Predicting Drug Release from Long-Acting Implants: Mechanisms, Modeling, and Simulation

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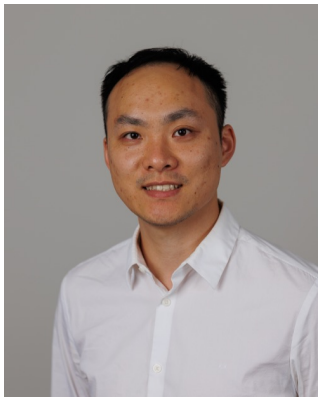

Current research: **long-acting drug delivery implants**

- Material processing and characterization
- Controlled release mechanisms/modeling

Industry experience: **oral dosage forms product development**

- Formulation and process development
- Pharmaceutical processing: granulation, tableting, functional coatings

Awards/scholarship

- **Two-time recipient of AAPS Best Abstract Award (2023, 2025)**
- Merck AAPS Travel Fellowship (2025)
- UT Austin Graduate Fellowship (2024, 2025)

Education

• New Jersey Institute of Technology	MS in Chemical Engineering	2014 - 2016
• South China Agricultural University	BS in Chemistry	2010 - 2014

Disclaimer

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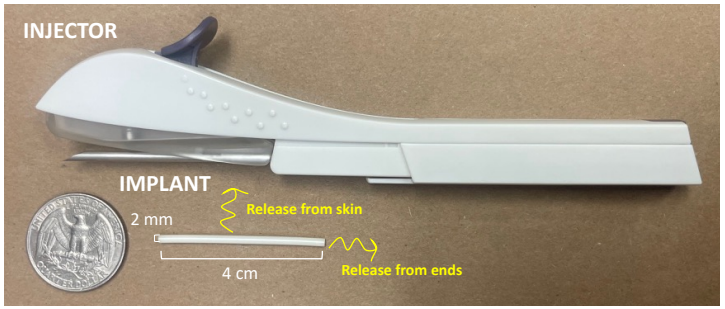
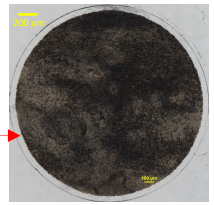
System Description and Objectives

Nexplanon®

Etonogestrel subdermal implant

- Three years birth control
- Non-biodegradable, removable





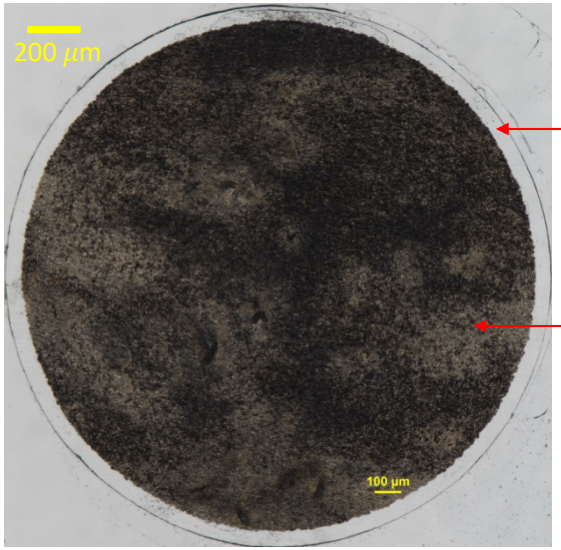
Implant 'skin'

Objectives:

1. Understand drug release mechanisms
2. Elucidate correlations between materials, structure, and drug release
3. To **predict** long-term (3 years) drug release (real-time) based on short-term experimental data

In this talk, we will focus on skin release. For ends release, please refer to our latest publication.

Core/shell structure



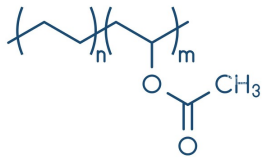
Light microscopy of Nexplanon® cross section

Composition of Nexplanon®

Layer	Component	Function	Amount per implant (mg)
Skin	Ethylene Vinyl Acetate (VA content: **15%**)	Rate-controlling membrane	15.0
ETO Core	Etonogestrel (ETO)	Drug	68.0 **(54 % of core)**
	Ethylene Vinyl Acetate (VA content: **28%**)	Carrier	43.0
	Barium Sulfate	Radiopaque Agent	15.0
	Magnesium Stearate	Glidant	0.10
Total			141.1

Reference: Nexplanon® product label, Implanon NXT® Australian filling

1. Lower VA content of skin (15% < 28%) → higher crystallinity → lower drug permeability
2. Drug release mainly controlled by diffusion through skin
3. $C_0/C_s \approx 360$ (>> 3), drug release can be modeled using pseudo steady state assumption (PSSA) [1]

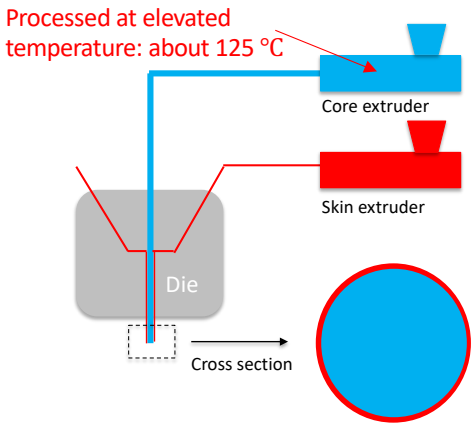


EVA

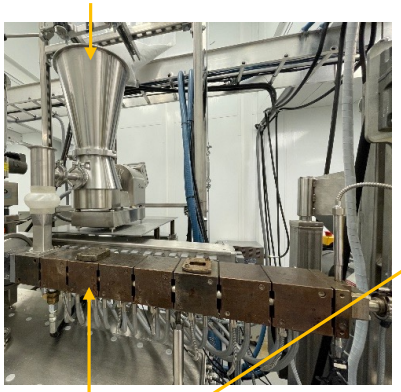
[1] Lee, Ping I. "Modeling of drug release from matrix systems involving moving boundaries: Approximate analytical solutions." *International Journal of Pharmaceutics* (2011)

Manufacturing of Nexplanon – a co-axial extrusion process

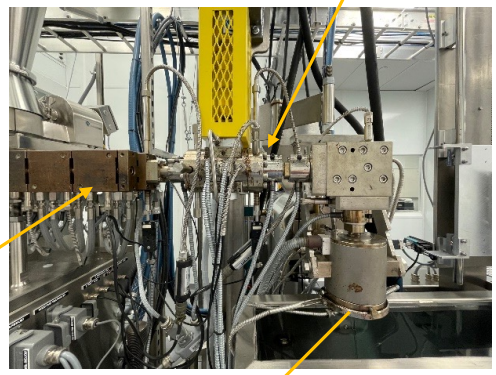
Co-axial extrusion



Feeder



Skin extruder (view blocked)

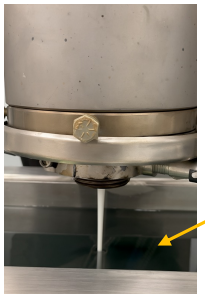


Laser micrometer

Puller

Core extruder:
mixing + heating + drug solubilization

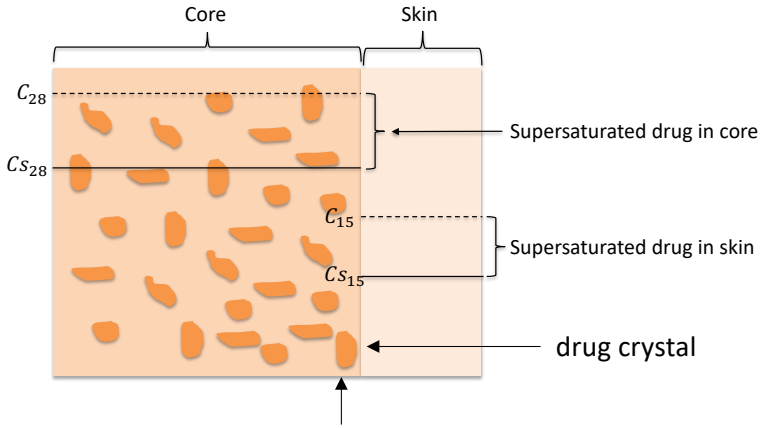
Die



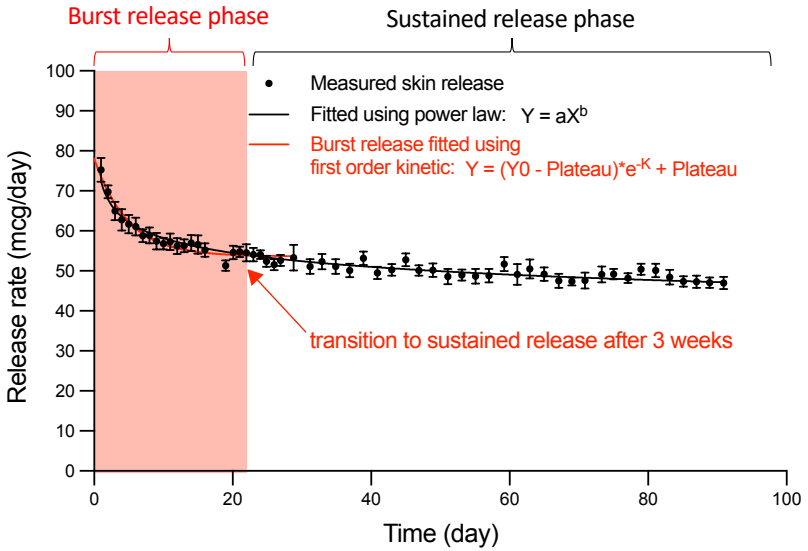
Water bath:
cooling and drug recrystallization

Initial burst release through implant skin

1. High temperature (≈ 125 ℃) → **drug solubilization** → cooling → **partial recrystallization** → **supersaturation** → initial burst release (follows first order kinetic [1])
2. Degree of supersaturation: extrusion and storage conditions [2]
3. Skin burst release transitions to sustained release after 3 weeks [1]



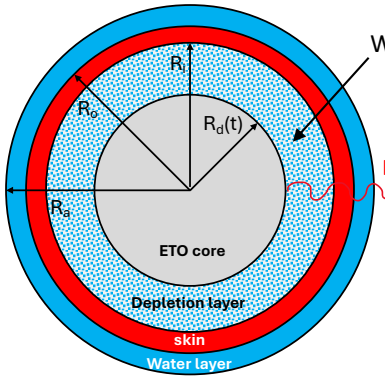
Released of supersaturated drug → **dissolution/diffusion** of drug crystals → **transition to sustained release**



[1] Zhong, Ziyue, et al. "Correlation between material, structure, and drug release of Nexplanon®: an ethylene vinyl acetate (EVA) based long-acting implant." *International Journal of Pharmaceutics* (2025)

[2] Ren, Angela, **Zhong, Ziyue**, et al. "Manufacture, characterization, and elucidation of drug release mechanisms of etonogestrel implants based on ethylene vinyl acetate." *Journal of Pharmaceutical Sciences* (2025)

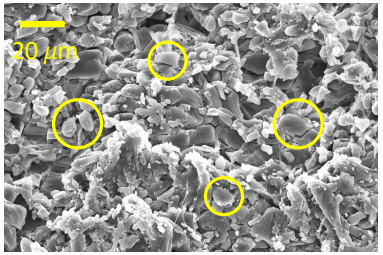
Formation of depletion layer and model development



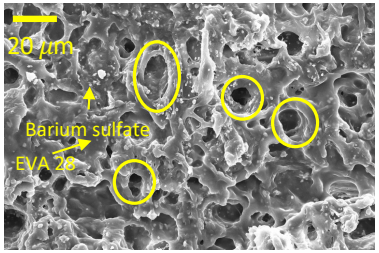
(not to scale)

R_d (ETO core radius): reduces overtime
R_i (inner radius): 0.94 mm
R_o (outer radius): 1.00 mm
R_o - R_i (skin): 0.06 mm
R_a - R_o (un-stirred water layer): h_a

Before drug depletion
(Drug particles circled)



After drug depletion
(Drug depletion induced pores circled)



1. Drug dissolution/diffusion → pore formation
2. Water permeation → water-filled pores
3. Depletion layer developed overtime

Two skin release models

#1
As a function of **ETO core radius (R_d)**

Mechanistic understandings

#2
As a function of **time (t)**

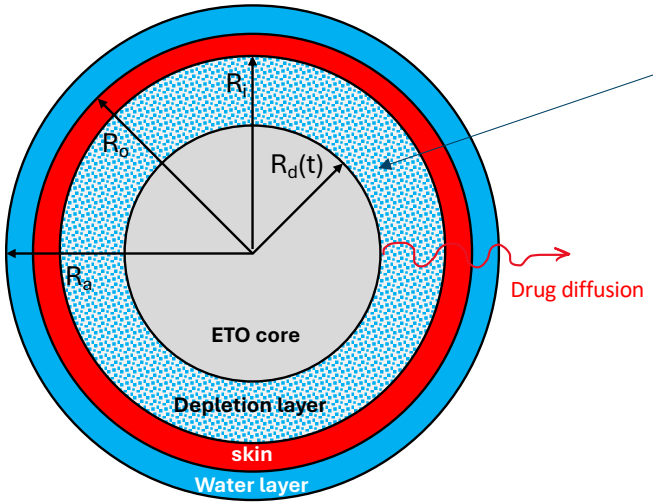
Drug release prediction

Drug release model #1: as a function of **ETO core radius (R_d)**

$$\frac{2\pi L * (Cs_{DL} - \frac{C_{media}}{K_2 K_3})}{\frac{1}{D_{DL}} \ln \frac{R_i}{\boldsymbol{R_d(t)}} + \frac{1}{K_2 D_{15}} \ln \frac{R_o}{R_i} + \frac{1}{K_2 K_3 D_a} \ln \frac{R_a}{R_o}}$$

Modification of existing tri-layer diffusion model [1]

1. Non-sink condition of release media
2. Reducing ETO core radius (R_d) overtime
   - **Less available surface area**
   - **Longer diffusion path**



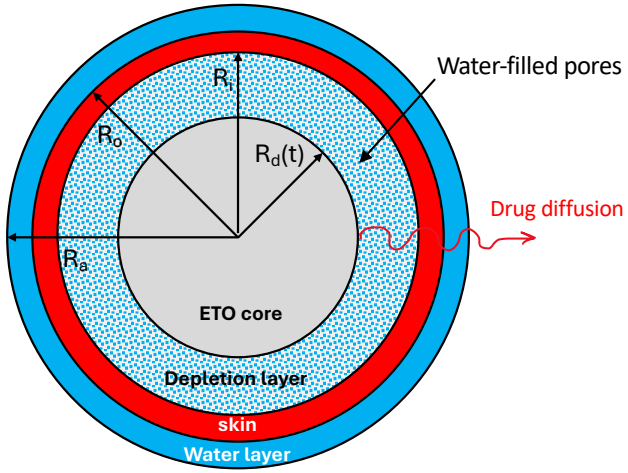
Pseudo steady state assumption **in depletion layer**:

1. High drug loading →'Slow' depletion
2. Dissolution is NOT rate-limiting
3. No crystal drug exists
4. **Steady state diffusion**

[1] Flynn, Gordon L., et al. "Analysis of diffusion through concentric right circular cylinders and concentric spheres." *Journal of Pharmaceutical Sciences* (1976)

Drug release is controlled by:

1. Implant geometry

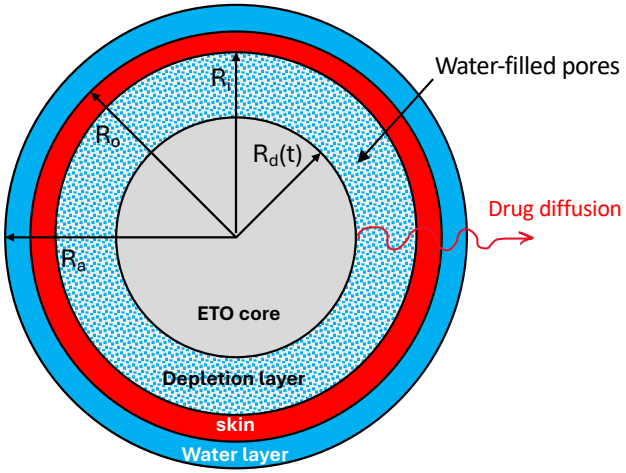


$$\frac{dM}{dt}_{skin} = \frac{2\pi L * (Cs_{DL} - \frac{C_{media}}{K_2 K_3})}{\frac{1}{D_{DL}} \ln \frac{R_i}{\boldsymbol{R_d(t)}} + \frac{1}{K_2 D_{15}} \ln \frac{R_o}{R_i} + \frac{1}{K_2 K_3 D_a} \ln \frac{R_a}{R_o}}$$

Diffusion Layers	Depletion layer	Skin layer	Water layer
Composition	EVA 28 + barium sulfate + water-filled pores	EVA 15	Dissolution media
Structure	• Porosity • Pore size • Pore connectivity	• EVA crystallinity • EVA crystal size • EVA crystal orientation	• Thickness of h_a
Material/processing attributes	• Drug particle size • Extrusion mixing	• EVA VA content • Cooling rate • Draw down ratio	• Stirring • Media volume
Diffusivity (D_i)	D_{DL}	D_{15}	D_a
Solubility (Cs_i)	Cs_{DL}	Cs_{15}	Cs_a
Partition Coefficients	$K_1 = \frac{Cs_{\mathrm{eff.}}}{Cs_{28}}$, $K_2 = \frac{Cs_{15}}{Cs_{\mathrm{DL}}}$, $K_3 = \frac{Cs_a}{Cs_{15}}$		

Drug release is controlled by:

2. Drug solubility/diffusivity in each layer ← material, structure, and processing conditions [1]



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Diffusion Layers	Depletion layer	Skin layer [1]	Water layer [2]
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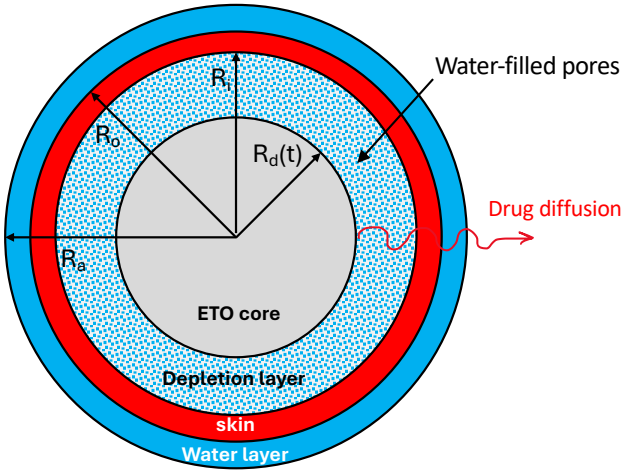
[1] Zhong, Ziyue, et al. "Correlation between polymer properties, extrusion process parameters and permeability of etonogestrel in ethylene vinyl acetate films." *Journal of Pharmaceutical Sciences* (2025)
[2] Zhong, Ziyue, et al. "Correlation between material, structure, and drug release of Nexplanon®: an ethylene vinyl acetate (EVA) based long-acting implant." *International Journal of Pharmaceutics* (2025)

Drug release is controlled by:

3. Release testing conditions [2]



$$\frac{dM}{dt}_{skin} = \frac{2\pi L * (Cs_{DL} - \frac{C_{media}}{K_2 K_3})}{\frac{1}{D_{DL}} \ln \frac{R_i}{\boldsymbol{R_d(t)}} + \frac{1}{K_2 D_{15}} \ln \frac{R_o}{R_i} + \frac{1}{K_2 K_3 D_a} \ln \frac{R_a}{R_o}}$$

Diffusion Layers	Depletion layer	Skin layer [1]	Water layer [2]
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[1] Zhong, Ziyue, et al. "Correlation between polymer properties, extrusion process parameters and permeability of etonogestrel in ethylene vinyl acetate films." *Journal of Pharmaceutical Sciences* (2025)
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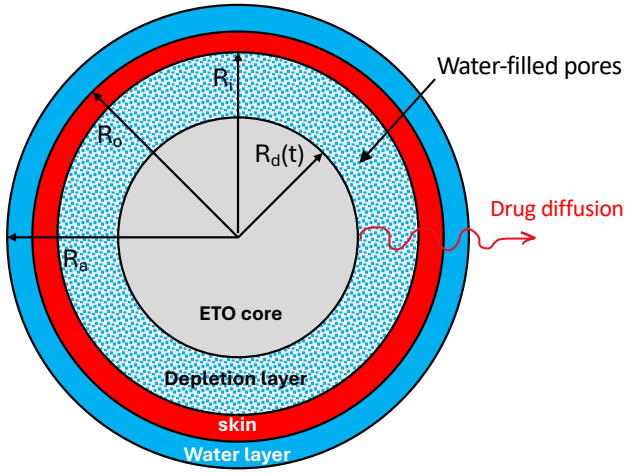
Drug release is controlled by:

3. Release testing conditions [2]

Cannot be measured, fitted using release data

$$\frac{dM}{dt}_{skin} = \frac{2\pi L * (Cs_{DL} - \frac{C_{media}}{K_2 K_3})}{\frac{1}{D_{DL}} \ln \frac{R_i}{\boldsymbol{R_d(t)}} + \frac{1}{K_2 D_{15}} \ln \frac{R_o}{R_i} + \frac{1}{K_2 K_3 D_a} \ln \frac{R_a}{R_o}}$$



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[2] Zhong, Ziyue, et al. "Correlation between material, structure, and drug release of Nexplanon®: an ethylene vinyl acetate (EVA) based long-acting implant." *International Journal of Pharmaceutics* (2025)

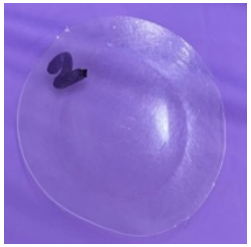
Determination of model parameters for drug release calculation

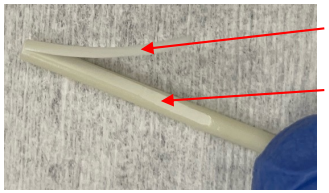
- Method: film permeation in diffusion cell [1]
  - ➢ Deletion layer ← drug-depleted Nexplanon core film
  - ➢ Skin layer ← EVA 15 free film

Side-by-side diffusion cells

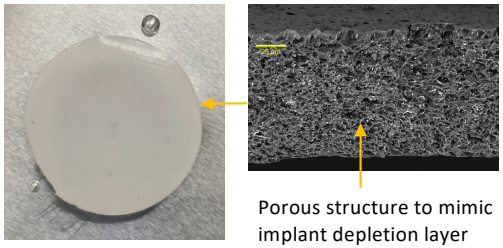
EVA free film extrusion

EVA free film





Water-filled drug-depleted Nexplanon core film



- Water layer
  - ➢ Solubility: measured in house
  - ➢ Diffusivity: chromatographic broadening method [2]

Diffusion layer	Diffuse in	Permeability ($\times 10^{-12}$ g•cm^{-1}•s^{-1})	Solubility ($\times 10^{-3}$ g•cm^{-3})	Diffusivity ($\times 10^{-9}$ cm^2•s^{-1})
ETO core	EVA 28 free film [1]	6.65 ± 0.36	2.15 ± 0.25	3.13 ± 0.37
Depletion layer	Depleted ETO core film	14.1 ± 0.64	1.71 ± 0.21	8.37 ± 0.75
Skin	EVA 15 free film [1]	2.70 ± 0.22	1.00 ± 0.03	2.59 ± 0.02
Water layer	Water	42.8	0.0061 ± 0.0001	7020 ± 40 [2]

[1] Zhong, Ziyue, et al. "Correlation between polymer properties, extrusion process parameters and permeability of etonogestrel in ethylene vinyl acetate films." *Journal of Pharmaceutical Sciences* (2025)
[2] Seki, Toshinobu, et al. "Measurement of diffusion coefficients of parabens and steroids in water and 1-octanol." *Chemical and pharmaceutical* (2003)

Dissolution capacity > Diffusion capacity → drug release is controlled by diffusion

- **Relative capacity → % of change overtime**
- Up to 85% of drug released: relative $\Phi_{\text{dissolution}} >$ relative $\Phi_{\text{diffusion}}$
- 85% drug release ≈ 5 years drug release @ 54% drug loading
- Higher drug loading → longer diffusion-controlled time

Dissolution capacity $[\Phi_{dissolution}(t)]$: reduces due to

less available surface area → $\propto R_d(t)$

↓

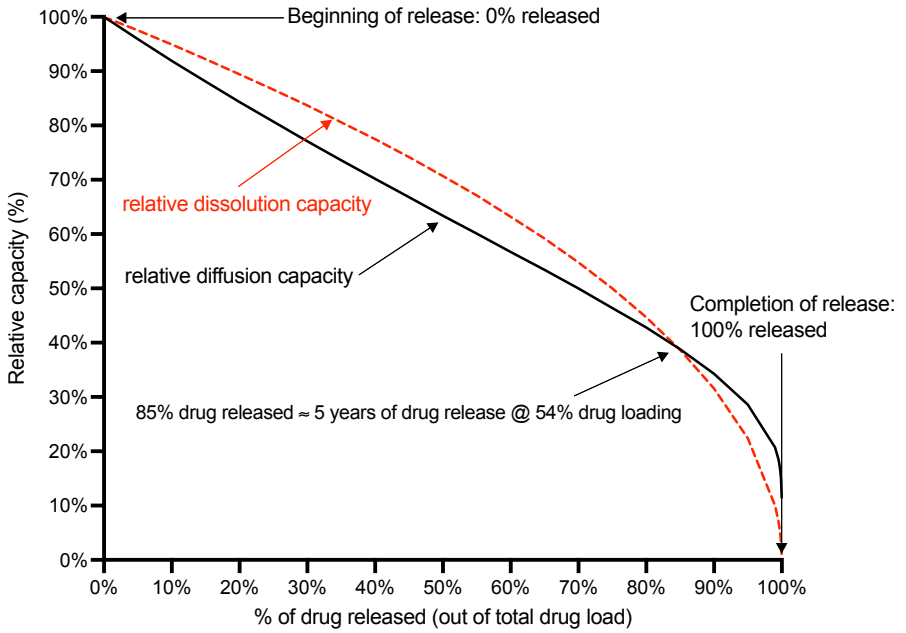
Relative dissolution capacity: $\Phi_{\text{dissolution}(t)} / \Phi_{\text{dissolution}(t=0)} = \frac{R_d(t)}{R_i}$

Diffusion capacity $[\Phi_{diffusion}(t)]$: reduces due to

less available surface area + **longer diffusion path** → $\propto \frac{1}{C_1 \ln \frac{R_i}{R_d(t)} + C_2}$

↓

Relative diffusion capacity: $\Phi_{\text{diffusion}(t)} / \Phi_{\text{diffusion}(t=0)} = \frac{1}{C_1 / C_2 * \ln \frac{R_i}{R_d(t)} + 1}$

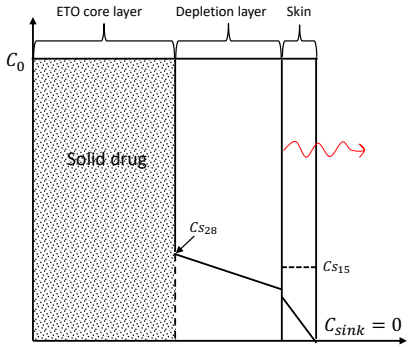


Skin release model #2: as a function of time (t)

Matrix-membrane diffusion model (Paul, 1984)

Assumptions:

- Slab geometry
- No un-stirred boundary layer



$$\frac{SA_{skin}}{\sqrt{\frac{1}{J_m^2} + \frac{2t}{C_{DL}D_{DL}(C_0 - 0.5C_{DL})}}}$$

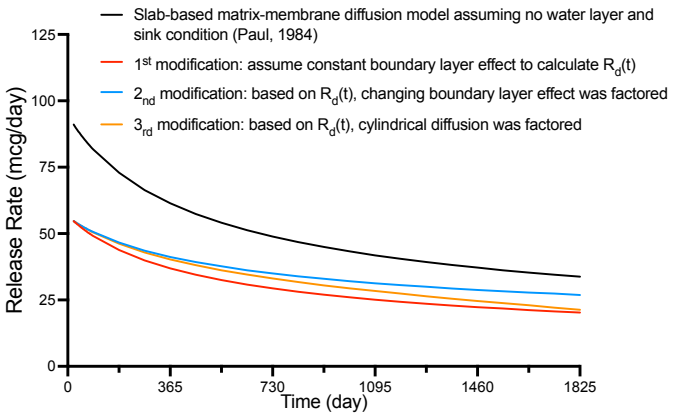
$$J_m = \frac{2\pi L D_{15} Cs_{15}}{ln(^{R_o}/_{R_i}) * SA_{skin}}$$

SA_{skin}: skin surface area
J_m: max flux through skin
C_{DL}: drug solubility in depletion layer
D_{DL}: drug diffusivity in depletion layer
C_0: drug loading

UT modified model

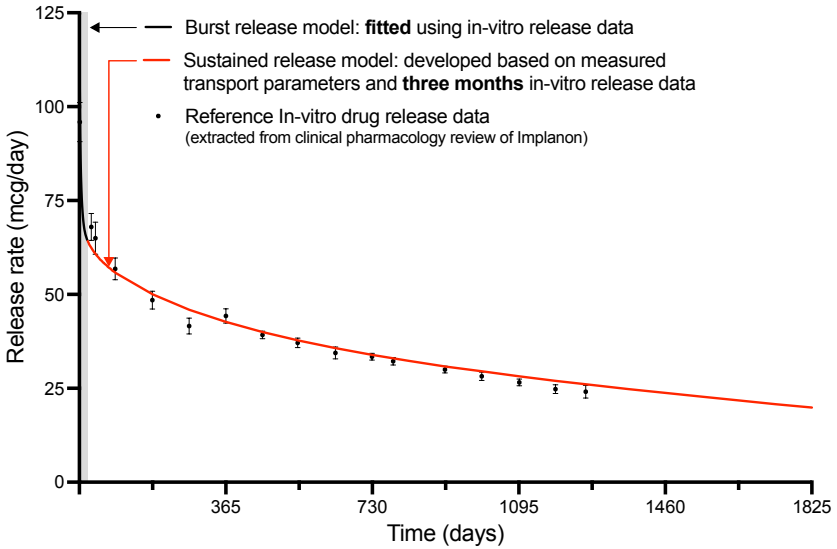
1. Assuming constant boundary layer effect → R_d (t)
2. R_d (t) → factored boundary layer effect (t)
3. R_d (t) → factored cylindrical diffusion (t)

$$\frac{SA_{skin}}{\sqrt{\frac{1}{J_m^2} + \frac{2t}{C_{DL}D_{DL}(C_0 - 0.5C_{DL})}}} * F_{boundary\ layer} * F_{cylindrical\ diffusion}$$



Paul, D. P. "Solute release from membrane—matrix composites." *Journal of membrane science* (1984)

Predicting drug release as a function of time



$$Predicted\ total\ release = Effective\ skin\ release + Effective\ ends\ release$$

$$Effective\ skin\ release = Predicted\ skin\ release \times F_{ends\ depletion}$$

$$F_{ends\ depletion} = \frac{Predicted\ Ends\ Release\ Amount}{Total\ Drug\ load}$$

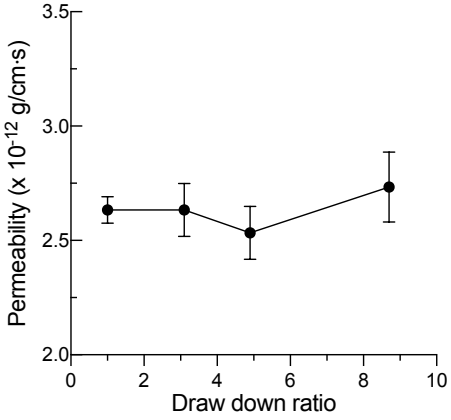
- Burst release must be measured (fitted using first order kinetic)
- Sustained release can be predicted by
  - ➢ Measuring transport parameters
  - ➢ Factoring boundary layer effect
  - ➢ Factoring cylindrical diffusion
  - ➢ Verifying the model using three months data
- More sophisticated models are being developed:
  - ➢ Analytically solving skin release model as a function of time
  - ➢ Numerically solving skin/ends release at the same time (Finite element analysis using COMSOL Multiphysics®)

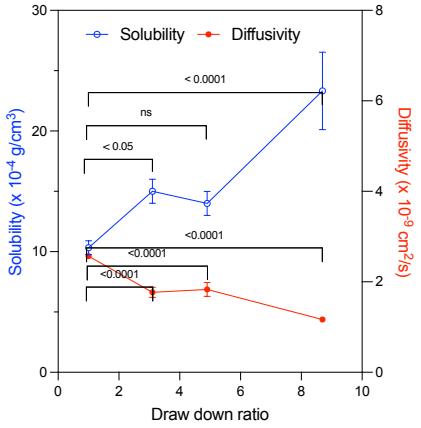
Takeaway

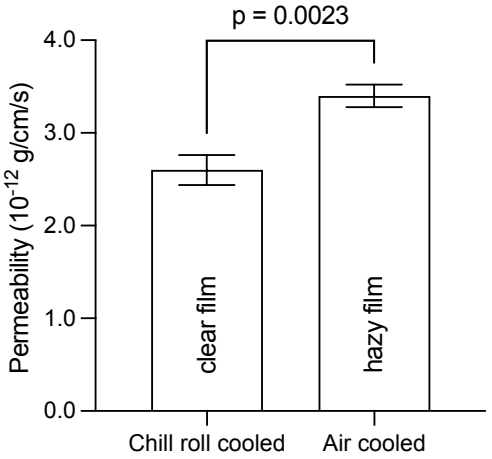
- Short term release data is necessary to determine burst release, factor boundary layer effect, and verify the model.
- All model parameters can be experimentally measured except the thickness of un-stirred boundary layer, which must be factored based on release conditions.
- Drug release is controlled by diffusion within the three-year simulation period.
- The model can be used to study what variables are causing different release profiles between two prototype implants.
- Future work include solving the complex diffusion models analytically and numerically.

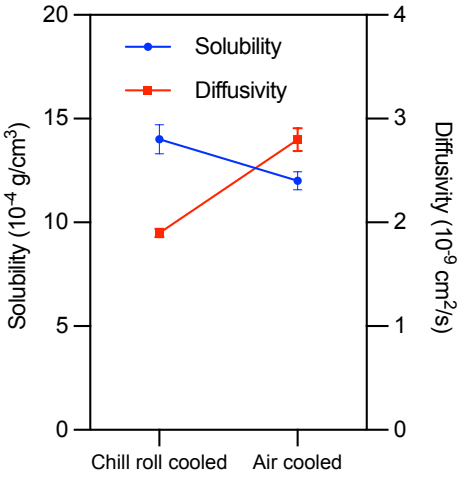
Supplemental slides

EVA free film study estimated that effect of different crystalline property leads to ±15% difference in permeability.



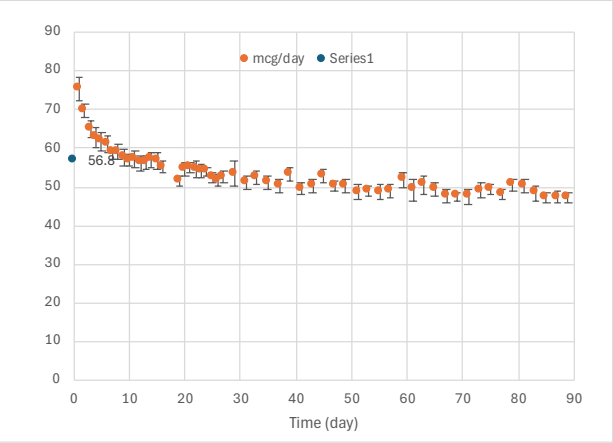




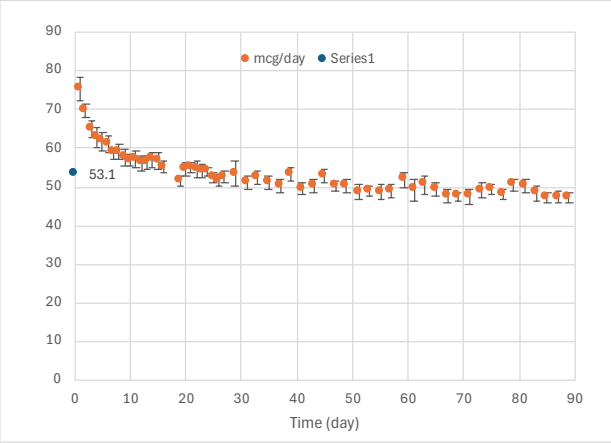


Experimentally determine un-stirrer water layer thickness

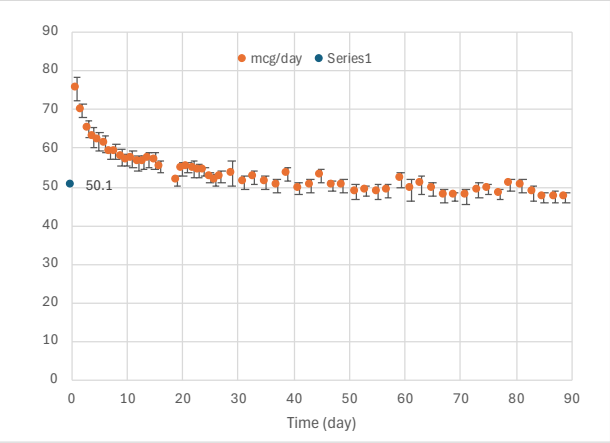
Ra = 0.8 x Ri



Ra =1.0 x Ri



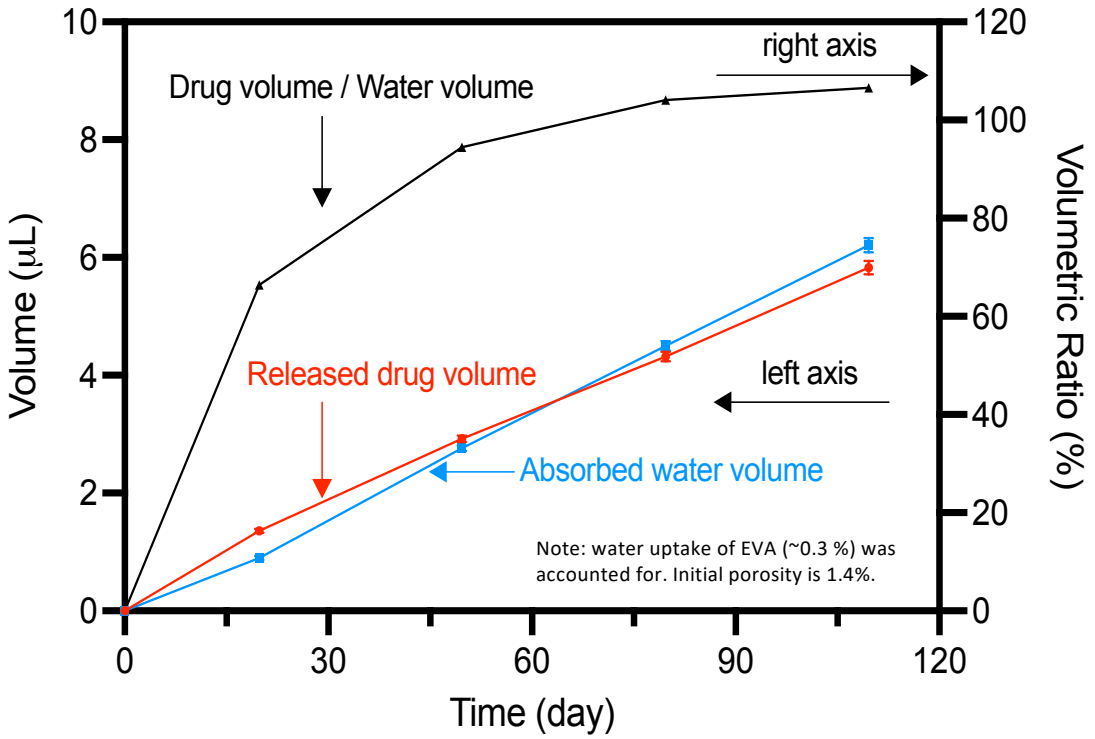
Ra =1.2 x Ri



ha = X Ri	3rd term (s/cm^2)	2nd term (s/cm^2)
0.8	2.95E+07	4.53E+07
1	3.47E+07	
1.2	3.95E+07	

$$\frac{dM}{dt}_{skin} = \frac{2\pi L * (Cs_{DL} - \frac{C_{media}}{K_2 K_3})}{\frac{1}{D_{DL}} \ln \frac{R_i}{\boldsymbol{R_d(t)}} + \frac{1}{K_2 D_{15}} \ln \frac{R_o}{R_i} + \frac{1}{K_2 K_3 D_a} \ln \frac{R_a}{R_o}}$$

Kinetic and extent of water absorption



Drug dissolution
↓
Drug diffusion
↓
Drug depletion
↓
Pore formation
↓
Water-filled pores ← Water diffusion

Occur at the same time

Determining diffusivity using chromatographic broadening method

Diffusivity in water is controlled by:

Internal factors:

- Molecular weight (MW)
- Lipophilicity

External factors:

- Viscosity of water

$$D = \frac{0.231 \cdot r^2 \cdot t_R}{W_{1/2}}$$

- 0.231: constant determined from calibration runs
- r: the radius of the capillary tube
- t_R: residence time
- $W_{1/2}$: eluted peak width at half height

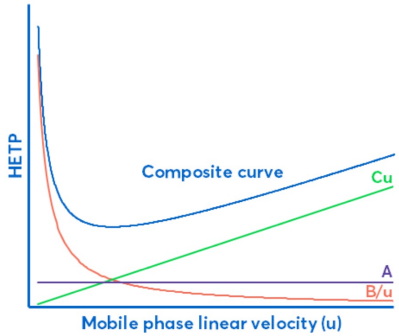


Figure 1: van Deemter curve

HETP = A + B/u + Cu Equation 2

The three terms correspond to the following processes:

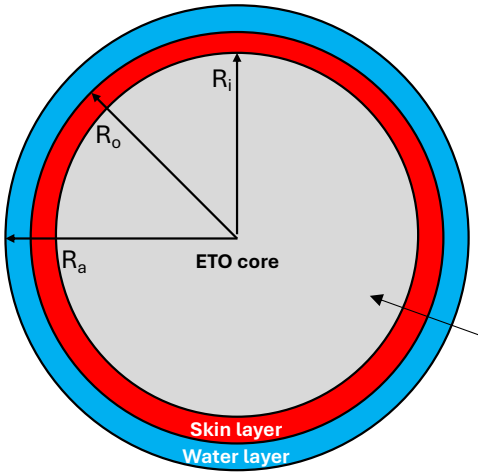
A Eddy diffusion,

B Longitudinal diffusion,

C Mass transfer.

Formation of depletion layer

Before drug release



(not to scale)

R_d (ETO core radius): reduces overtime
R_i (inner radius): 0.94 mm
R_o (outer radius): 1.00 mm
R_o - R_i (skin): 0.06 mm
R_a - R_o (un-stirred water layer): h_a

Before drug depletion
(Drug particles circled)