Hybrid Modelling and AI to Predict Barrier Membrane Controlled Drug Release from Multiparticulates

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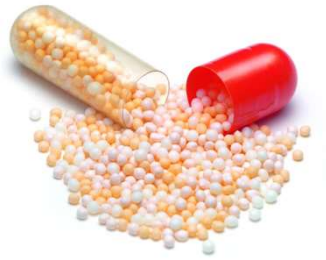
Why this Matters



- Ethylcellulose-based barrier membrane coatings remain the gold standard for oral extended-release multiparticulates
- But development has traditionally required extensive iterative trial-and-error testing
- Each new active pharmaceutical ingredient (API) typically demands fresh dissolution experiments because empirical relationships between formulation and release lack transferability
- Time-consuming formulation and dissolution testing often requires weeks or months per batch making rapid formulation screening impractical
- A predictive framework could dramatically accelerate speed-to-market by enabling computational-led formulation design

The Challenge

- CMAs of ER polymers and excipients are well understood but limited to characterizing one specific formulation
- Any change to API descriptors or transport alters the relationship between geometric parameters and drug release requiring re-characterization through additional experimentation.
- Existing models cannot extrapolate to new molecules because they lack a universal descriptor of drug transport
- Need **a transferable parameter** that works across different APIs and coating formulations to enable predictive design

Measure
Experimental dissolution profiles

↓

Reduce
Transform to kinetic constant k

↓

Isolate
Calculate apparent permeability (Papp)

↓

Predict
Train model for new APIs

The idea

- **Hybrid** modeling integrates first-principles diffusion with machine learning (ML) to predict drug release from coated multiparticulates (MP)
- **Apparent permeability (Papp)** incorporates intrinsic film properties and kinetics as **system-specific lumped parameter**
- ML identifies key API **molecular descriptors** driving permeability enabling prediction
- Framework leverages historical dataset to establish underlying principles of drug transport

Why this matters?

Global Market Size (2023): $3.6 B

Regional Market Size (2023):

- North America: 29.6%
- Europe: 25.9%
- Japan: 5.6%
- India: 5.6%
- China: 4.4%

Market Growth Rate (CAGR, 2023 – 2033): 3.6%

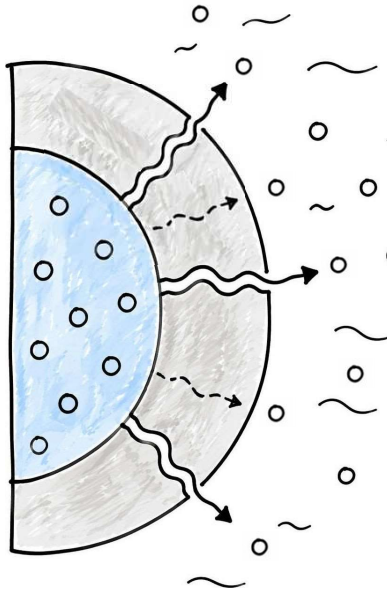
Market Size Forecast (2033): $5.2B

Mechanistic Framework

Fick's 1st law of diffusion:

$$J = \frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h}$$

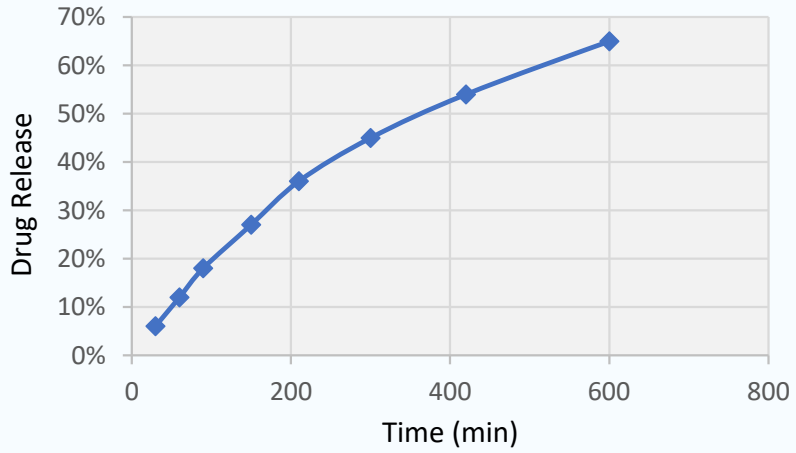
S = surface area (cm^2)
D = diffusion coefficient
h = thickness of barrier
C = concentration
K = partition coefficient
J = Flux



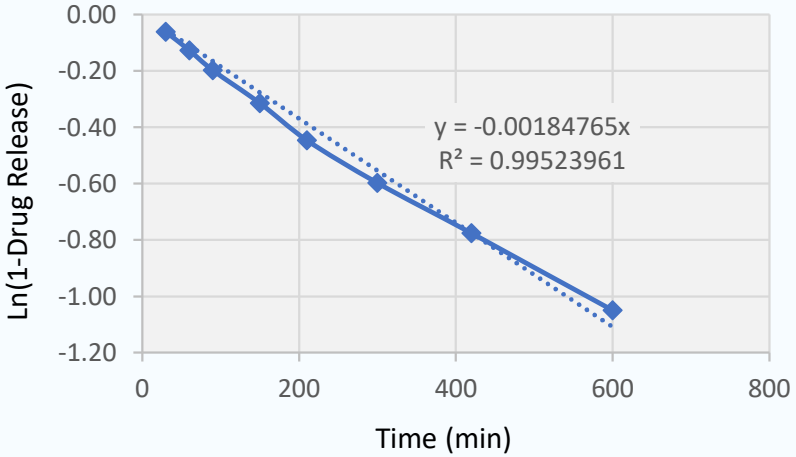
- Fick's law defines flux (*J*) as mass transfer rate determined by diffusion coefficient (*D*), surface area (*S*), partition coefficient (*K*), concentration gradient, and film thickness (*h*)[1]
- Surface area and film thickness are critical design variables known from prior work[2]
- Mechanistic model provides **structure**, **interpretability** and **constraints** while data-driven component handles complexities hard to derive analytically

***Image**: Generated by Microsoft Copilot and edited by C. Vesey*

Kinetic Simplification



First Order Kinetic Transformation

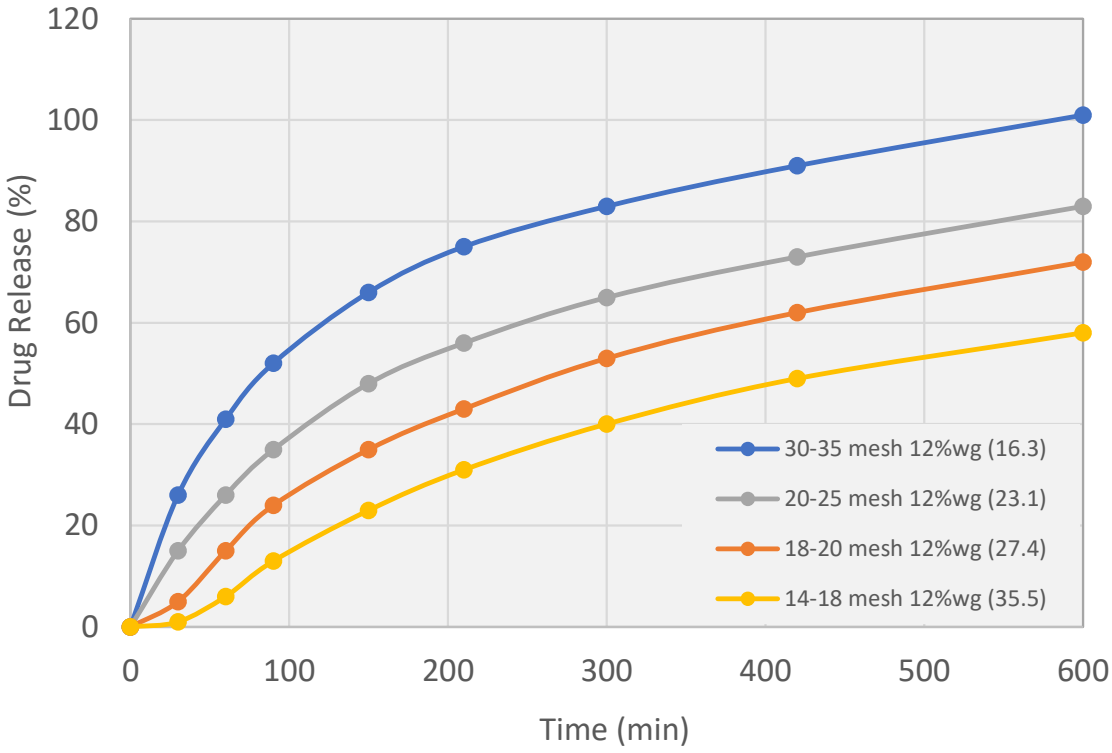


- Dissolution profiles for MP follow first-order release kinetics
- Equation ln(1 - Drug Release) dissolution data into linear relationship where slope equals first-order rate constant k
- k captures the overall release behavior for each formulation providing simplified mathematical representation
- Linear transformation enables isolation of rate-limiting transport parameters

$$\frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h}$$

$$\frac{k \cdot h}{S} = D \cdot P = P_{app}$$

- Substrate size and density change the coating surface area
- Coating weight gain or density changes the amount of coating applied to the substrate
- Together these result in the film thickness and surface area of the final coated particle.



Reference: *Comparative Study of Theoretical Versus Actual Weight Gain for a Surelease® Barrier Membrane on Coated Pellets*, Colorcon, AAPS, 2004

Enabling Technologies

- Computational design tools
  - Rapid calculation of product characteristics
- Dynamic Image Analysis and PAT
  - At-line instrument measurement
  - In-line fluid bed measurements

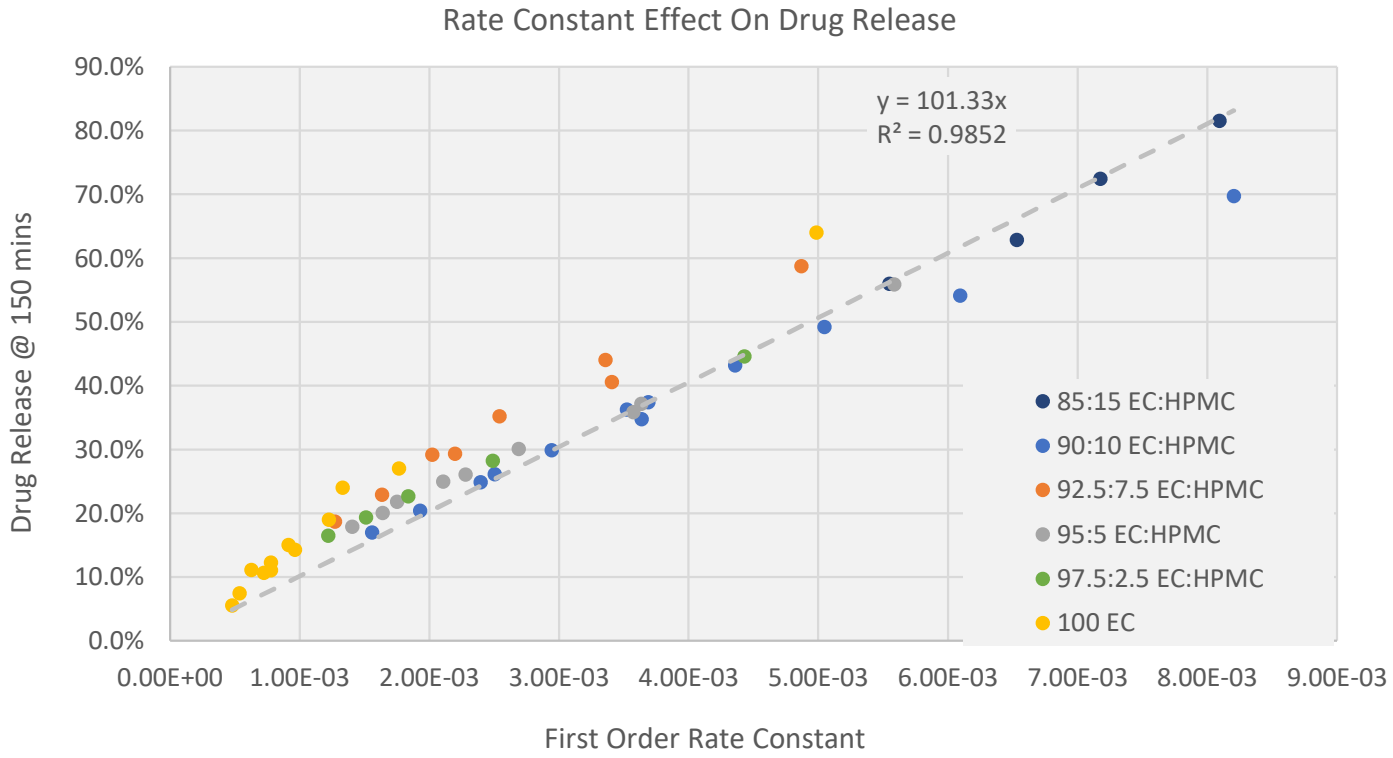
Images courtesy of InnoGlobal Technology

Data Set

- Historical dataset included 93 distinct formulations utilizing 10 unique active ingredients
- Molecular diversity covered hydrophilic to lipophilic compounds with wide range of solubilities and molecular weights
- Formulation variables included geometric parameters from small to large surface areas, thin to thick coatings, and pore-former concentrations from zero to twenty percent
- Release profiles ranged from rapid 1.5-hour to extended 50-hour dissolution across ER targets

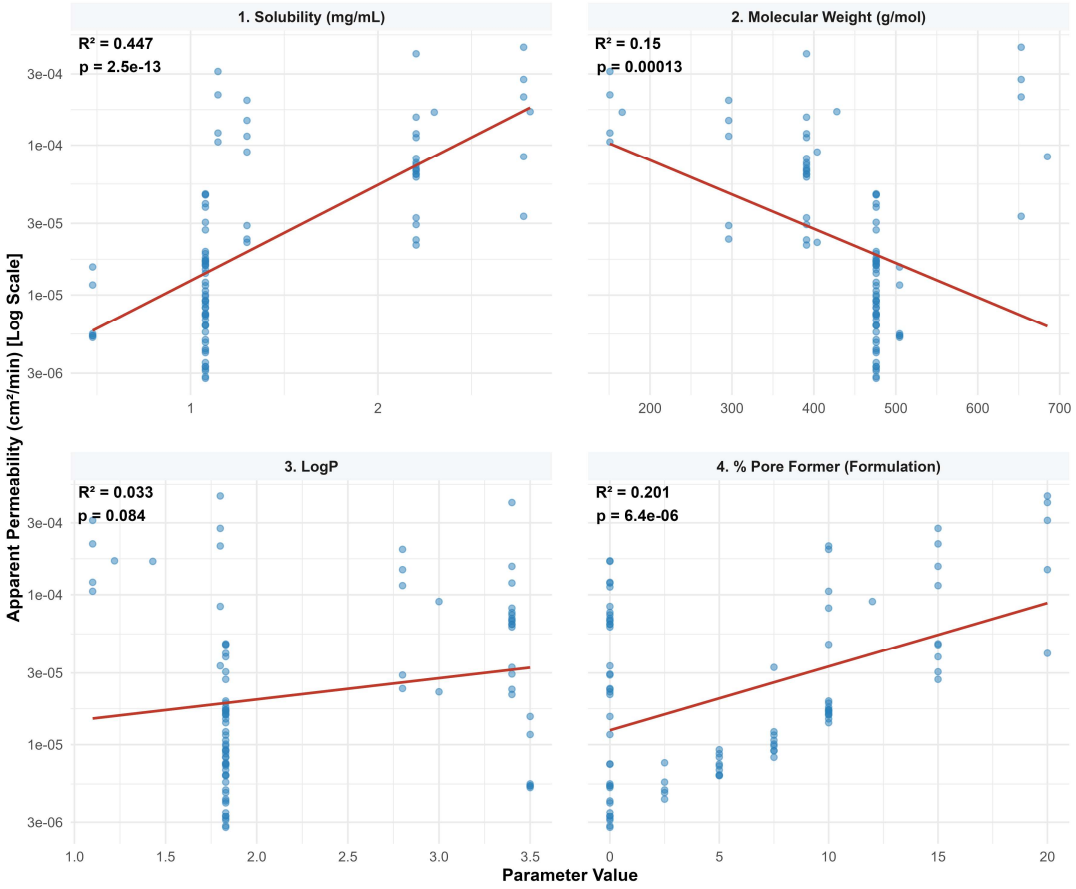
Parameter	Range
API Molecular Weight	75 - 685 g/mol
API Solubility	3 - 500 mg/mL
LogP Range	-3.5 to 3.5
Surface Area	7.85 - 3485.67 cm^2
Film Thickness	1 - 55 µm
Pore-Former Level	0 - 20%
Release Time (T80)	1.5 - 50.3 hours

Rate Constant Effect on Drug Release



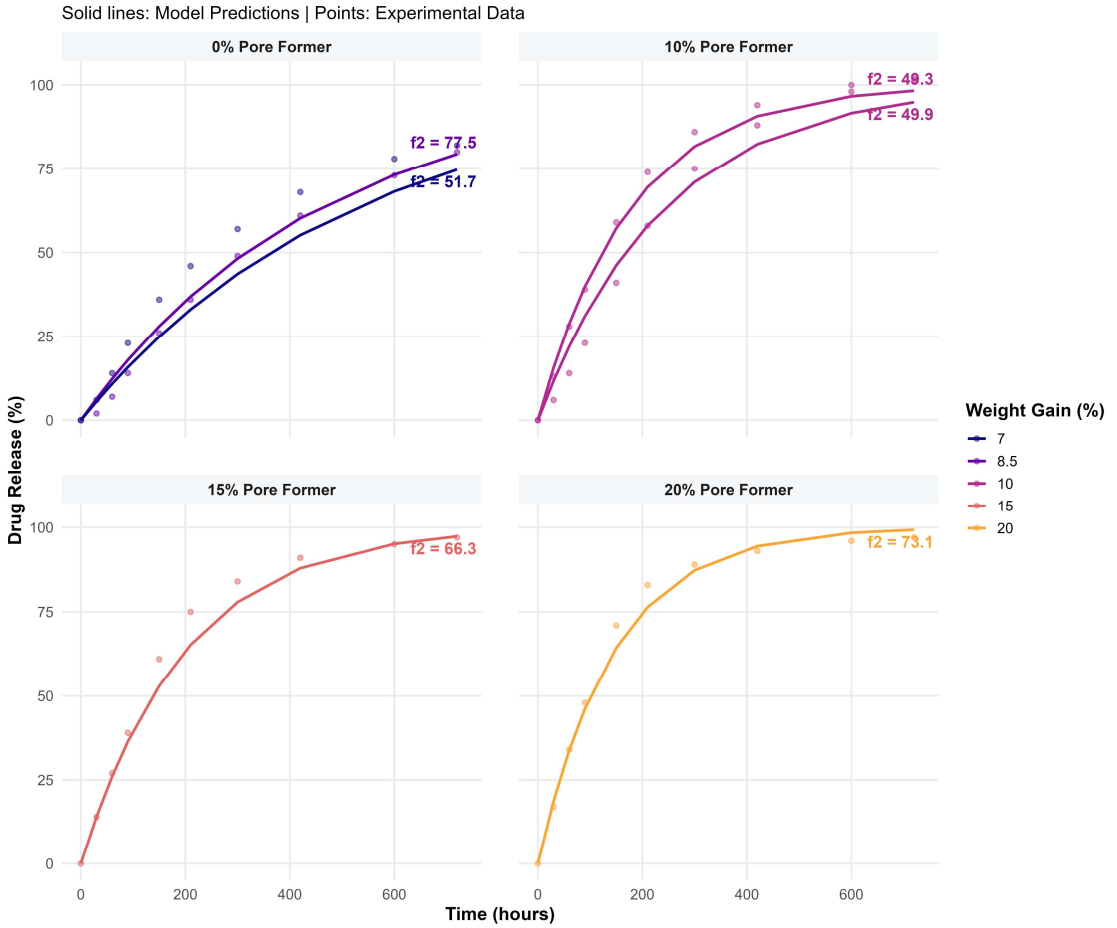
What drives Papp

- Regression analysis revealed **solubility** and **molecular weight** as primary drivers of Papp enabling quantification of their effects
- Smaller, more hydrophilic actives exhibited highest apparent permeability while larger, more lipophilic actives showed significantly lower transport rates
- Accounting for these factors isolated coating's apparent permeability (Papp) providing baseline for comparing performance across different formulations



Validation Results

- Validation used six unique formulations to test predictive power on API not included in dataset
- Model estimated Papp values from molecular descriptors and formulation variables, combined with calculated S/h ratios to generate predicted dissolution curves
- Predicted profiles showed strong alignment with empirical data across all six validation formulations capturing nuances of varying coating weights (h) and pore-former (permeability) concentrations
- Successful extrapolation to new API demonstrates model's ability to predict release for untested compounds based on molecular properties alone



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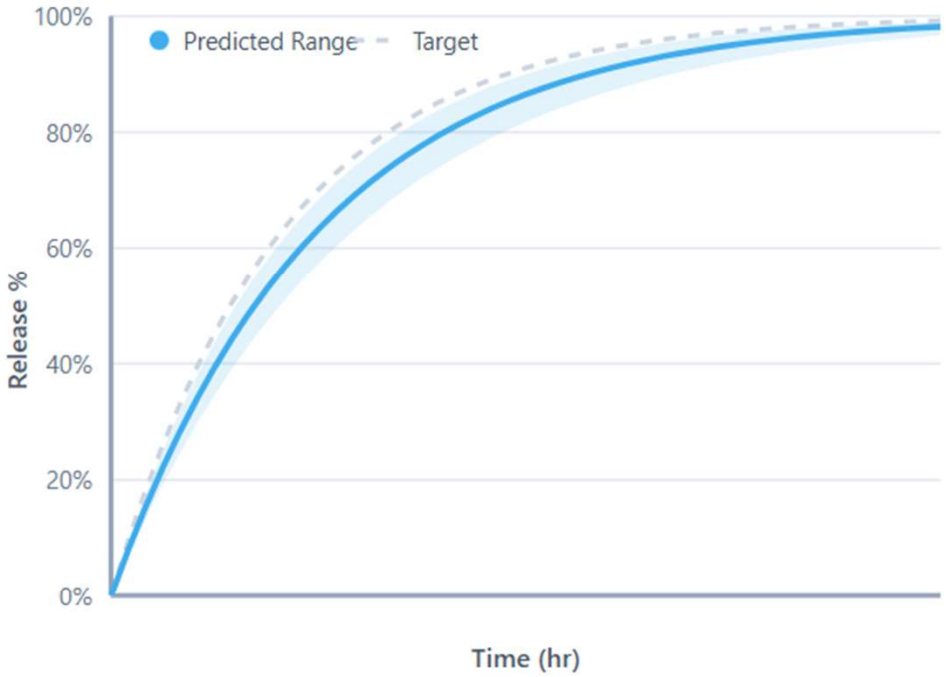
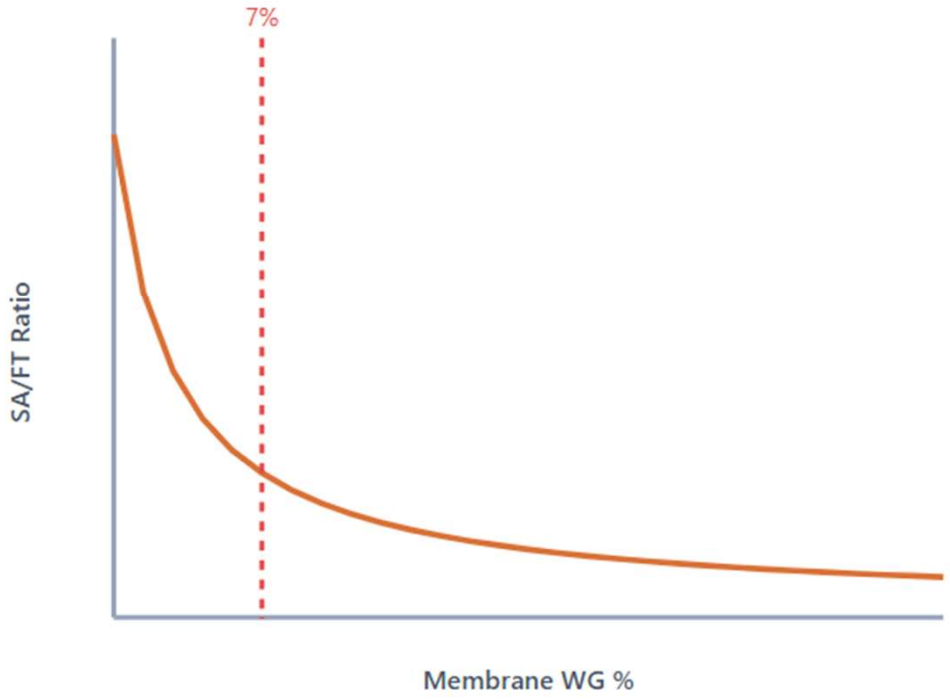
Dissolution Profile



SA/FT Stability Sensitivity



Limitations

- Manufacturing process conditions including spray rates, temperatures, and atomization pressures directly influence film formation and coalescence but not yet incorporated
- Process variables affect resulting membrane morphology which in turn impacts permeability and drug release kinetics from coated systems
- Current model predicts well for defined coating formulations but cannot yet account for batch-to-batch variability introduced by process parameter changes
- Model assumes fully coalesced, uniform films which may not reflect real-world coating defects or morphological variations from processing conditions

Key Takeaways

- Progression from classical mechanistic models to hybrid approaches a natural evolution
- Maintains the scientific credibility while overcoming the API specificity and iteration
- Methodology accelerates development by enabling computational screening before lab work providing speed-to-market advantage for new compounds

Areas to Explore

- Industry feedback
- Integration of manufacturing process conditions to enhance prediction accuracy
    - Process directly influence film formation, coalescence (latex), density, and membrane morphology
- Additional trial work at outer edges of molecular descriptors
- Incorporation of lag time
- Expand model to include formulation variants
- Build a user-friendly interface and rollout to users

References

- A. Martin, P. Bustamante, and A.H.C. Chun (1993). Diffusion and Dissolution, in Physical Pharmacy, Fourth Edition, Lea and Febiger, Philadelphia, London.
- Patel, P., Godek, E., & O'Callaghan, C. (2017). My Dosage Design Tool Predicts, Process Analytical Technology Confirms Film Thickness of Fully Formulated Aqueous and Organic Ethylcellulose Coating. AAPS Poster Reprint. Colorcon, PA, USA; Glatt Air Techniques, NJ, USA; Innopharma Technology, Dublin, Ireland
- Tang, L., Wigent, R. J., & Schwartz, J. B. (1999). Drug Release from Film-Coated Chlorpheniramine Maleate Nonpareil Beads: Water Influx and Development of a New Drug Release Model. Pharmaceutical Development and Technology, 4(4), 481–490.

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Questions?

Using Hybrid Modelling and AI to Predict Barrier Membrane Controlled Drug Release

Poster #143, Pavilion 2

Artificial Intelligence and Predictive Models

Colorcon Booth #23