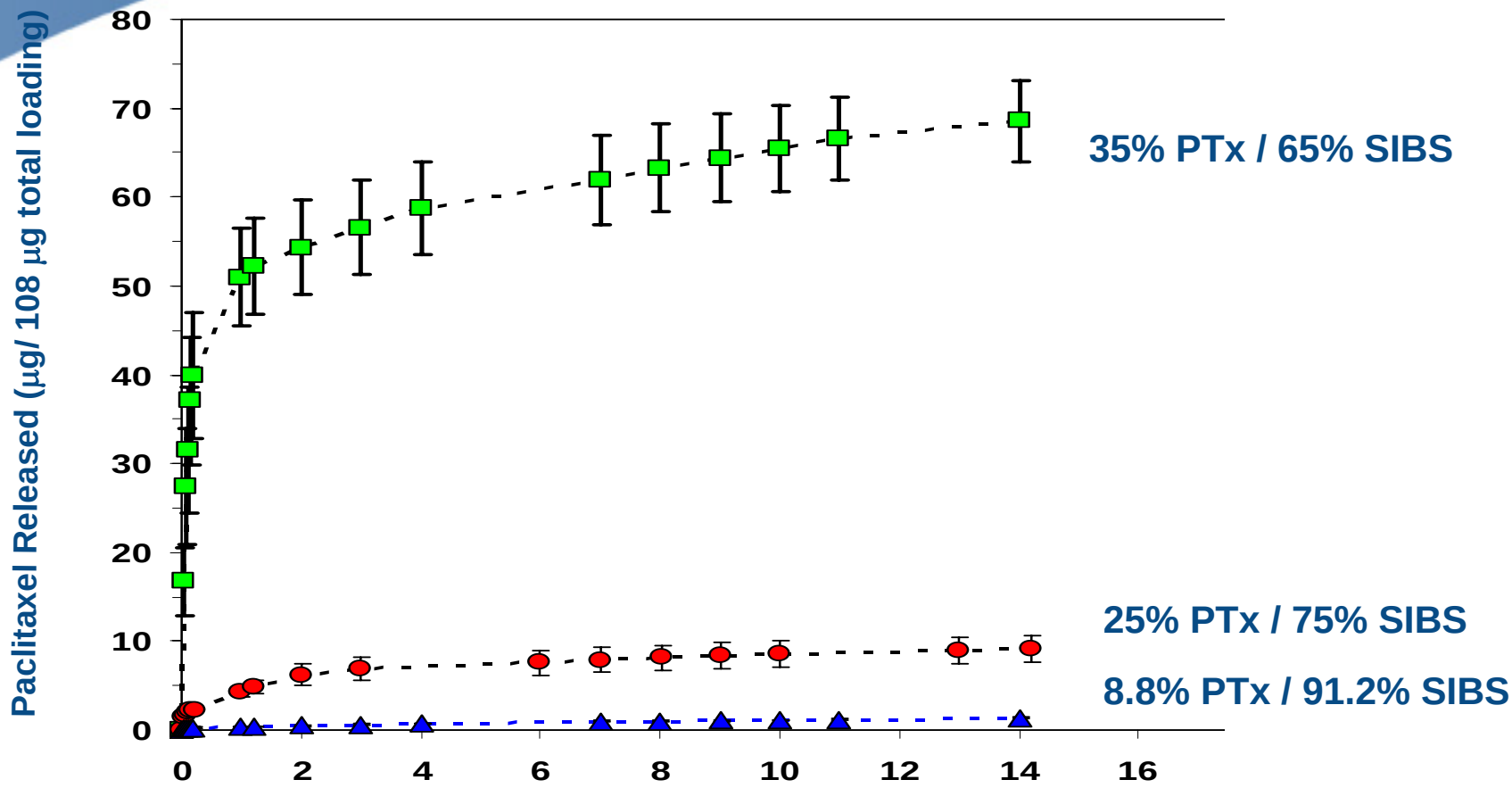
- **Patent lumen (similar across doses)**
- **Thin neointima covering all struts (similar across doses)**
- **Preserved media (similar across doses)**
- **Uniform healing across all doses (similar across doses)**

TAXUS™ Express²™ Clinical Trial
Slow Release (SR) Formulation
8.8% Paclitaxel : 91.2% Translute™
1μg/mm²



Range of In vitro release profiles

Release Media: PBS-Tween 20 @ 37^{0}C



Transmission Electron Microscopy
Paclitaxel-SIBS Solvent Cast Films

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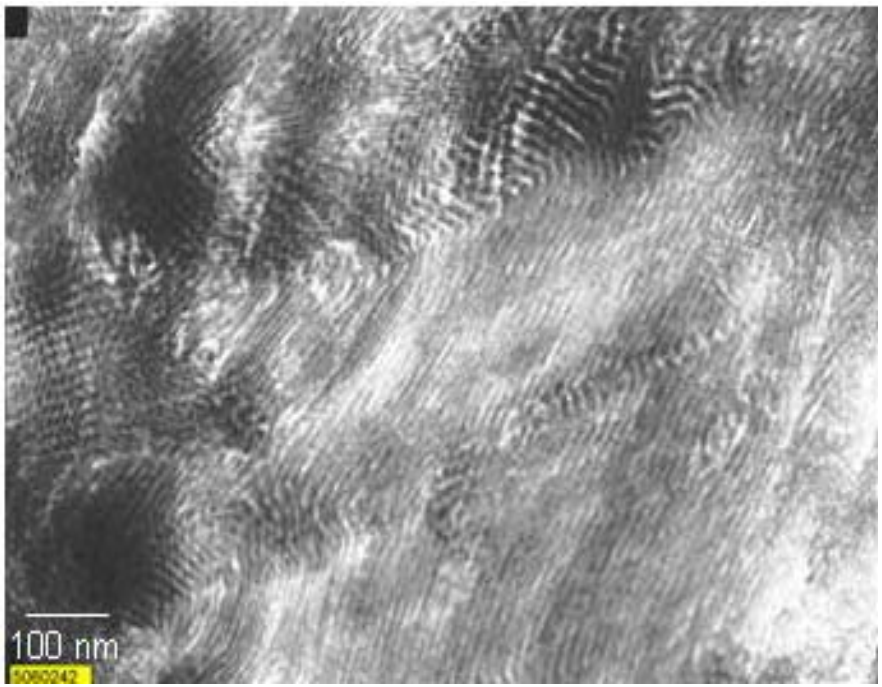
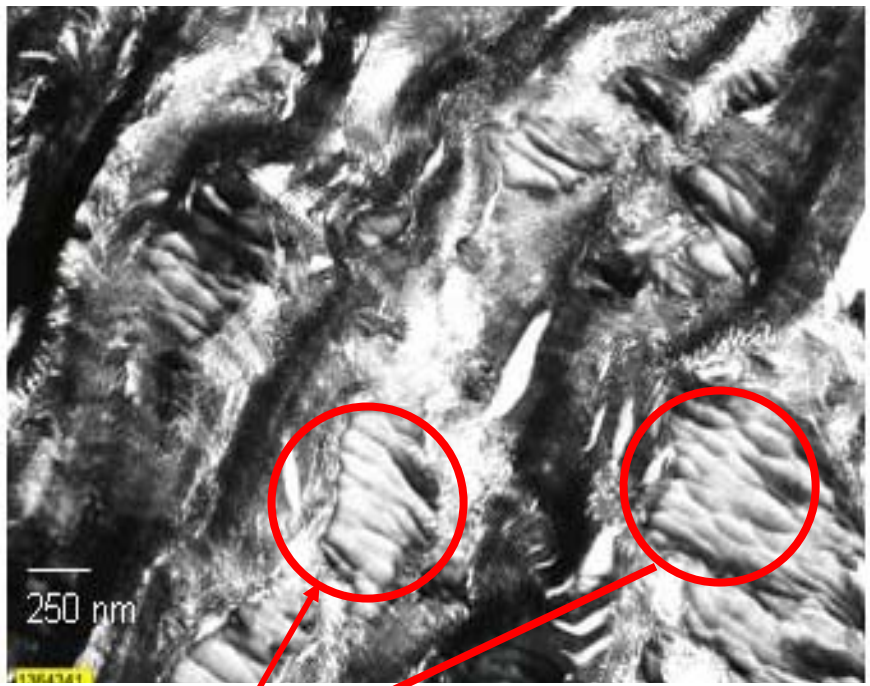
SIBS - 50,000X - RuO_4 stain



25% PTx / 75% SIBS
14,000X - RuO_4 stain

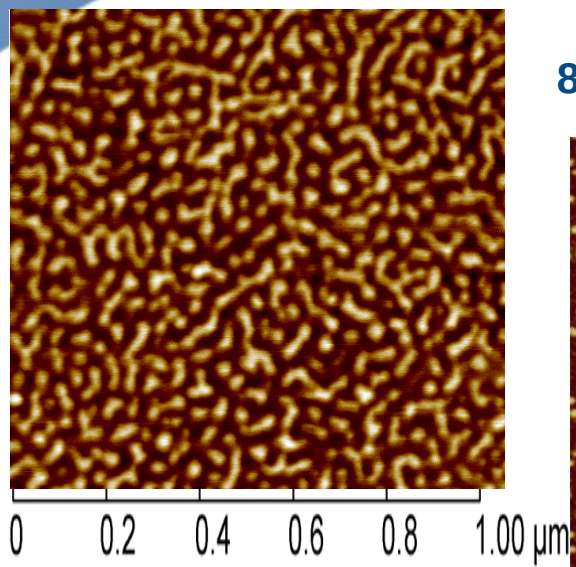


Paclitaxel

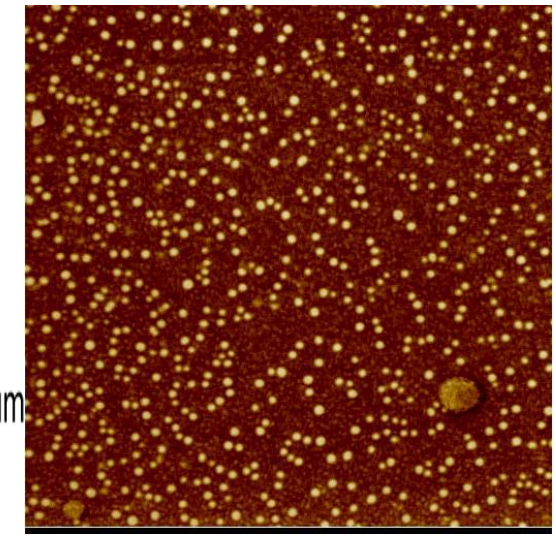
Atomic Force Microscopy: Paclitaxel-SIBS Coating Surface

AFM Phase Images. Paclitaxel appears as discrete white particles.

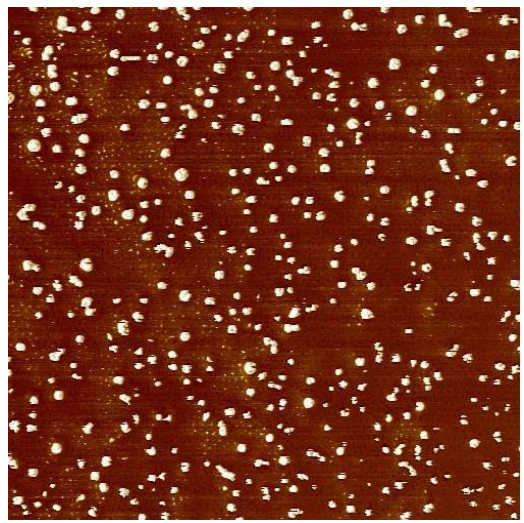
SIBS (1µm)



8.8% PTx – 91.2% SIBS (5µm)



35% PTx – 65% SIBS (5µm)



Changes in Surface Morphology of Stent Coating Post Drug Elution

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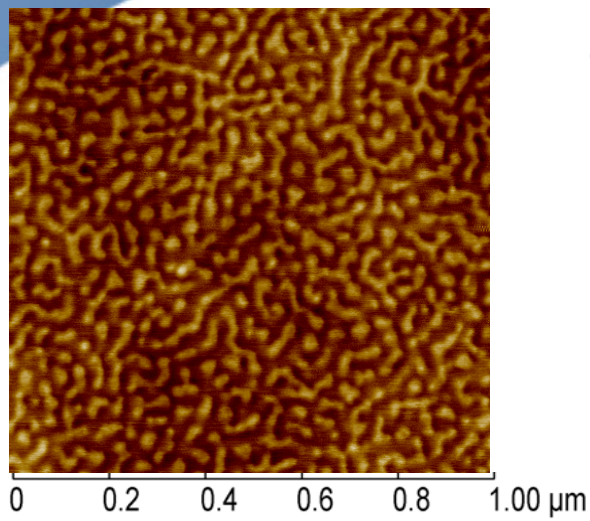
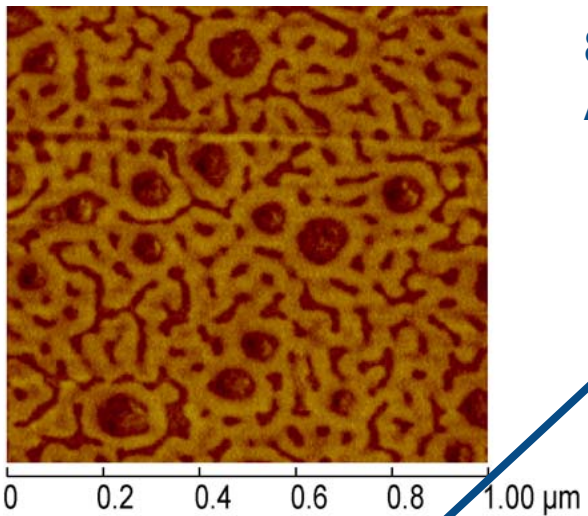
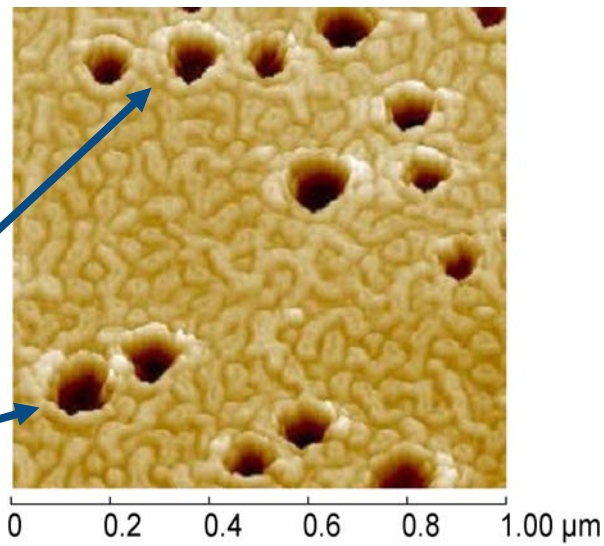
SIBS Only



8.8% PTx / 91.2% SIBS



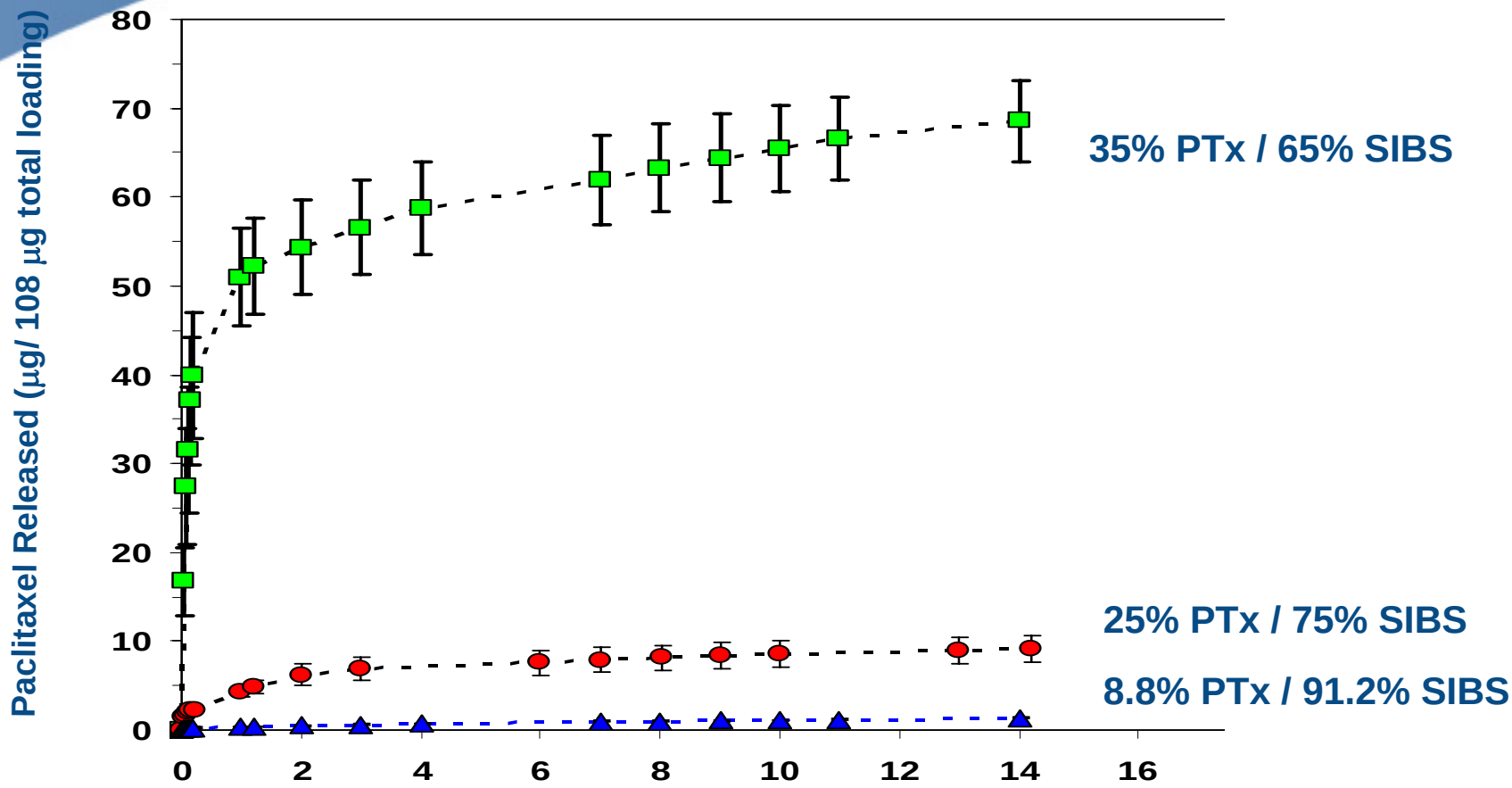
8.8% PTx / 91.2% SIBS
After extraction of PTx



Holes, previously occupied by PTx, appear on surface after 25 hrs of *in vitro* extraction in PBS / Tween 20. Topography images.

Range of In vitro release profiles

Release Media: PBS-Tween 20 @ 37^{0}C



Sub-surface Morphology Changes of Coated Stents Pre and Post Drug Elution

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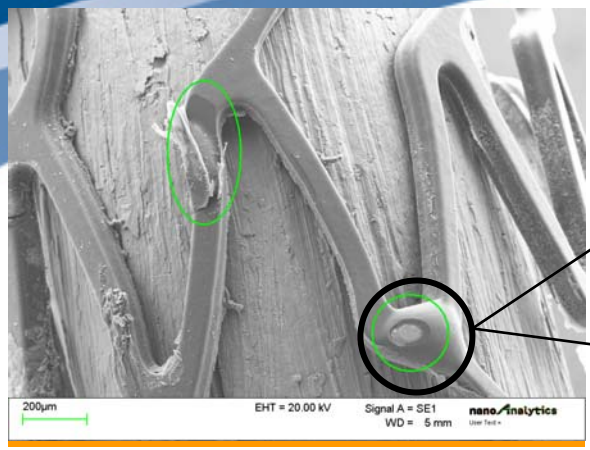
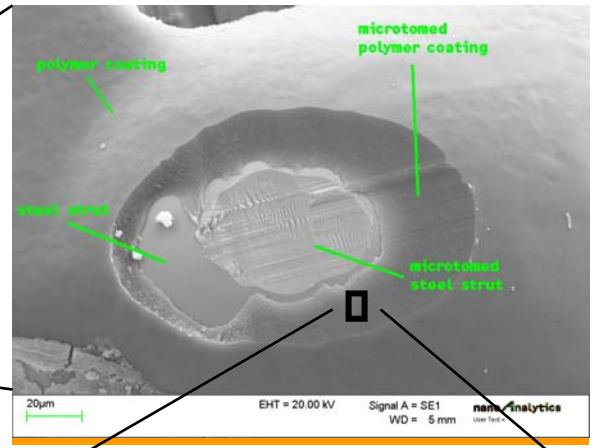
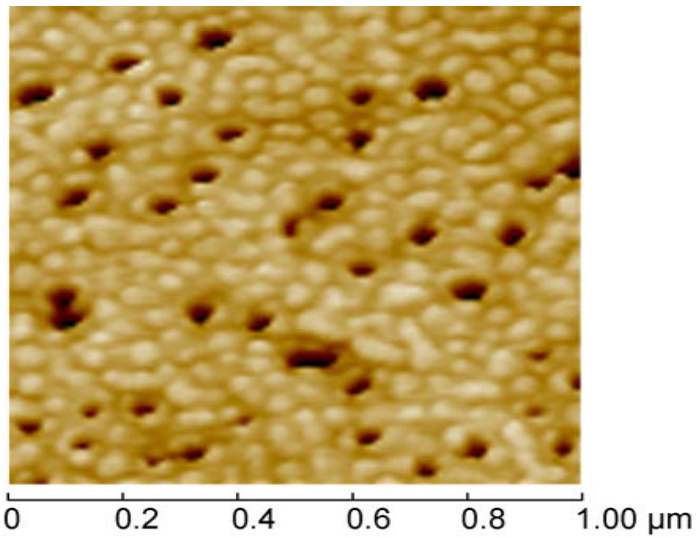
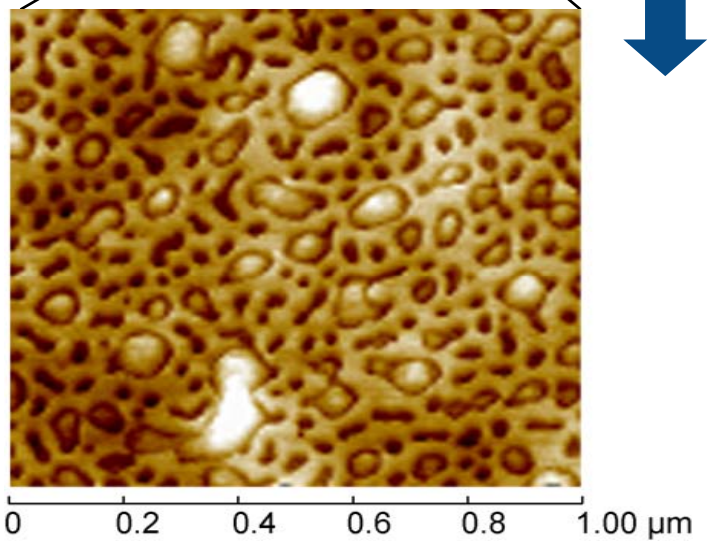






After 2 days of elution w/PBS-Tween 20



Effect of Drug Loading on Sub-surface Morphology

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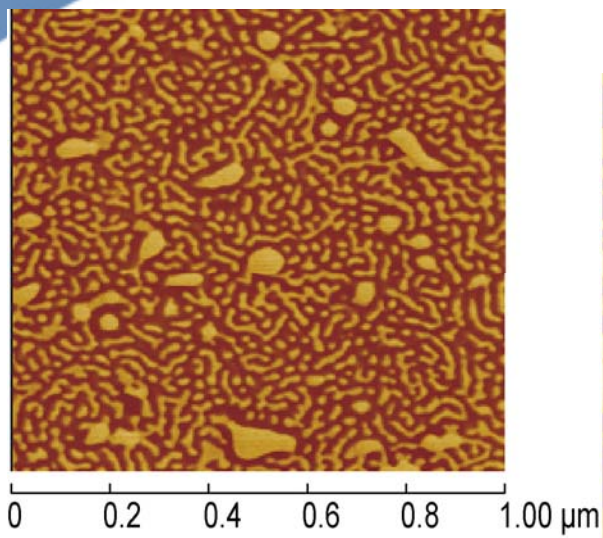
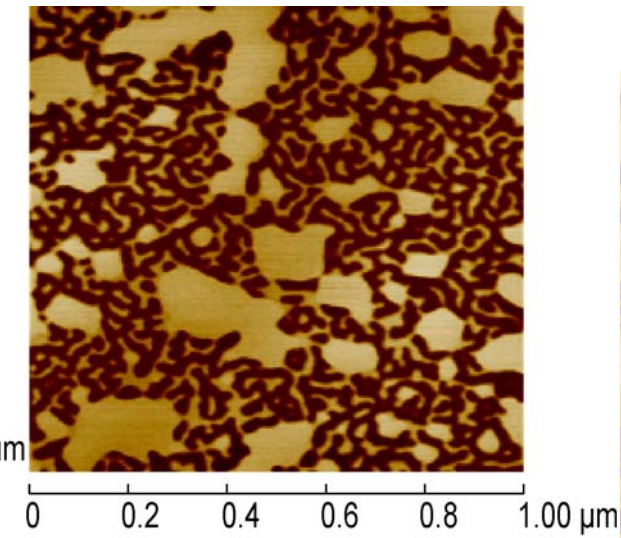
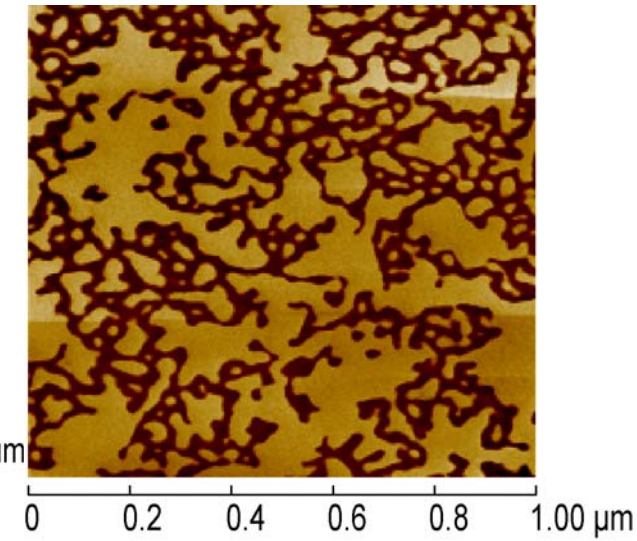
8.8% PTx / 91.2% SIBS



25% PTx / 75% SIBS



35% PTx / 65%SIBS



AFM shows that the frequency and size of paclitaxel-containing domains increases with increasing paclitaxel content in the matrix.

Chemistry, Manufacturing and Controls (CMC) Drug Evaluation

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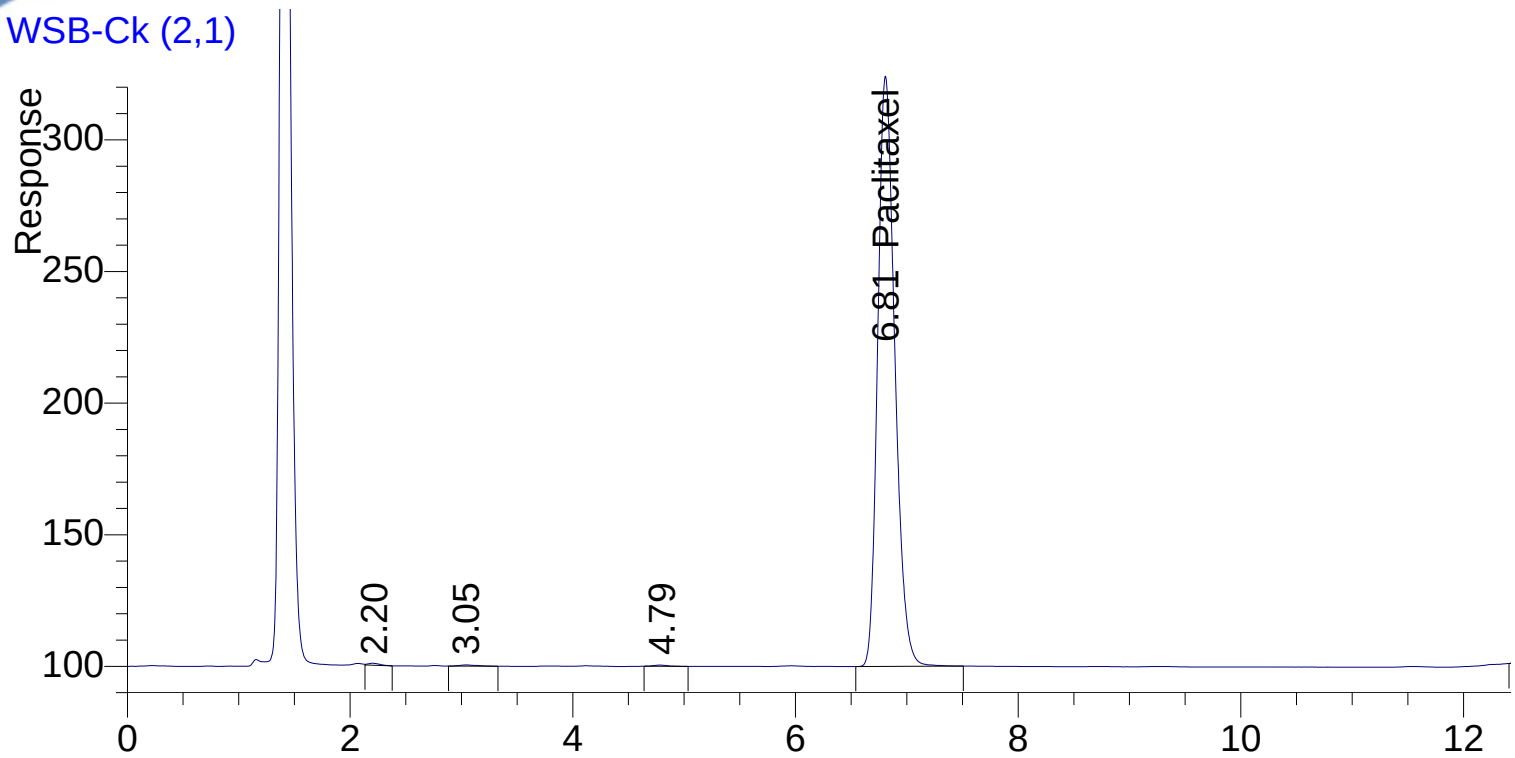
Drug Substance

- Structure, physicochemical properties, manufacturing information
- Equivalent to NDA, IND, NCE

Drug Product

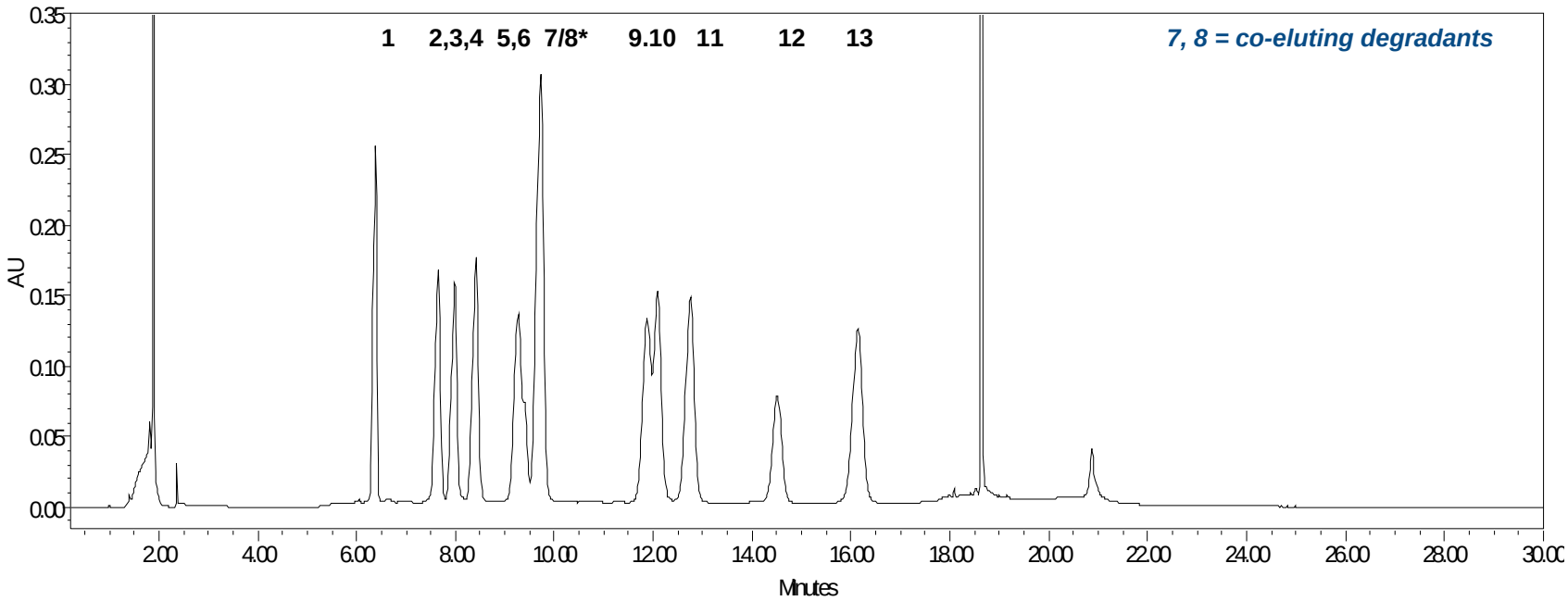
- Chemical characterization
- Manufacturing process
- Controls
  - ***Drug content / Impurities / degradants / residuals / kinetic drug release***
  - Stability
  - Toxicity threshold
  - Pharmacokinetics, Pharmacodynamics (MOA)

Product Release Testing:
Drug Content Analysis (Assay)
Typical HPLC Chromatogram for Sample



Product Release Testing: Degradant Analysis

HPLC Chromatogram 13-Taxane Mixed Degradant Standard

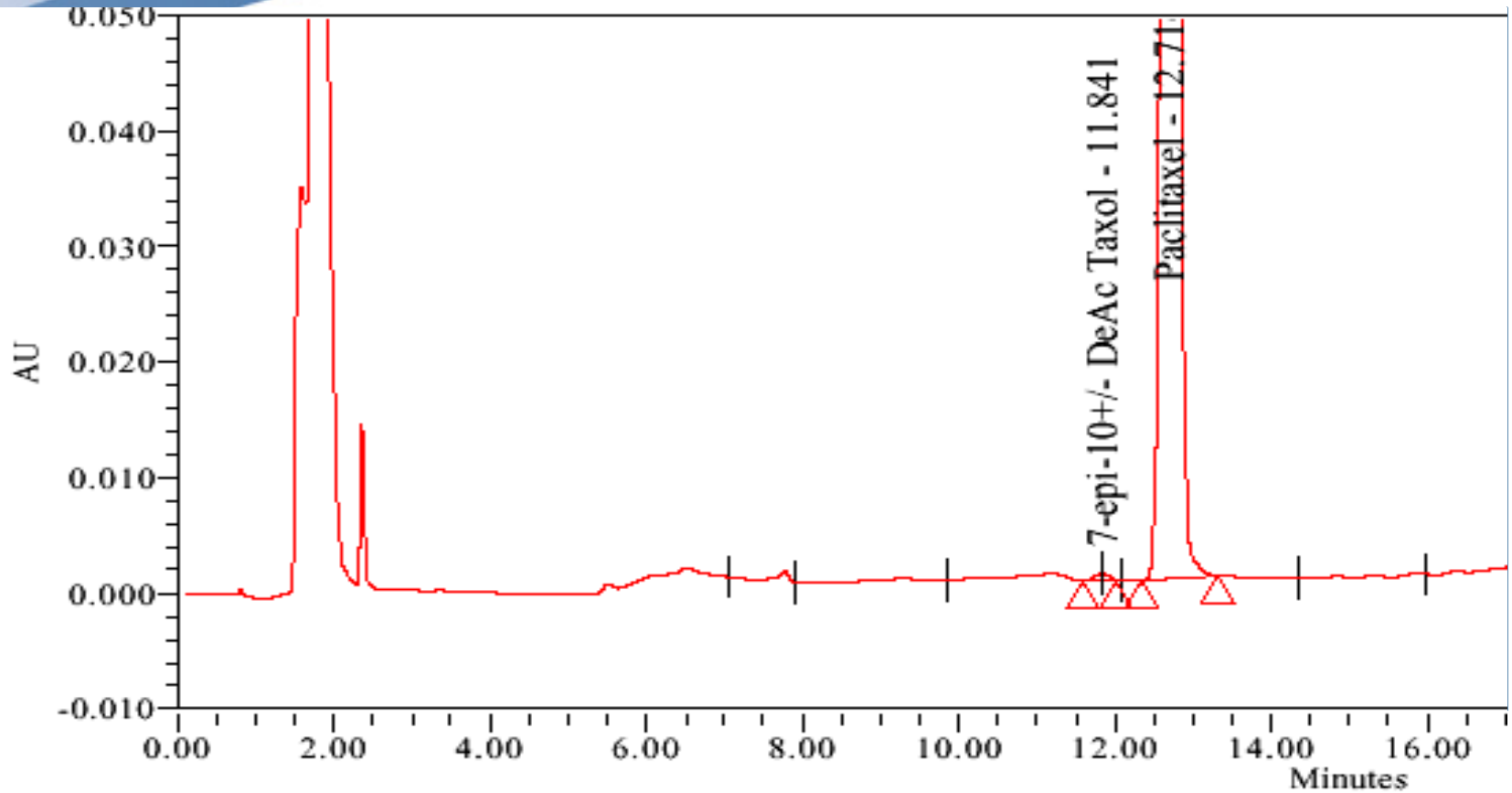


1. 10-Deacetylbaccatin III
2. Baccatin III
3. 7-xylosyl-10-deacetyl cephalomannine
4. 7-xylosyl-10-deacetyl paclitaxel
5. Taxinine
6. 7-xylosyl-10-deacetyl paclitaxel C

7/8. 10-deacetylpaclitaxel / 7-xylosylpaclitaxel

9. Cephalomannine
10. 7-epi-10-deacetyl paclitaxel
11. Paclitaxel
12. Paclitaxel C
13. 7-epi-paclitaxel

Product Release Testing:
In-process SR Coating Solution



Paclitaxel: 99.83 % area

7-epi-10-deacetylpaclitaxel: 0.17 % area

Product Release Testing: Finished Product Degradant Analysis

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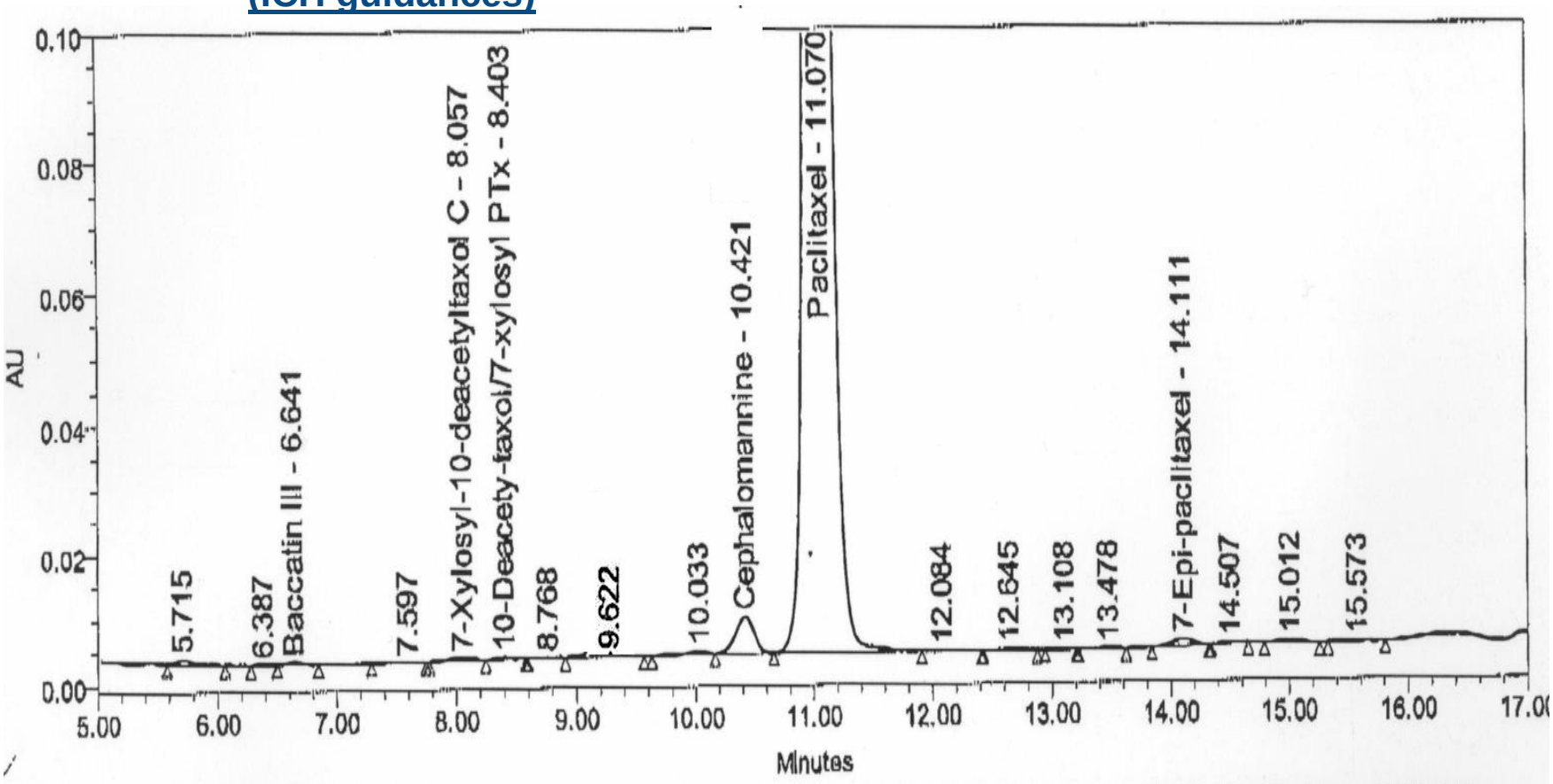
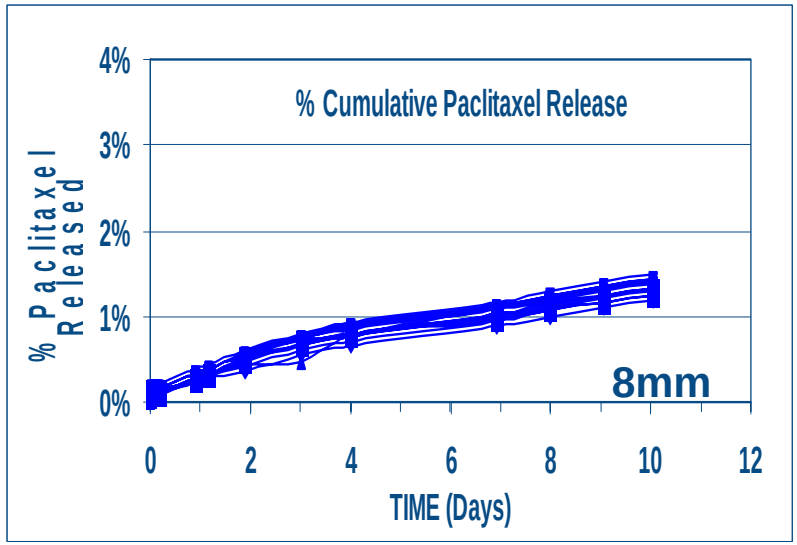
Example of Acceptable Paclitaxel Degradant Profile

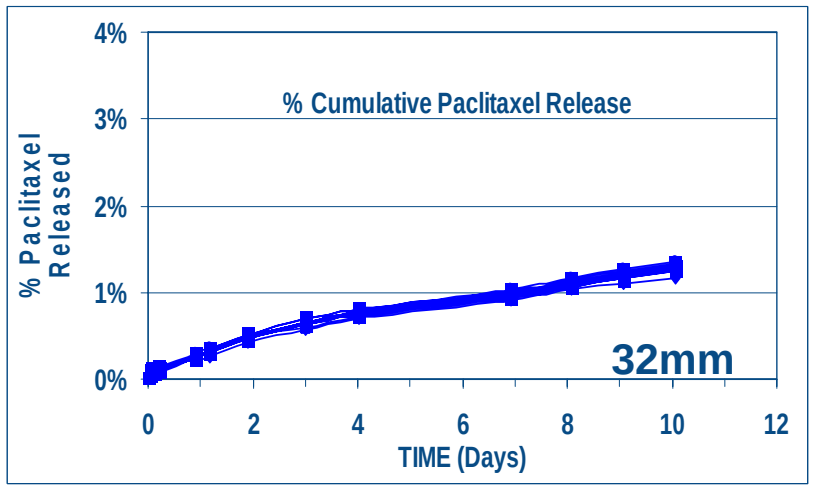
No individual degradant is > 1.0%, and total degradants < 2.0% (ICH guidances)



Product Release Testing: Kinetic Drug Release (KDR)

- KDR required for each lot (n=12)
- 10 Day Assay
- Manufacturing Control
- Uniform % Cumulative Paclitaxel Release from Express ™ over full range of stent lengths (8mm to 32mm)
- Translute™ polymer carrier
- 1.0 ug/mm² Slow Release (SR) dose





Drug Release Profile of 8.8% Paclitaxel : 91.2% SIBS

90 Day In Vitro Release Assay, PBS-Tween 20 Medium

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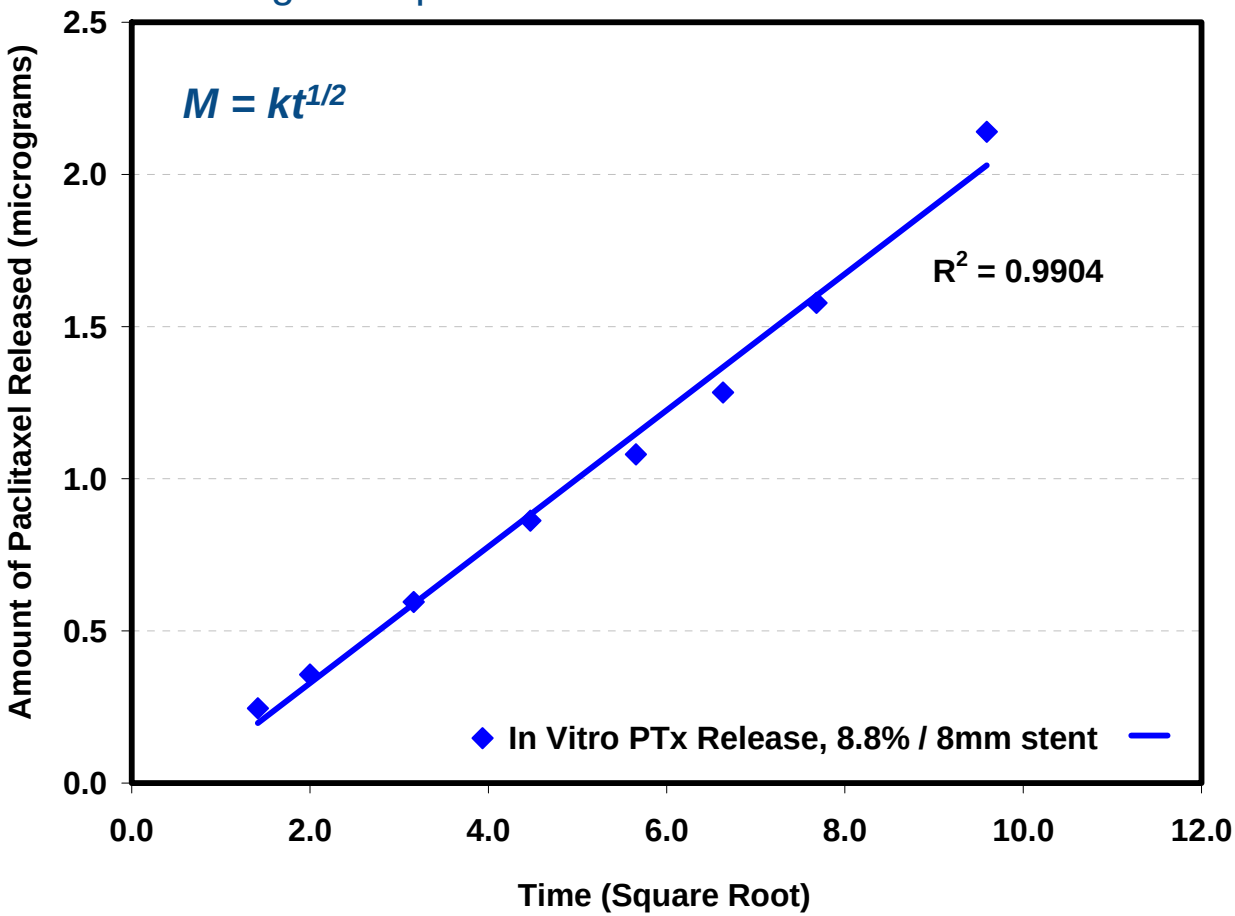
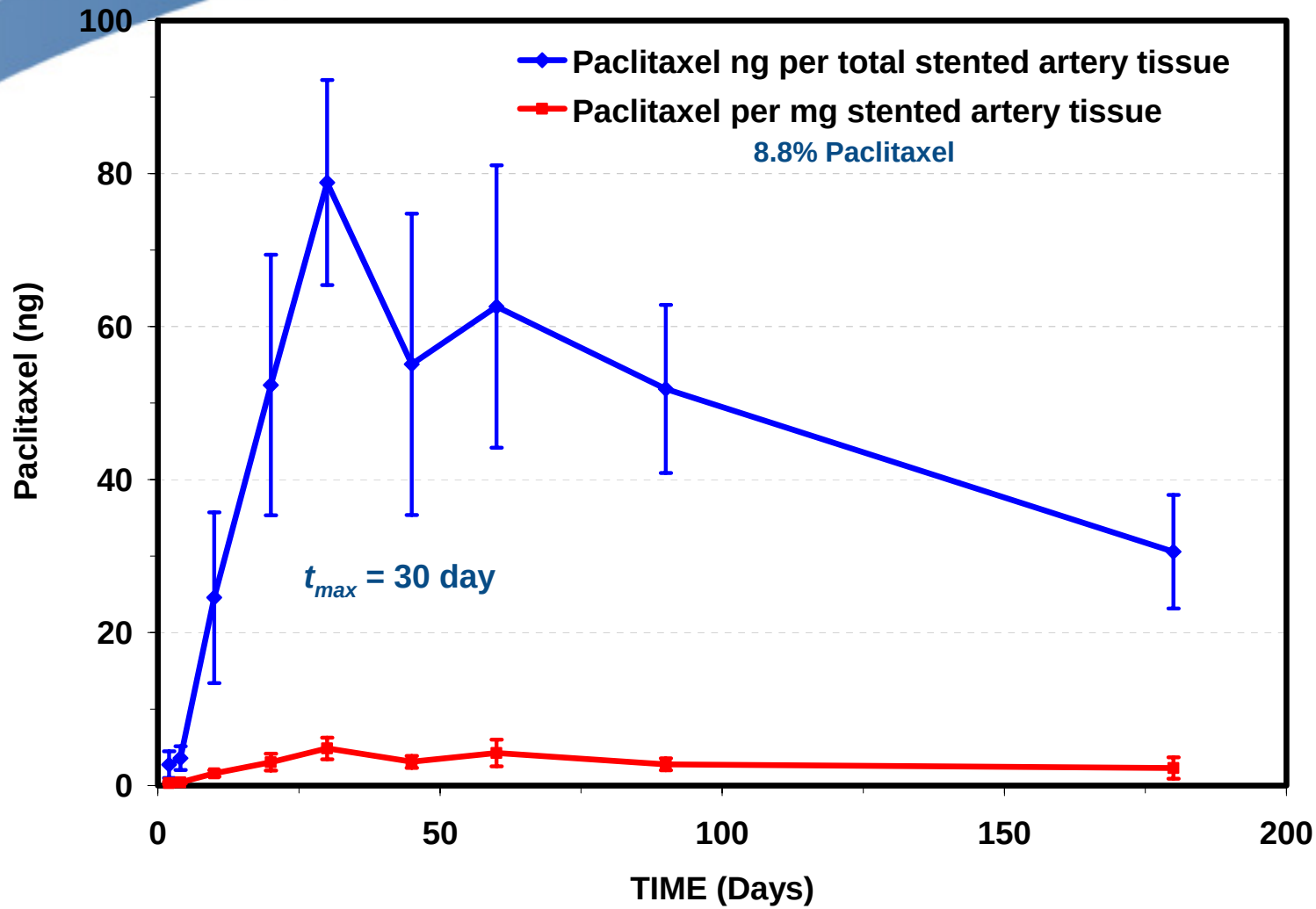
Evidence for pseudo steady-state, diffusion controlled release behavior, based on Higuchi's planar slab matrix diffusion model.



Paclitaxel Concentration in Stented Artery Tissue

Bilateral Rabbit Iliac Model



Attention to Both Materials and Manufacturing Results in Successful Product Development

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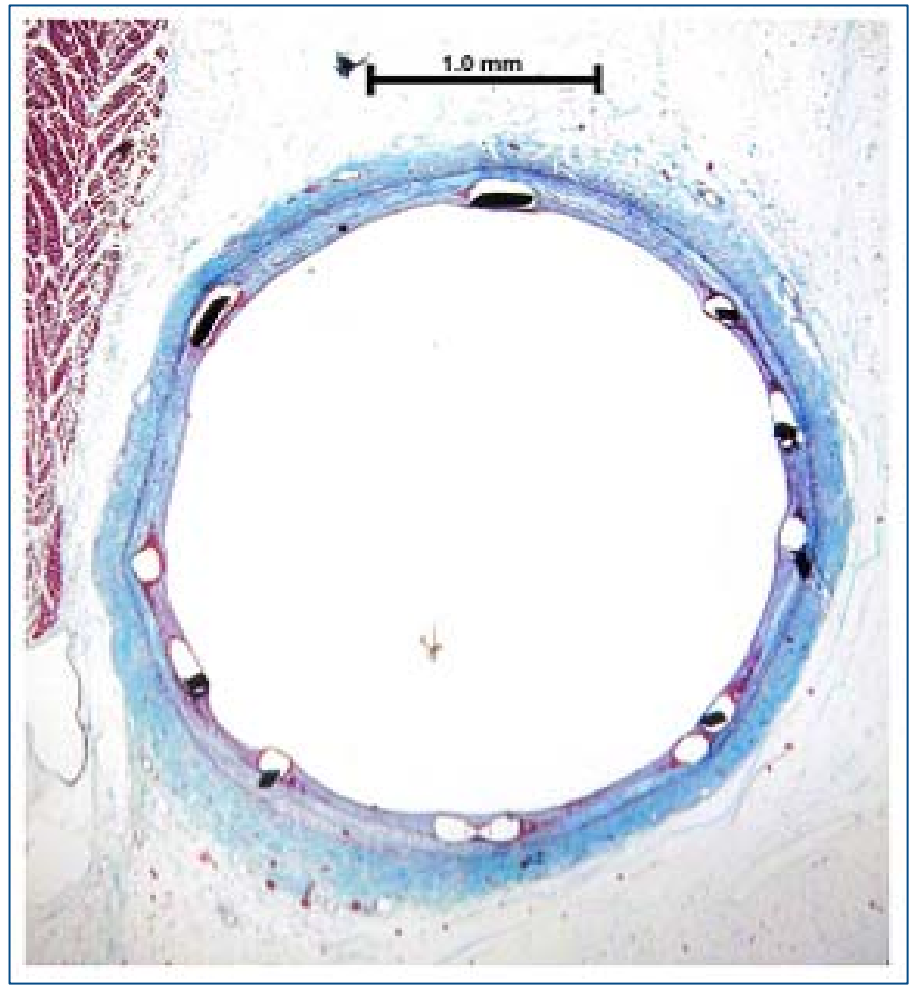
Multi-functional approach to developing the DES combination product has demonstrated:

- Translute™ carrier in combination with Paclitaxel is compatible and safe
- Formulation selected for clinical trials (**SR 1ug/mm^2**) is safe
- The product complies with drug product manufacturing controls to support product safety



TAXUS Clinical Trial Summaries

Boston Scientific

TRIAL	PATIENT ENROLLMENT	IN-STENT RESTENOSIS RATE		THROMBOSIS	TIME AT FOLLOW-UP
		CONTROL	TAXUS DES	TAXUS DES	
TAXUS I (S/E) 3 sites	61	10%	0%	0%	12 months
TAXUS II (*de novo lesions*) 38 sites, 15 countries	536	19% 15.5%	2.3% 5.5%, 3.9%	0%	12 months 24 months
TAXUS III (non-*de novo*, up to 2 stents)	29	N/A	4%	0%	12 months
TAXUS IV (Pivotal I Trial, S/E, *de novo*)	1,326	11.3% 14.7%	3.0% 4.2%	0%	9 months (8/2003) 12 months (11/2003)
TAXUS V (Pivotal II Trial, Complex)	1,108				30 day (9/2003) 9 month (5/2004)
TAXUS VI (MR, Complex)	448	18.9%	6.8%	0%	30 day (5/2003) 9 month (1/2004)
Total Patient Enrollment	3,479				

SUMMARY

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Combination drug-device products offer a unique challenge to product development and manufacturing.

Successful designs and applications are based on the integration of many disciplines:

- **Materials Sciences**
- **Engineering Fields (Mechanical, Chemical, Bioengineering)**
- **Pharmaceutical Sciences**
- **Pre-clinical and Clinical evaluation of *both drugs and devices***
- **Pilot and Scale-up manufacturing for *both drugs and devices***
- ***Regulatory appreciation for both devices and drugs, with the ability to***
  - ***recognize the novel***
  - ***rely on the standard***
  - ***blend the two seamlessly***