VITAL Dose®

Predicting Long-Term Drug Release Kinetics from One Week of Elution Data in Poly(Ethylene-co-Vinyl Acetate) Drug-Eluting Implants: A Method to Accelerate Product Development

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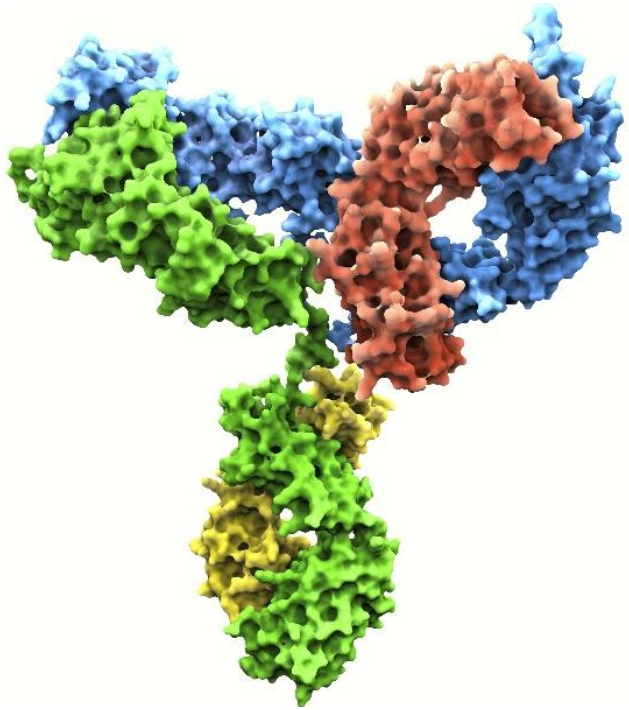
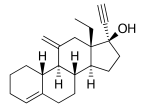
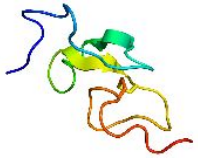
Today's Agenda

- Poly(Ethylene Vinyl Acetate) Drug-Eluting Implants
- Using the Higuchi Model to Extrapolate In Vitro Drug Release
- Examples of Higuchi Model Extrapolation





Etenogestrel
325



Epidermal GF
6,000

Lysozyme
15,000

mABs
100,000+

The Use of VitalDose® EVA Platform in Drug Delivery

Long History of Use in US & EMEA Approved Products

EVA has over 20 years of use in approved parenteral drug products in the US and EMEA

Ophthalmic Insert & Ocular Implant

Intravaginal Ring

Intrauterine Device

Subcutaneous Implant (rod)

Ease of design & formulation

Biostable and Inert

Months to years release

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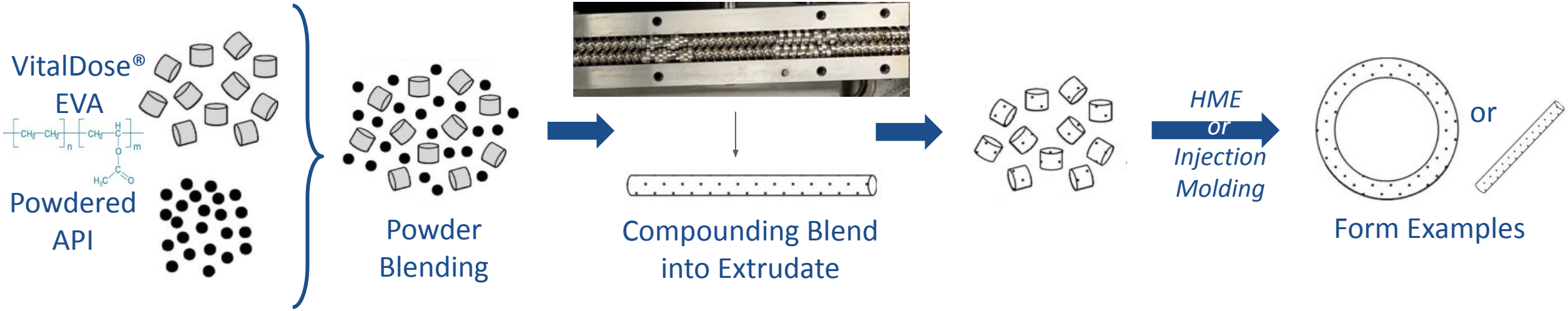
Hot Melt Extruded Drug Delivery Systems with EVA



- VitalDose® EVA is blended with powdered API
- **Low melt temperature options** offer optimal stability and compatibility

- Powdered API and EVA are **combined and compounded into extrudate**
- Small quantities of API can be used to generate small volume samples

- The extrudate is pelletized for use in **extrusion or injection molding**
- Processing flexibility results in a **versatile range of form factors**

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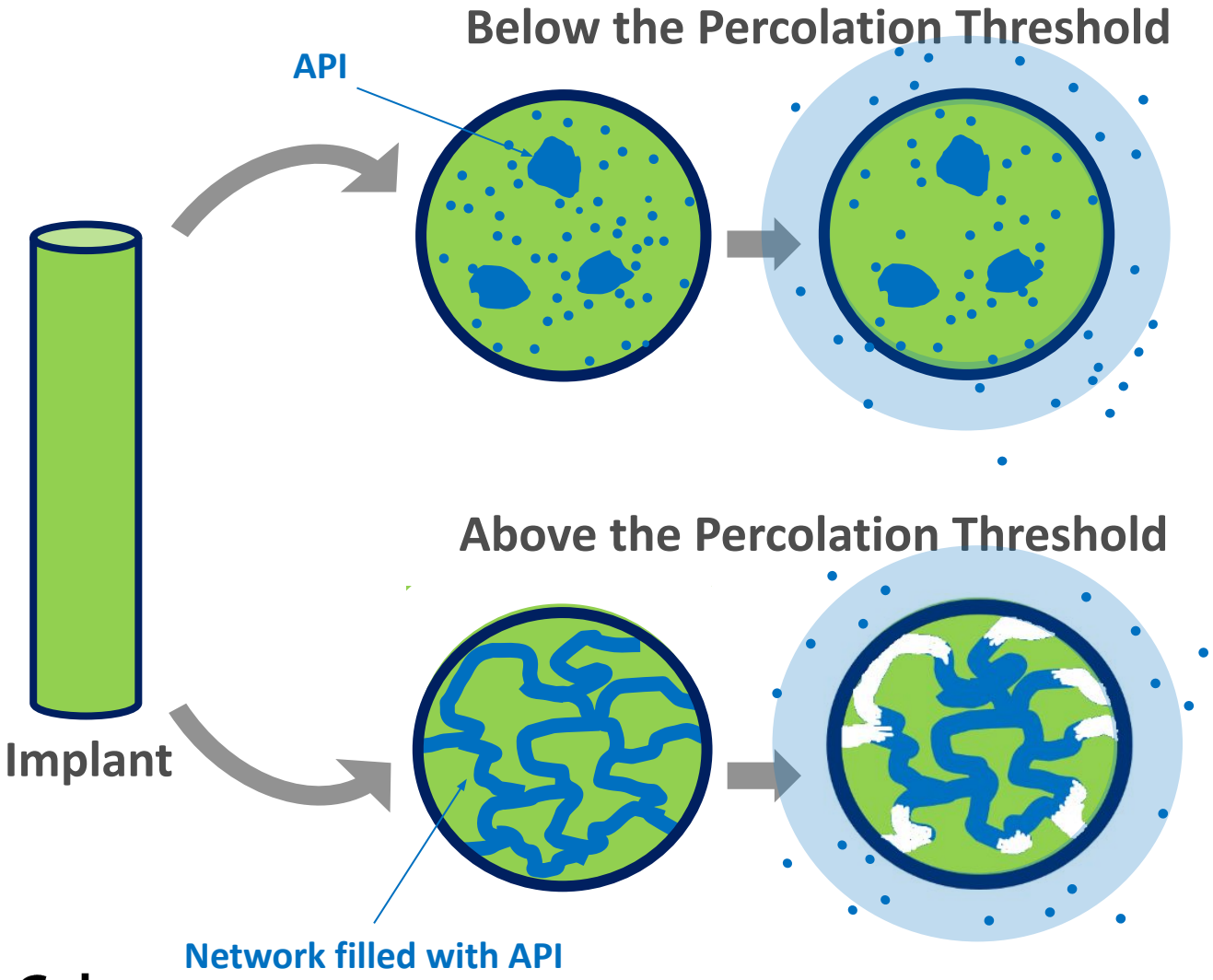
Images adapted from: Malcolm et al. *International Journal of Women's health (2012)*

Drug Release from EVA is Controlled by Diffusion



Drug loading < 30-40%

Drug loading > 30-40%

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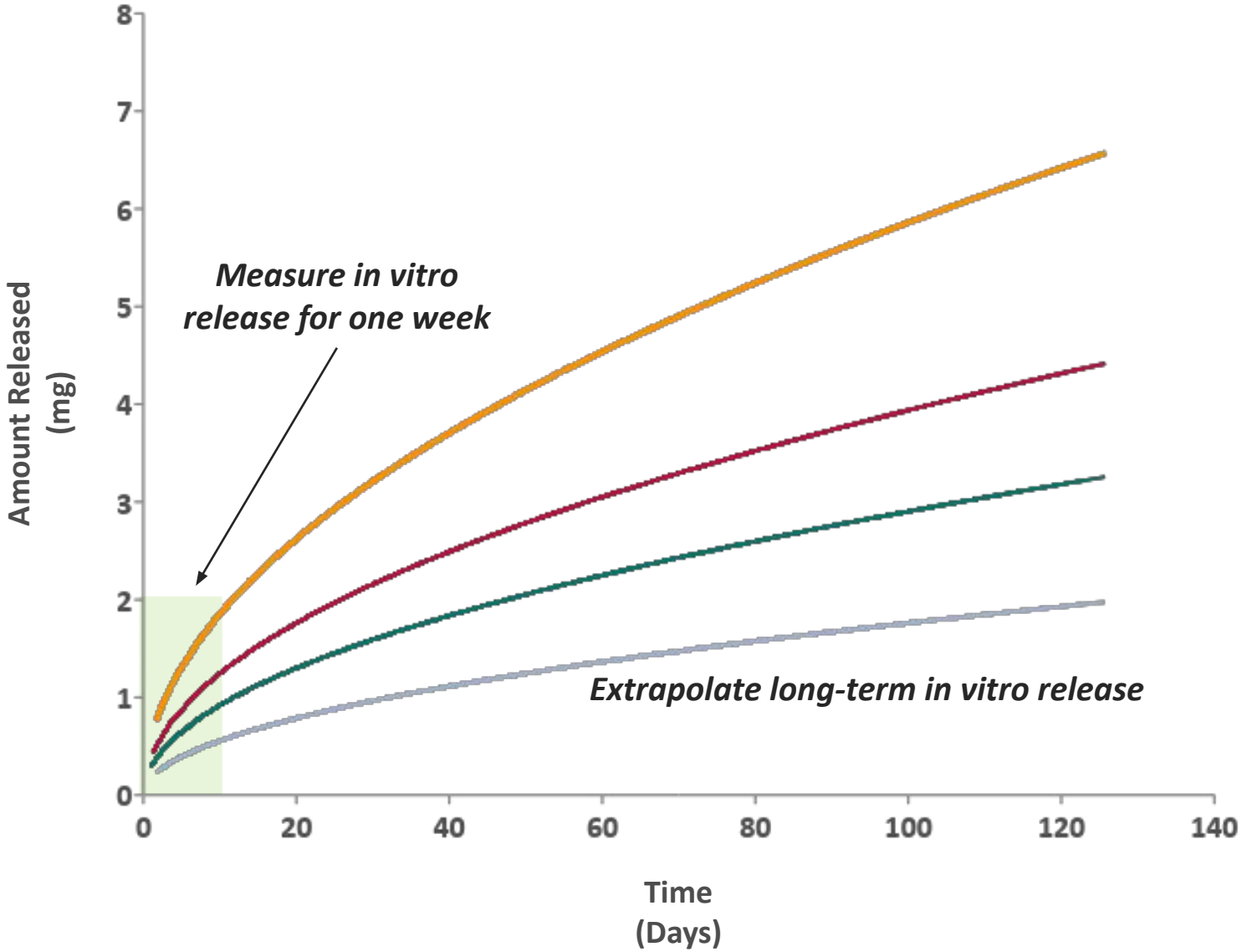
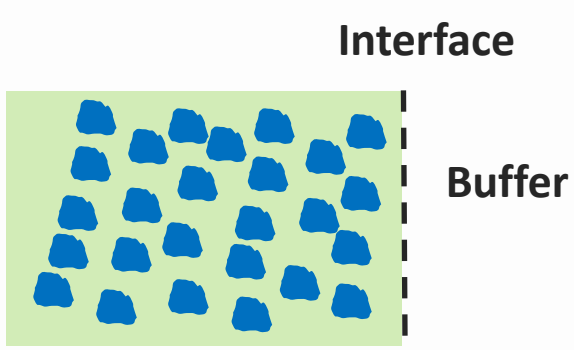
Problem Statement: Can We Apply Simple Mathematical Models to Extrapolate Long-Term Release Data?

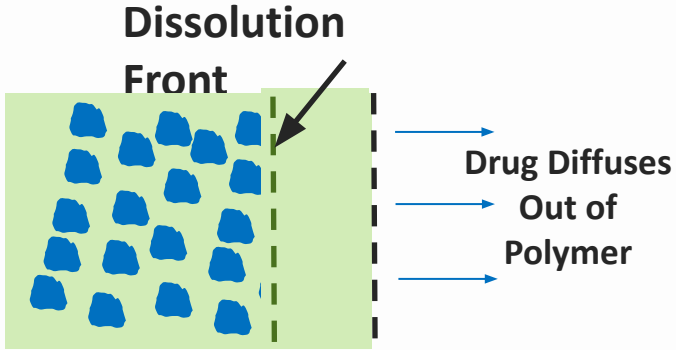
- In vitro release experiments for long-acting implants require lengthy periods of data collection.
- During early stages of proof-of-concept work, several rounds of iteration may be needed.
- Mathematical modeling streamlines development by extrapolating long-term release.

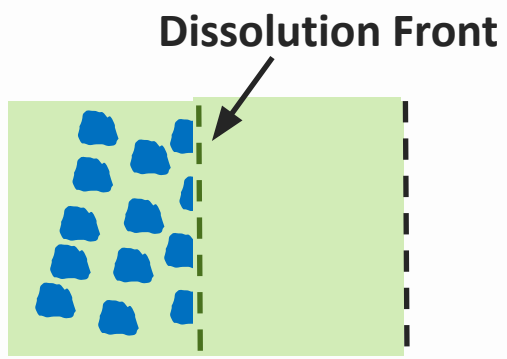


Interpreting Drug Release from Monolithic Systems Using the Higuchi Model

Time = 0 → **Time = t_1** → **Time = t_2**



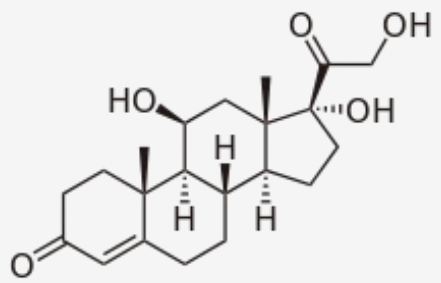




$$M(t) = A\sqrt{DC_s(2C_o - C_s)t}$$

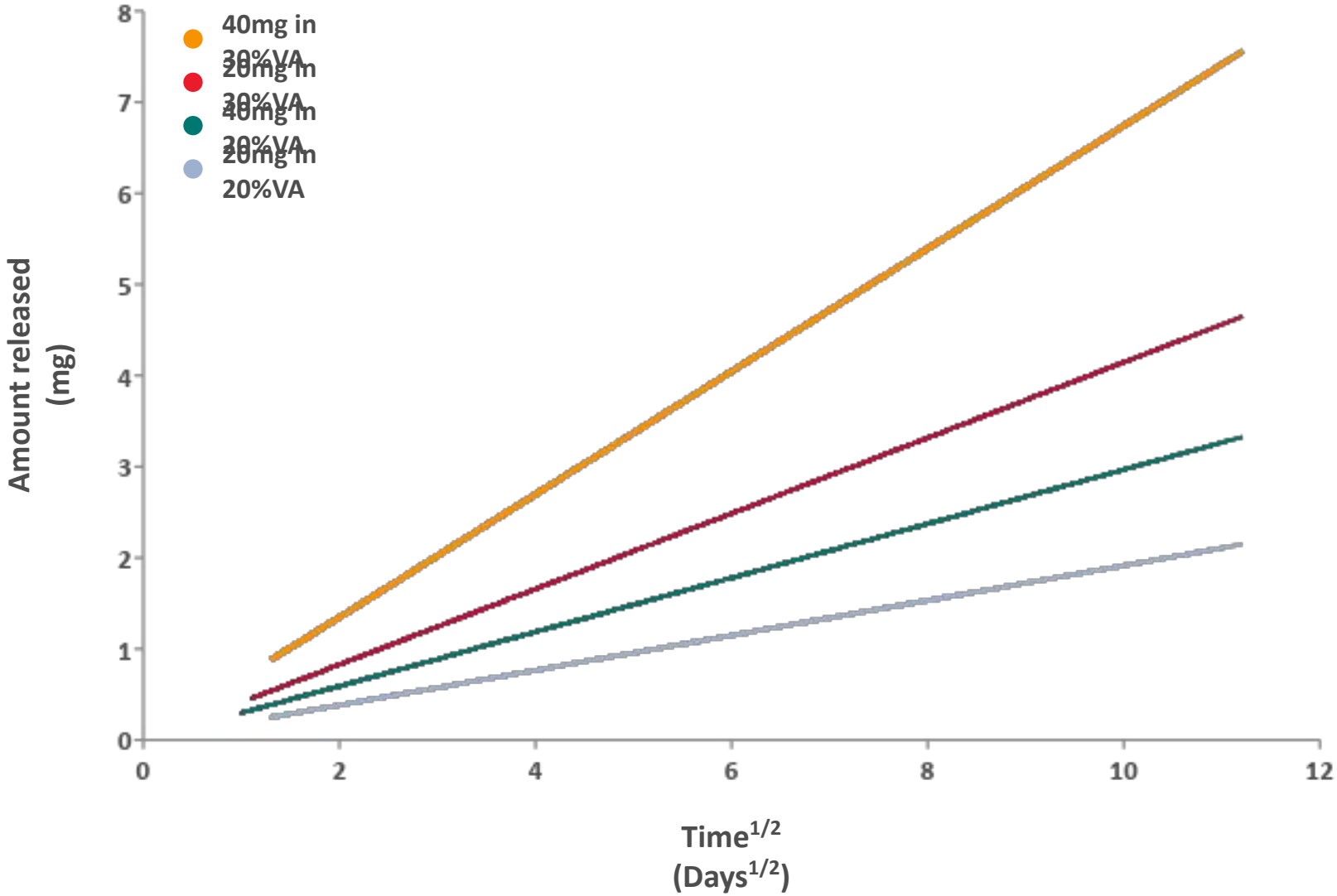
Higuchi, T. *J. Pharm. Sci.* **50**, 874 (1961).

The Higuchi Model Can be Used to Describe Drug Release from EVA



Hydrocortisone
MW = 362.46 g/mol

$$M(t) \sim \sqrt{t}$$



Data: Fu, Moyer, Hagemeier. *Journal of Biomedical Materials Research* 12 (1978).

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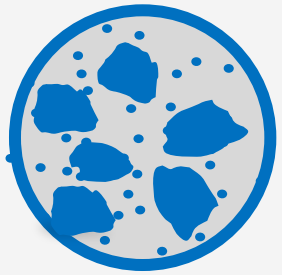
The Higuchi Model and the Percolation Threshold

Release kinetics have same functional dependance on time below and above the percolation threshold

Below the percolation threshold

Higuchi, T. *J. Pharm. Sci.* **50**, 874 (1961).



$$M(t) = A\sqrt{\underbrace{DC_s(2C_o - C_s)}t}$$

Time independent parameters that can be grouped into a constant

Above the percolation threshold

Higuchi, T. J. Pharm. Sci. 52, 1145 (1963).

$$M(t) = A\sqrt{\underbrace{\frac{D_w\epsilon}{\tau}C_{sw}(2C_o - \epsilon C_{sw})}\,t}$$

Time independent parameters that can be grouped into a constant

$$\boldsymbol{M(t) = A\,K\sqrt{t}}$$

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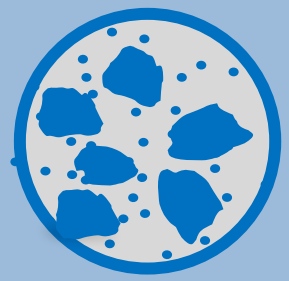
Testing Predictions Below The Percolation Threshold



Below the percolation threshold

- Hydrocortisone
- Niacin
- Cyclosporin

Above the percolation threshold

- Islatrivir
- BSA

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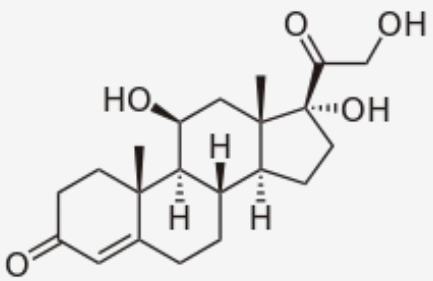
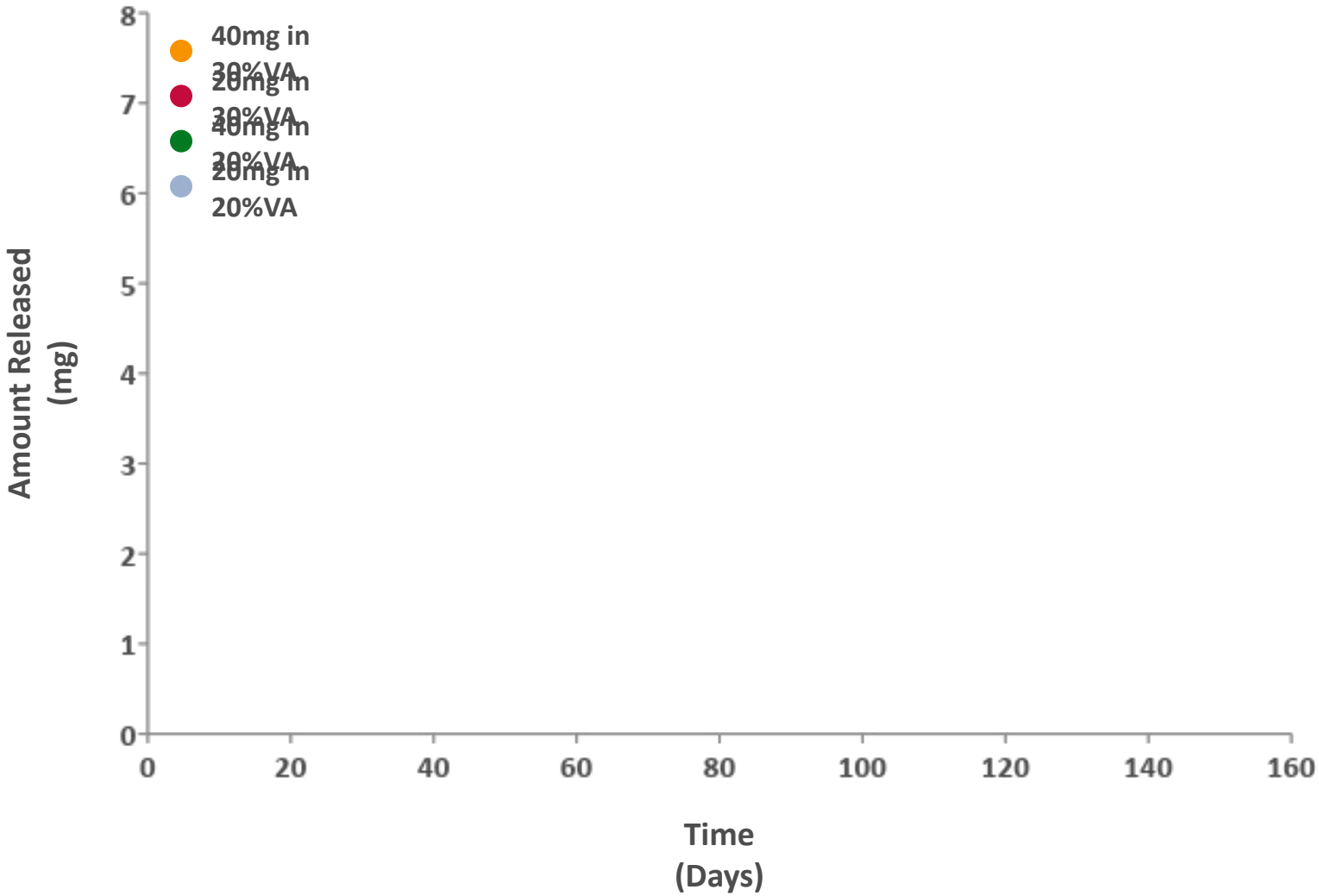
Extrapolating In Vitro Release with the Higuchi Model



Hydrocortisone
MW = 362.46 g/mol

20 mg loading: C_o = 0.075 g/cm^3
40 mg loading: C_o = 0.15 g/cm^3



Data: Fu, Moyer, Hagemeier. *Journal of Biomedical Materials Research* 12 (1978).

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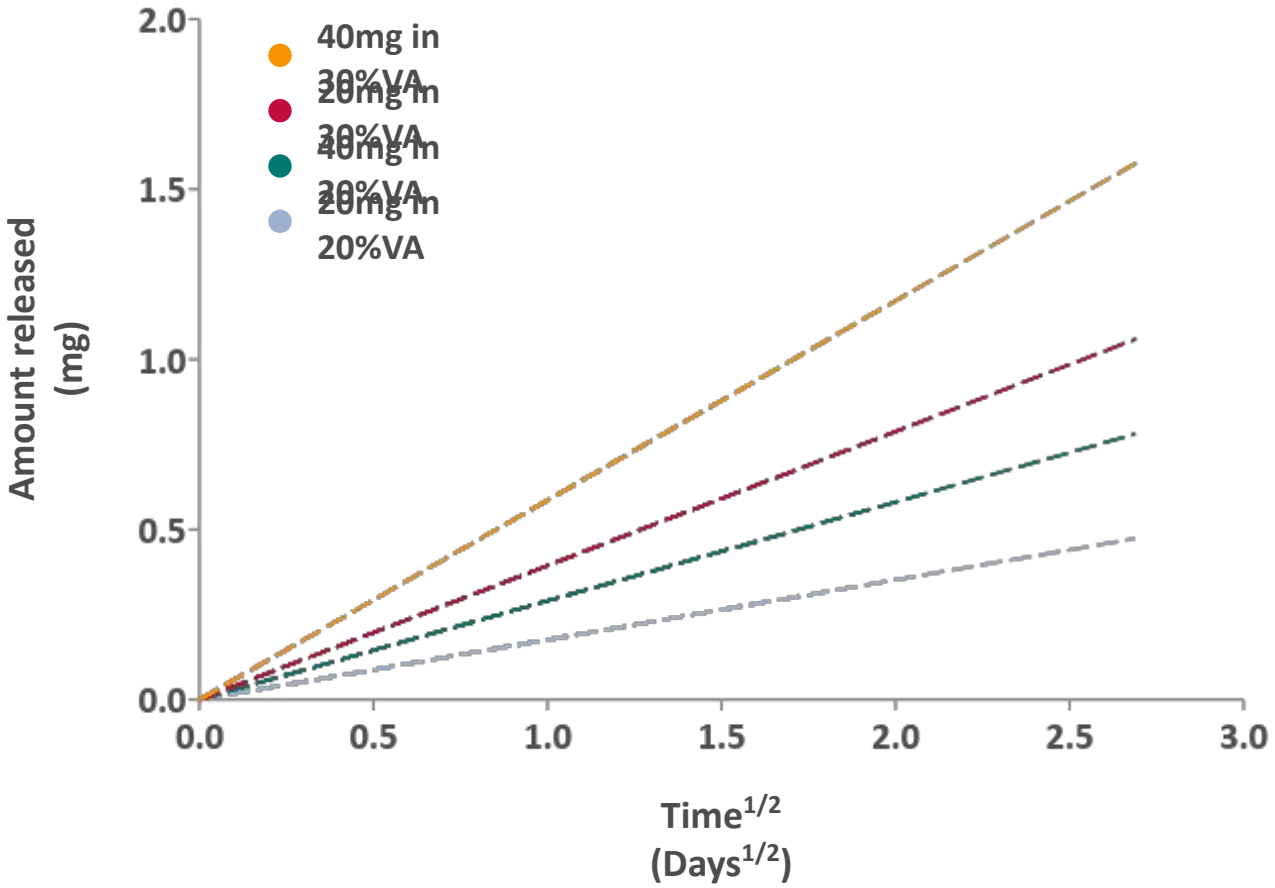
How Well Can We Predict the Full Release Curve Using Seven Days of Data?

A linear least squares fit can be used for the first seven days of data

$$M(t) = A\,K\sqrt{t}$$



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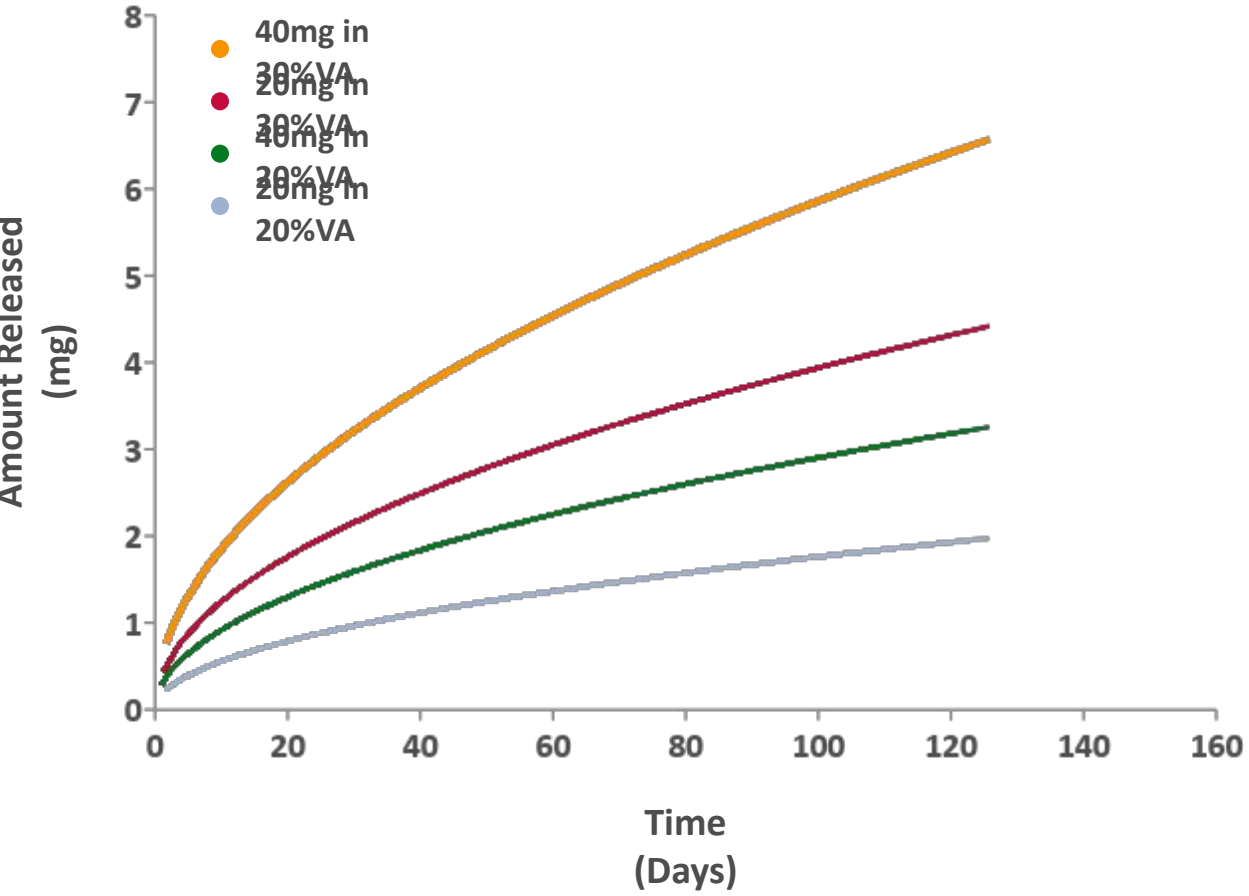
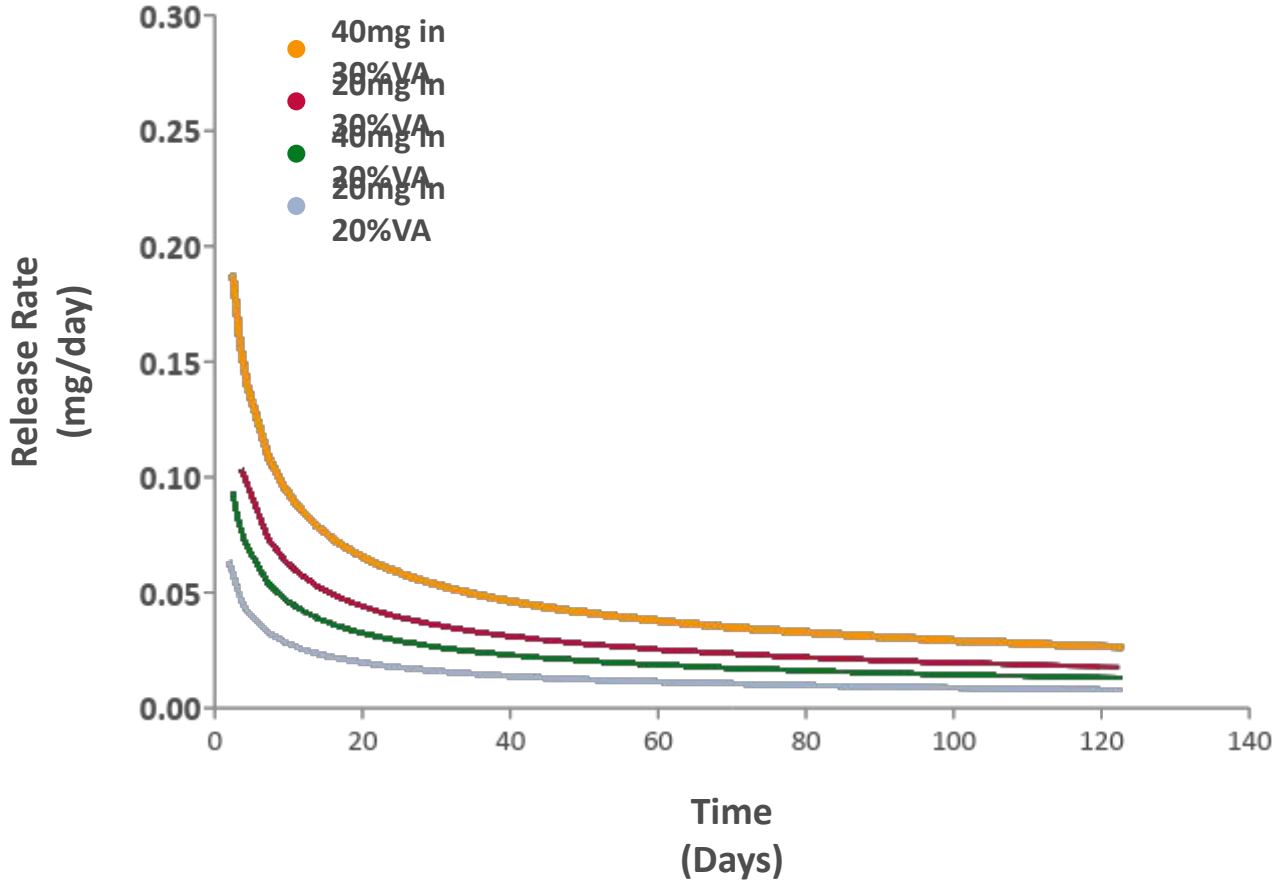
Seven-Day Extrapolations Align with Experimental Data



$$M(t) = A\,K\sqrt{t}$$



$$\frac{dM}{dt} = \frac{1}{2} A \frac{K}{\sqrt{t}}$$

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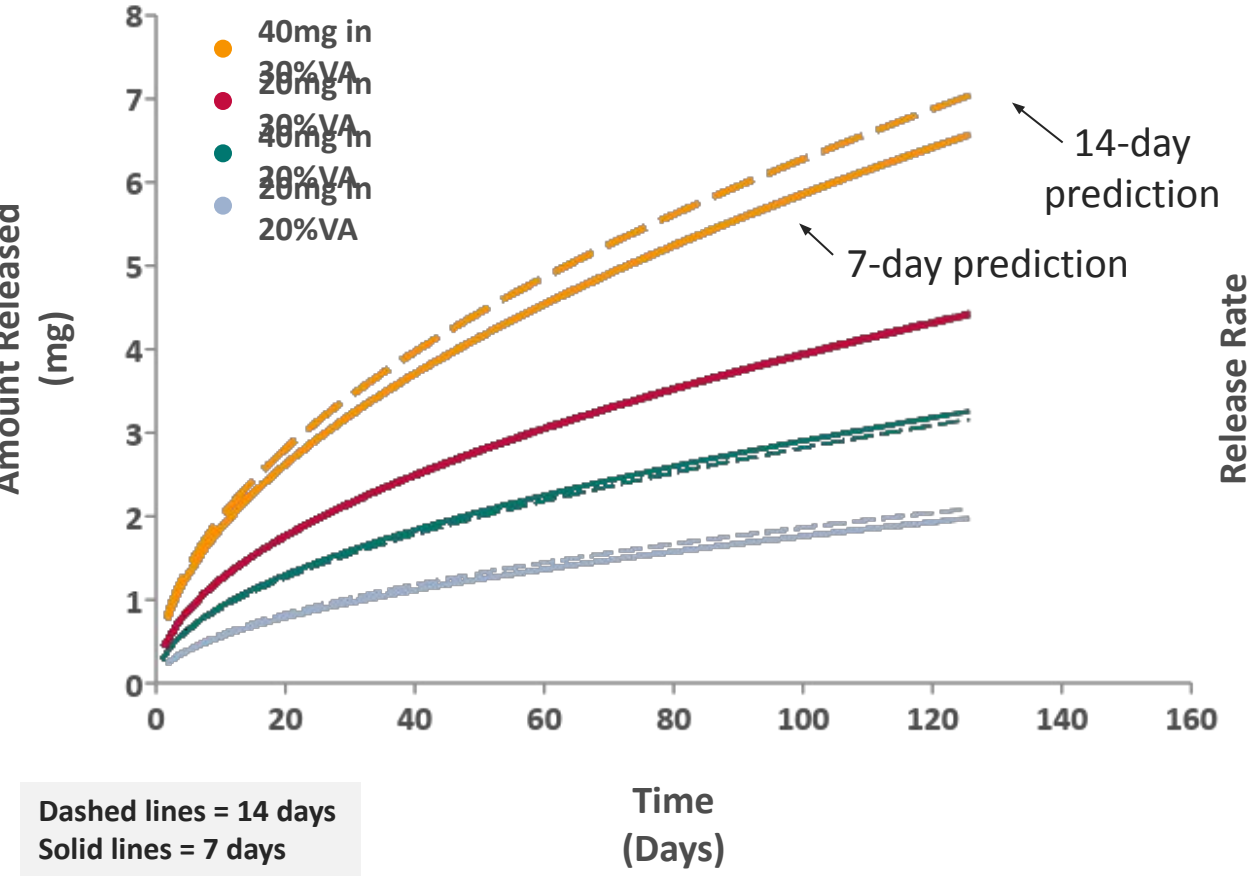
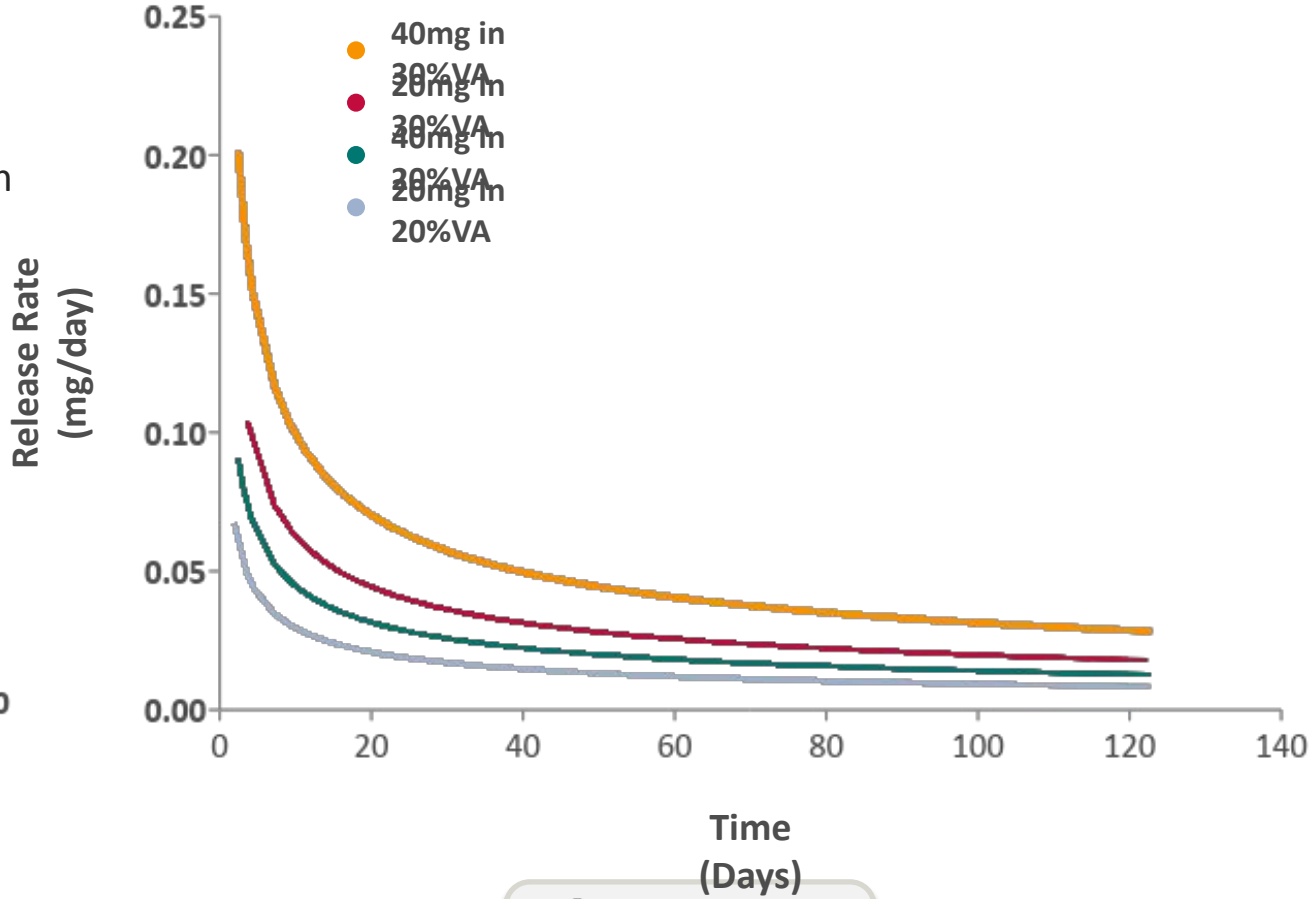
Limited Differences Exist in Prediction Quality Using 14 Days of Data



Dashed lines = 14 days
Solid lines = 7 days

$$M(t) = A\,K\sqrt{t}$$



$$\frac{dM}{dt} = \frac{1}{2}A\frac{K}{\sqrt{t}}$$

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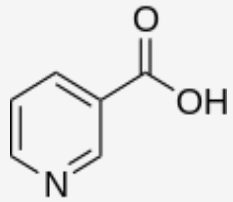
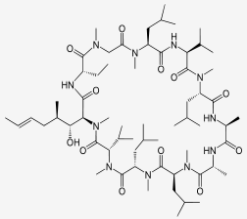
Additional Molecules Below the Percolation Threshold can be Extrapolated



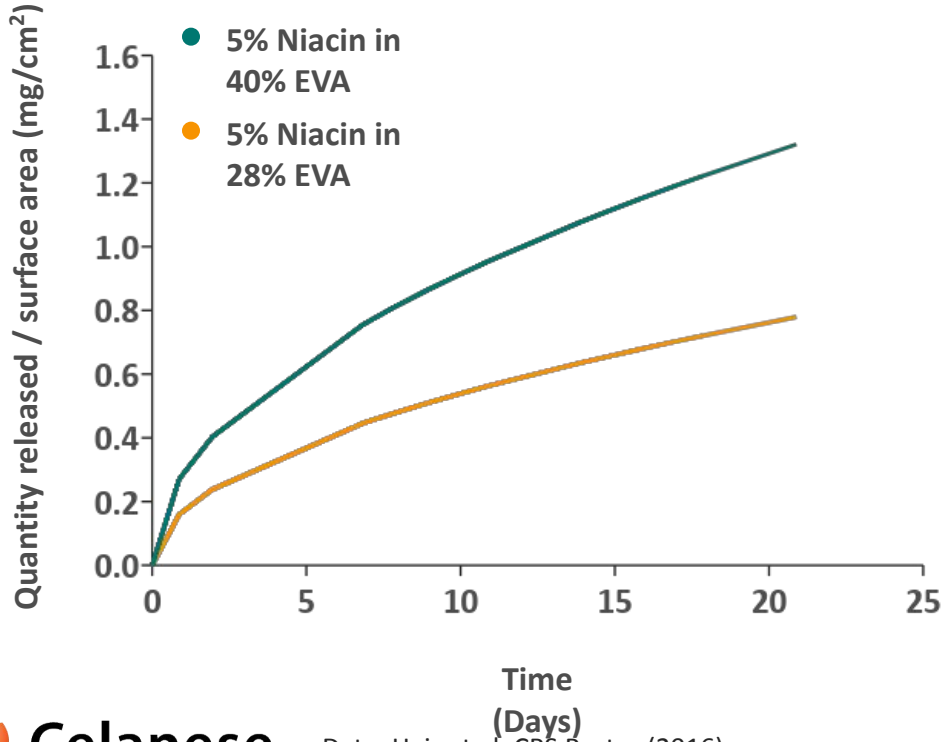
Niacin

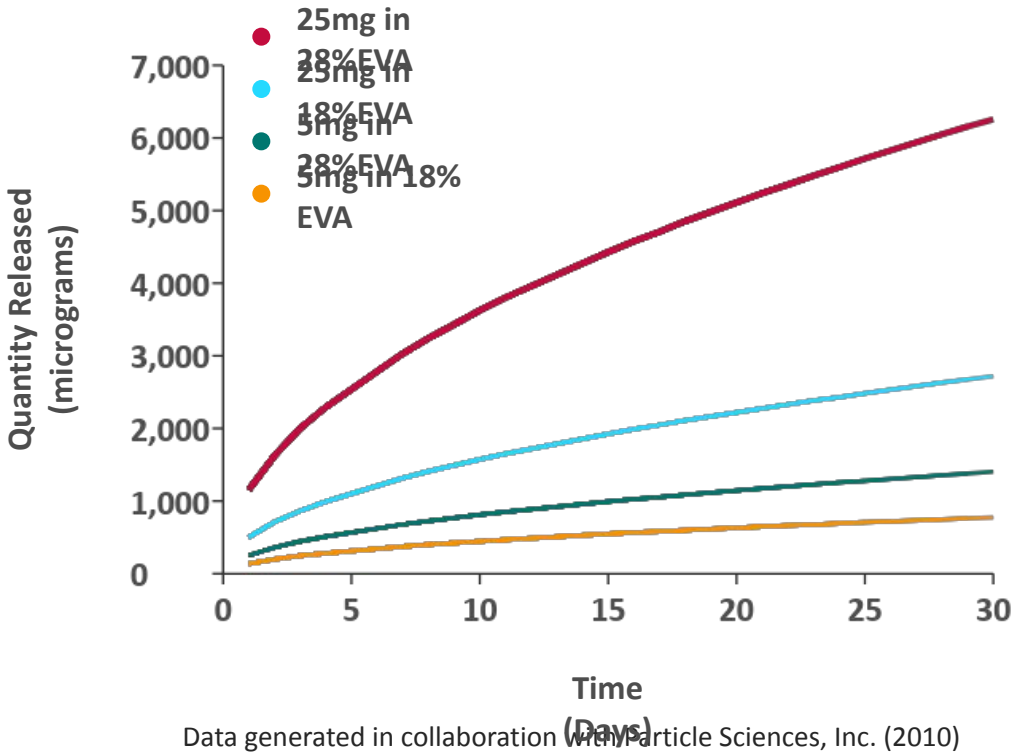
MW = 123.1 g/mol



Cyclosporin

MW = 1203 g/mol





Data: Hair et al. CRS Poster (2016).

Data generated in collaboration with Particle Sciences, Inc. (2010)

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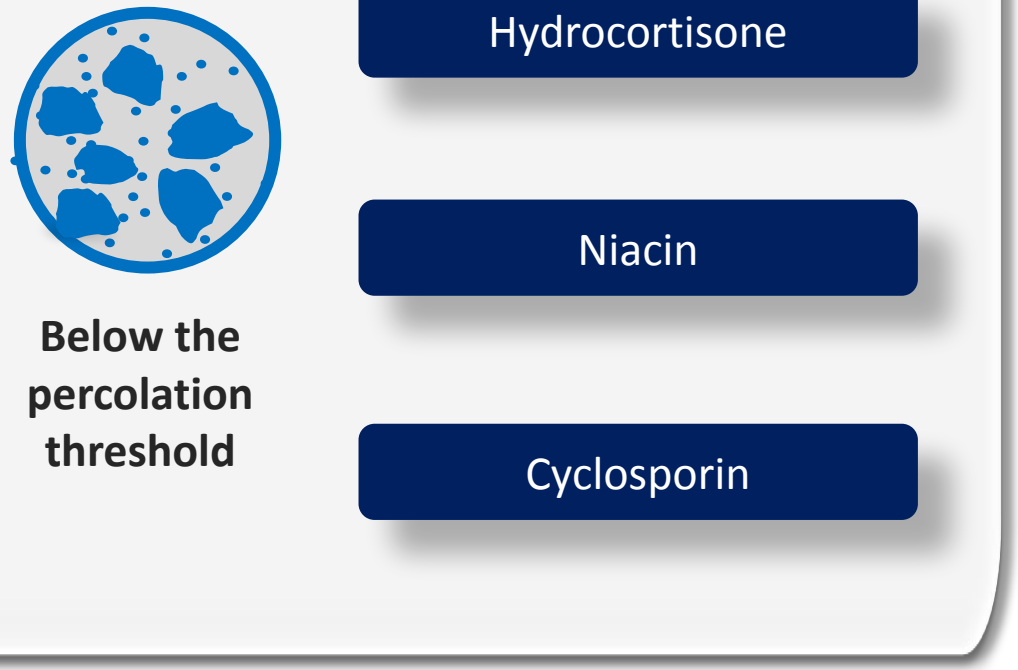
Testing Predictions Above The Percolation Threshold



Below the percolation threshold

Hydrocortisone

Niacin

Cyclosporin

Above the percolation threshold

Islatrivir

BSA

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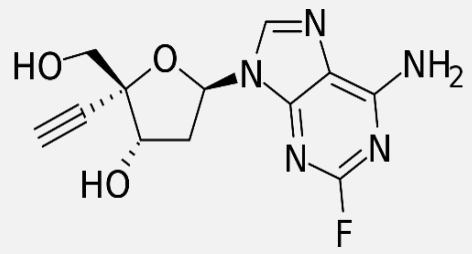
We Can Use Same Predictive Approach Above the Percolation Threshold

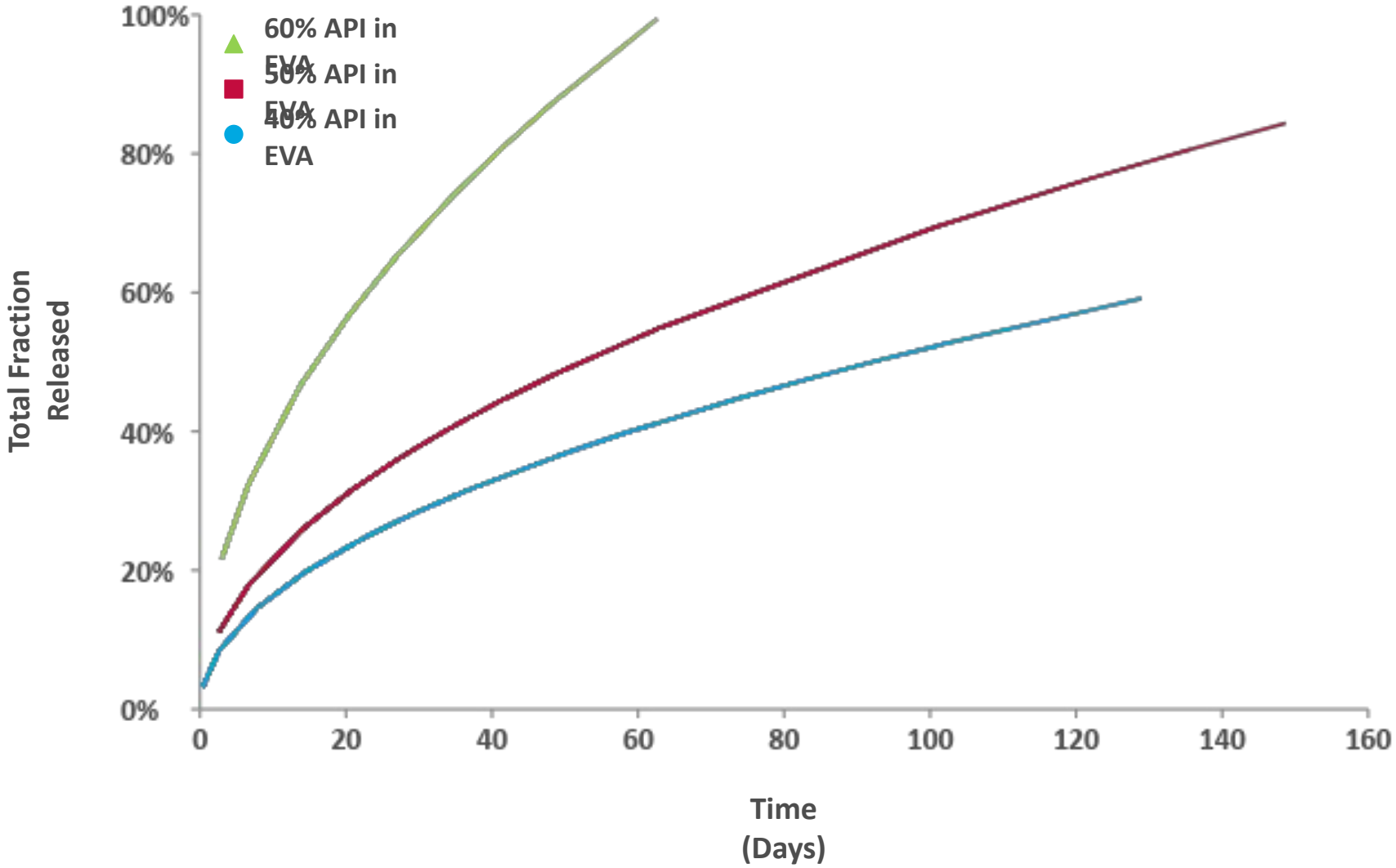
Extrapolating from Seven Days of Data



Islatravir

MW = 293.3 g/mol

EVA (9% VA) loaded with API at levels of 40%, 50%, and 60%.



Data: Barrett et al. Antimicrob Agents Chemother. 62 (2018).

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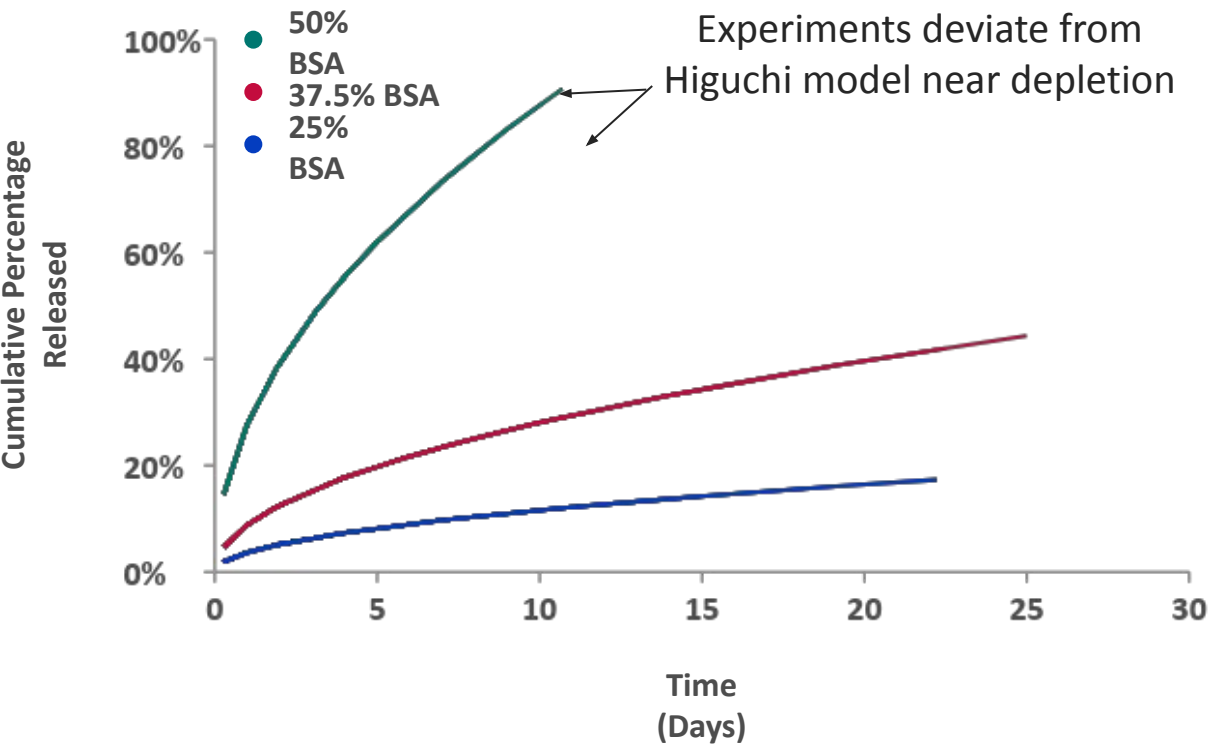
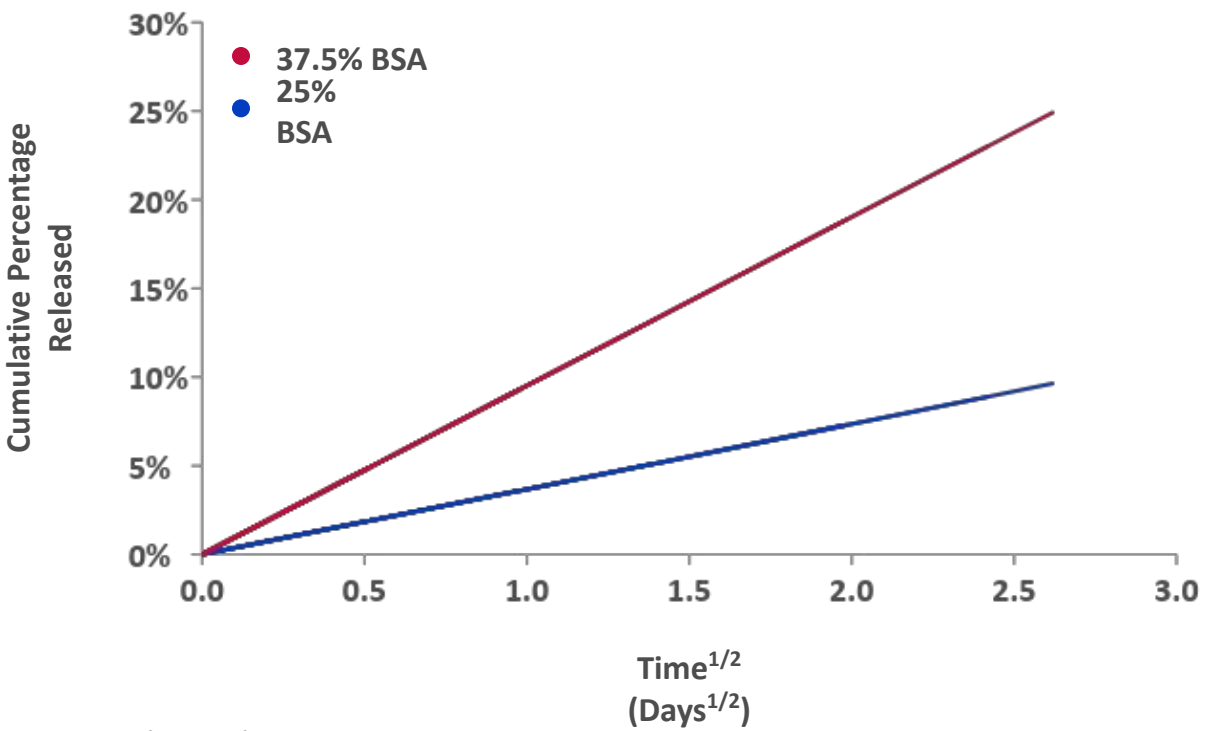
Long-Term BSA Release Can be Predicted from EVA

Extrapolating from Seven Days of Data

Samples exhibit small initial burst release that reduces the quality of the fit

Bovine serum albumin
MW ≅ 66K g/mol





Data: Rhine, Hsich, Langer. *J. Pharm. Sci.* **69**, 265 (1980).

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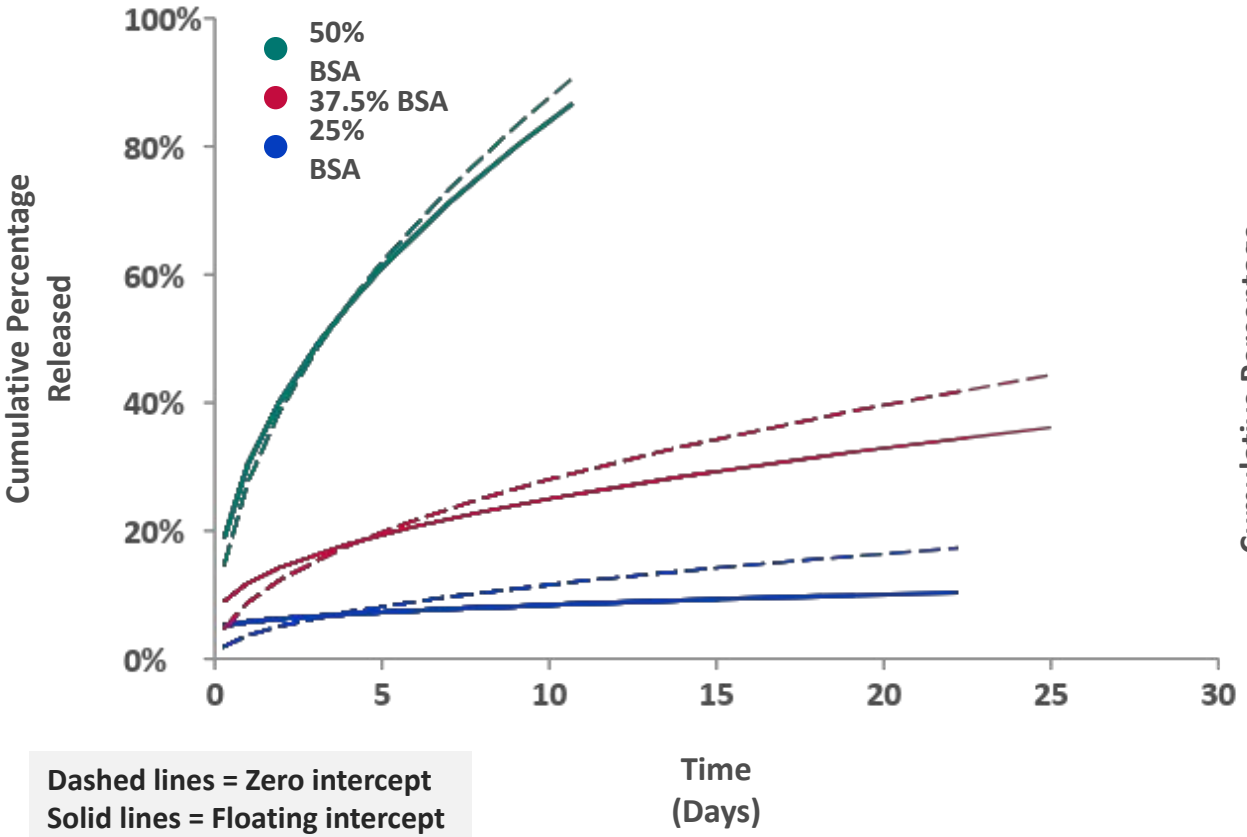
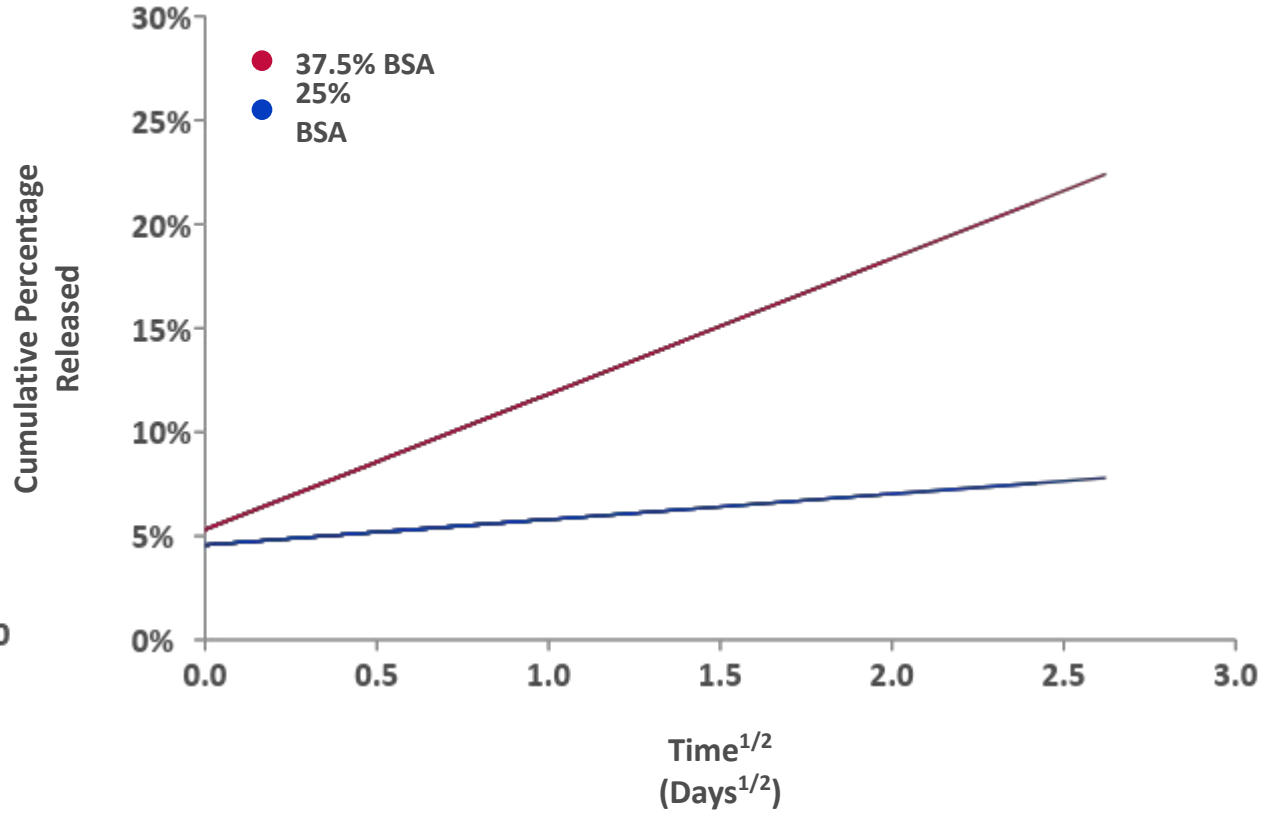
Long-Term BSA Release Can be Predicted from EVA

Treating the y-Intercept as a Fitting Parameter Improves the Extrapolation

Bovine serum albumin
MW ≅ 66K g/mol





Dashed lines = Zero intercept
Solid lines = Floating intercept

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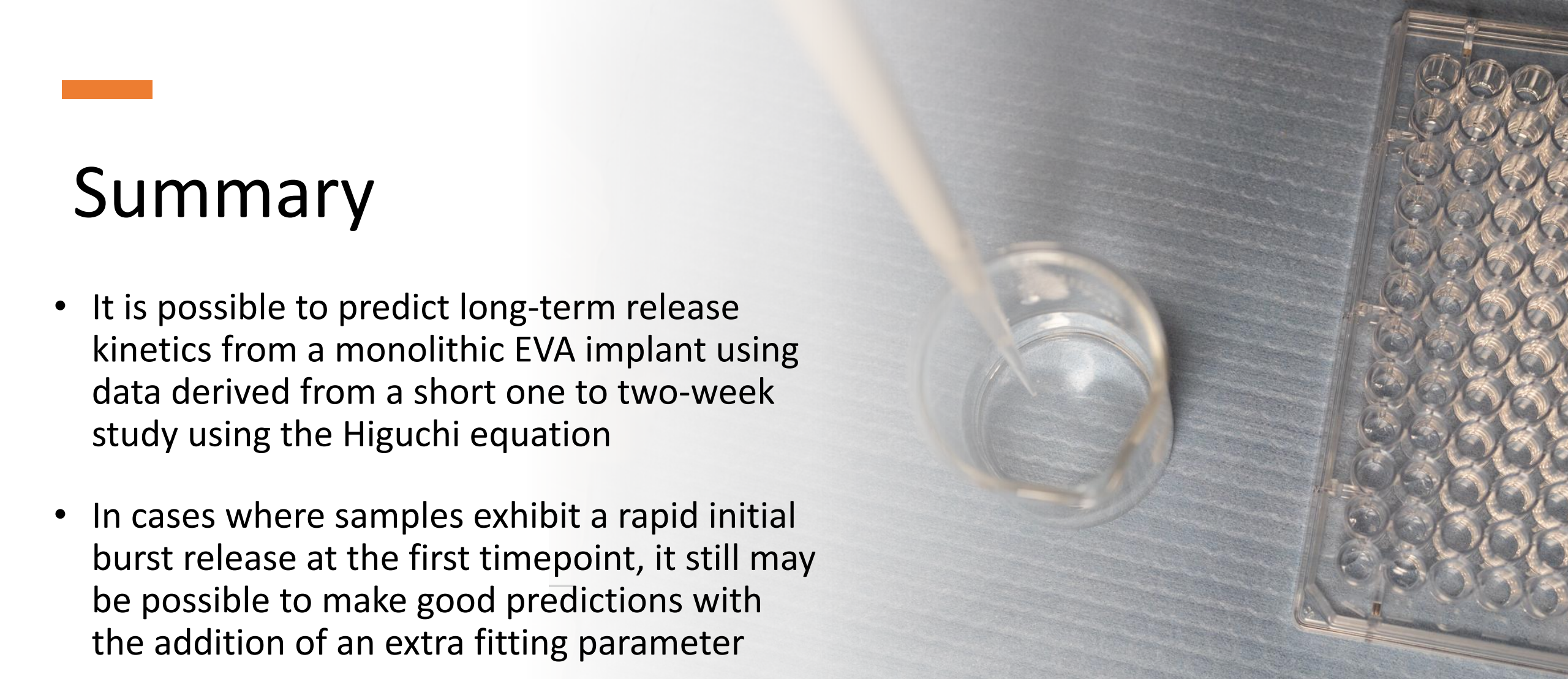
Summary

- It is possible to predict long-term release kinetics from a monolithic EVA implant using data derived from a short one to two-week study using the Higuchi equation
- In cases where samples exhibit a rapid initial burst release at the first timepoint, it still may be possible to make good predictions with the addition of an extra fitting parameter



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