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PREDICTING DRUG RELEASE FROM EVA-BASED LONG-ACTING IMPLANTS: MECHANISMS, MODELING, AND SIMULATION OF DRUG RELEASE

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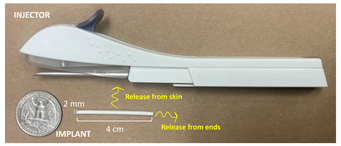
PURPOSE



Nexplanon®

Etonogestrel subdermal implant

- Three years birth control
- Non-biodegradable, removable
- Controlled release of etonogestrel (contraceptive hormone)

Long-acting implants can provide sustained and controlled release of therapeutic agents to improve drug safety, efficacy, and patient adherence. However, development of these products is challenged by its prolonged drug release testing. In this study, a semi-empirical modeling framework was developed to predict drug release based on measured model parameters and short-term experimental release data.

OBJECTIVE(S)

- Understand drug release mechanisms
- Establish correlations between material properties, implant structure, and drug release
- To predict long-term drug release

METHOD(S)

Side-by-side diffusion cells

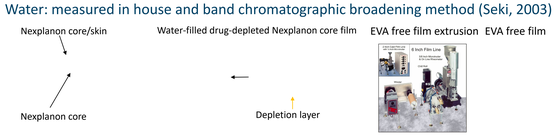
Transport properties:

Method: film permeation in diffusion cell at 37 °C

Depletion layer: skin was removed and core only materials were compressed into drug-loaded film.

Implant skin: EVA 15 free film [1]

Water: measured in house and band chromatographic broadening method (Seki, 2003)



In-vitro release testing:

- Method: bottle/shaker at 37 °C at 150 rpm.
- Skin-only release: tested using ends-sealed implants (Loctite® 4011 glue)
- Ends-only release: tested using skin-sealed implants
- Water uptake: mass balance based on wet implant mass

Model development:

- Ends-only release and skin-only release were modeled separately.
- Pseudo steady state assumption: dissolution is not rate-limiting, no dispersed drug exists and steady state diffusion in the depletion layer (due to high drug loading: $C_0/Cs_{28} >> 3$, ≈ 361, [2]).
- Justification of diffusion-controlled assumption
  - ➢ Dissolution capacity > diffusion capacity → drug dissolution is not rate-limiting
  - ➢ Instead of absolute capacity, relative capacity was calculated.

RESULT(S)

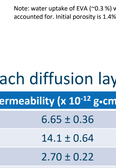
Structure and composition [3] of Nexplanon ®

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

- Lower VA content of skin (15% < 28%) → higher crystallinity → lower drug permeability
- Drug release mainly controlled by diffusion through skin.
- High drug loading (54%) → more sustained release → pseudo-steady assumption

Development of porous depletion layer and water permeation overtime

Simultaneously drug depletion and water permeation



Pore formation and water absorption

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

Occurs at the same time

Etonogestrel permeability in each diffusion layer

Diffusion layer	Material [1]	Permeability (x 10^{-12} g•cm^{-1}•s^{-1})
Core	EVA 28 free film*	6.65 ± 0.36
	Depletion layer	14.1 ± 0.64
Skin	EVA 15 free film*	2.70 ± 0.22
Water layer	Water	42.8

Higher permeability in water → Higher permeability in depletion layer

Initial burst release due to drug supersaturation [4, 5]

Manufacturing of Nexplanon: heating → drug solubilization → cooling → incomplete recrystallization → supersaturation

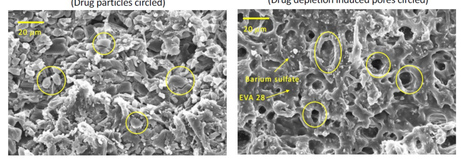
Processed at elevated temperature ≈ 125 °C

drug crystal

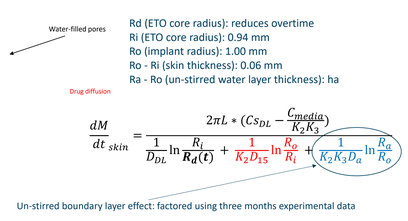
Depletion of supersaturated drug → dissolution of drug crystals → transitioning to sustained release

Before drug depletion (Drug particles circled)

After drug depletion (Drug depletion induced pores circled)



Drug release model #1: as a function of ETO core radius (R_d) [6]



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_{DL}	D_{15}	D_a
Solubility	Cs_{DL}	Cs_{15}	Cs_a
Partition Coefficients	$K_1 = \frac{Cs_{eff}}{Cs_{28}}, K_2 = \frac{Cs_{15}}{Cs_{DL}}, K_3 = \frac{Cs_a}{Cs_{15}}$		

Before 85% of total release:
relative dissolution capacity > relative diffusion capacity

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

Predicting drug release as a function of time

Matrix-membrane diffusion model (Paul, 1984) [7]

Assumptions:
- Slab geometry
- No un-stirred boundary layer

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

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

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

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

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

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

CONCLUSION(S)

- All model parameters can be experimentally measured except thickness of the un-stirred boundary layer.
- Short term release data is necessary for burst release determination, boundary layer effect factoring, and model verification.
- Drug release is controlled by diffusion within 3 years.
- The model can be used to study what variables are causing different release profiles between two prototype implants.
- Future work:
  - ➢ Mathematically solving drug release model #2 as a function of time (t)
  - ➢ Numerically solving skin and ends release at the same time (FEM using COMSOL Multiphysics®)
  - ➢ Sensitivity of drug release to parameters

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