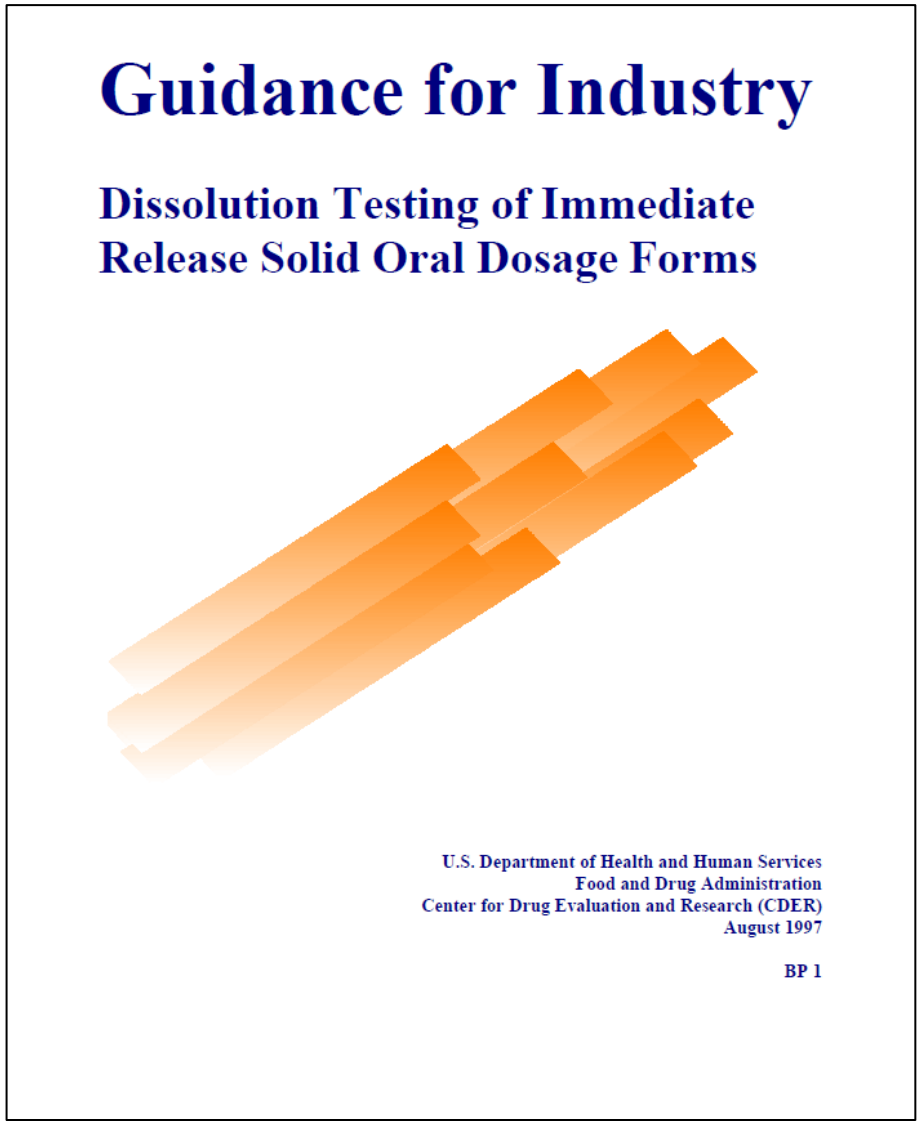
Underutilized and recent laboratory and data analysis approaches to assess oral biopharmaceutics risk

James E. Polli

University of Maryland, Baltimore

jpolli@rx.umaryland.edu

1997 FDA Guidance

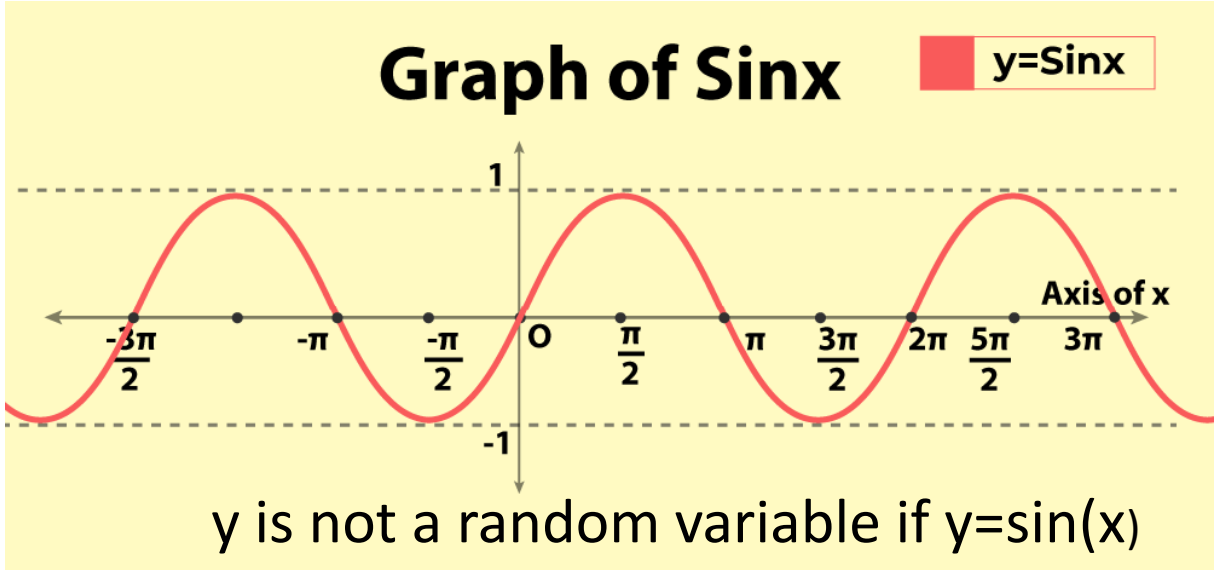


- Important document, esp at the time
  - Many elements incorporated into subsequent guidance (e.g. 2021 M9 BCS, 2018 IR disso testing of high solubility drugs, 2020 PBBM), further reflecting it importance, but …
- Does not fully reflect current thinking and best practices
- Raines K, et al. (2023): Drug Dissolution in Oral Drug Absorption: Workshop Report. AAPS J. 25:103.

Laboratory and data analysis tools

- Deconvolution and dissolution/permeation apparatus
  - Elucidating rate limiting step
- Additional promising tools: BioGIT system and lipolysis
- Prediction of in vitro dissolution
  - Surfactant systems
  - Transient pH film model
- Biorelevant media
  - Impact of low micelle diffusivity
  - Mimic solubility in biorelevant media or dissolution in biorelevant?
- ASD IVIVC: in vitro trituration of tablets to mimic in vivo
- Predicting ASD dissolution via solvent penetration rate model

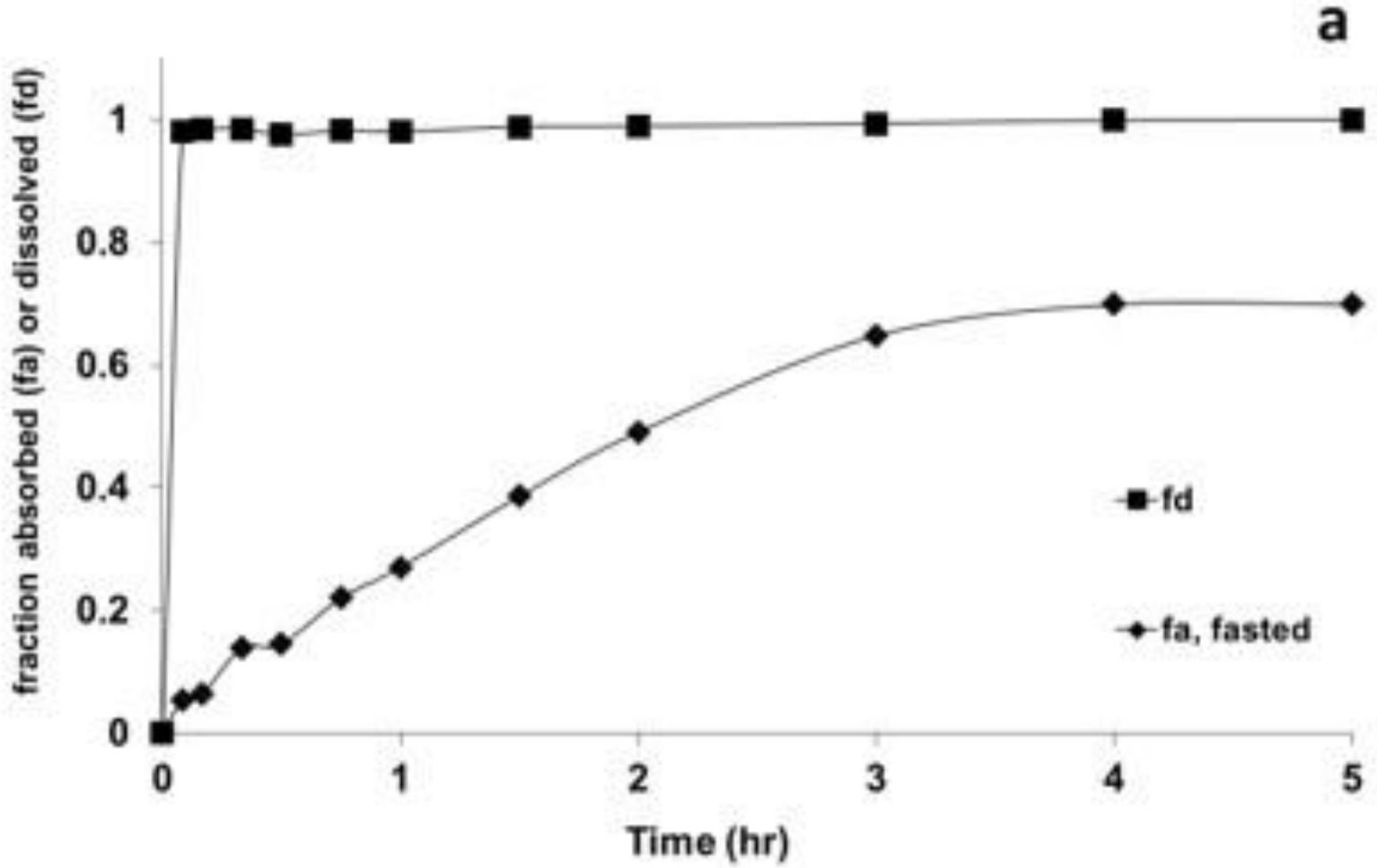
Correlation



y is not a random variable if y=sin(x)

- Correlation - "degree of relationship between two random variables"
  - e.g. assesses tightness of relationship
  - Kachigan, S.K. *Multivariate Statistical Analysis*; Radius Press, New York, 1991.
- "No correlation" is incorrect if x and y known to be related via y=sin(x)
- "No correlation" is incorrect if dissolution known to be not rate limiting

Fraction absorbed and fraction dissolved profiles of Norvir powder



in vitro dissolution in
60mM polyoxyethylene 10 lauryl ether
(or 3.76 % w/v)

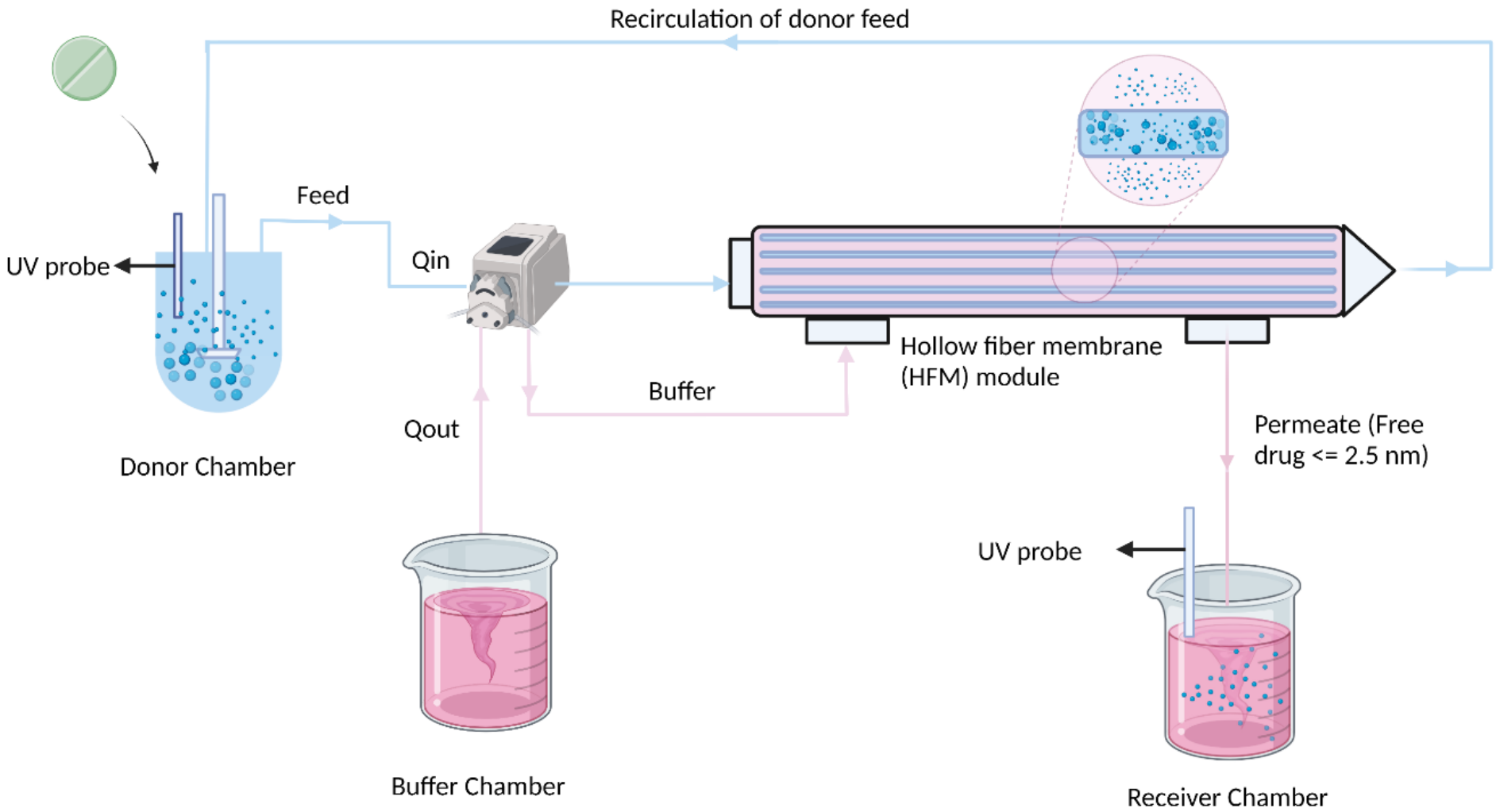
in vivo absorption
(= in vivo dissolution)

Oktay AN, Polli JE. Comparison of In Vitro and In Vivo Dissolution of Norvir Oral Powder: In Vivo Relevance of a too Rapid In Vitro Dissolution Test. Turk J Pharm Sci. 2025 Sep 5;22(4):270-278.

Oral drug absorption from tablets and capsules

- Need for dissolution/permeation apparatus
- Can involve dynamic inter-play, where drug permeation needed for additional drug dissolution
  - Many drugs are poorly soluble, but well absorbed

Dissolution-hollow fiber membrane (D-HFM) system



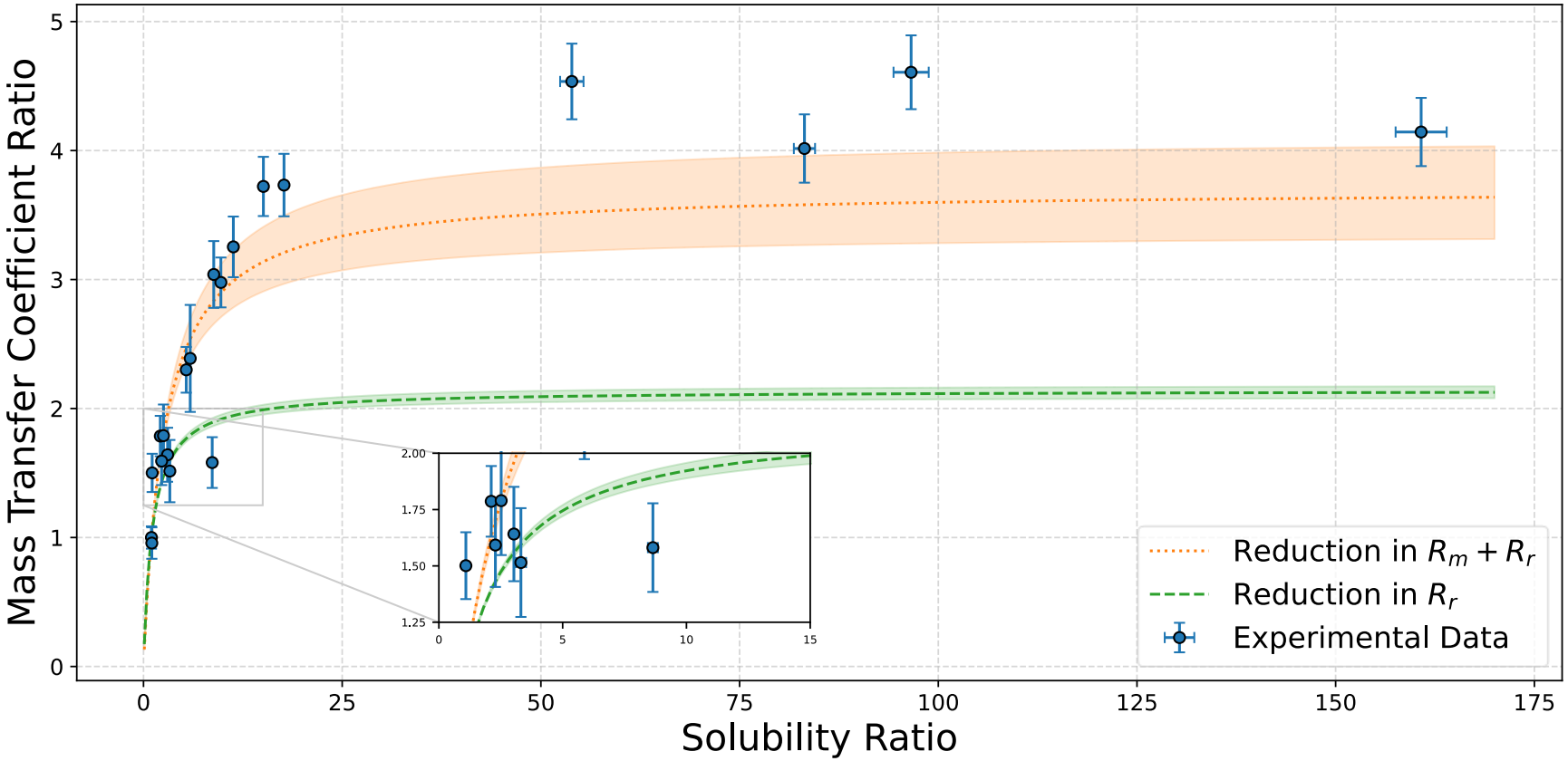
D-HFM study scope

- Adhikari A, Seo PR, Polli JE. Characterization of Dissolution-Permeation System using Hollow Fiber Membrane Module and Utility to Predict in Vivo Drug Permeation Across BCS Classes. J Pharm Sci. 2022 Nov;111(11):3075-3087.
  - Set-up and identify permeation model
- Adhikari A, Seo PR, Polli JE. Dissolution-Hollow Fiber Membrane (D-HFM) System to Anticipate Biopharmaceutics Risk of Tablets and Capsules. J Pharm Sci. 2023 Mar;112(3):751-759.
  - Biopharm risk assessment of tablets and capsules
- Patel RP, Taylor LS, Polli JE. Impact of drug incorporation into micelle on reduced griseofulvin and meloxicam permeation across a hollow fiber membrane. J Pharm Sci. 2025 Jan;114(1):402-415.
  - Surfactant in donor effect
- Murray JD, Patel RP, Bennett-Lenane H, O'Dwyer PJ, Griffin BT, Polli JE. Reduced-Resistances Model for Enhanced Drug Permeation via a Solubilizing Receiver Medium: A Mechanistic Study with Hollow Fiber Membranes. Mol Pharm. 2026 Mar 2;23(3):2036-2049.
  - Surfactant in receiver effect

D-HFM assessment to date

- Studies of drug pre-dissolved (i.e. HFM only)
  - Favorable Area/Volume ratio, although another 10-fold would be nice
    - A/V ratio of D-HFM = 1.15 cm^{-1} if V=100ml
    - In vivo human A/V ratios have been estimated to be 11 cm^{-1} , 2.2 cm^{-1} and 1.9 cm^{-1}
  - All drug are highly permeable (value similar to Caco-2 high permeability)
    - Not problematic if focus is dissolution of high permeability drugs
- In vitro D-HFM system has utility to predict in vivo biopharmaceutics risk of tablet and capsule performance
- Reduced-resistances model to analyze data involving surfactants in medium

Reduced-resistance model for effect of solubilization (in receiver)



$$\frac{1}{P_{app}} = \frac{1}{P_d} + \frac{1}{HP_m} + \frac{1}{HP_r}$$

H= partition coefficient

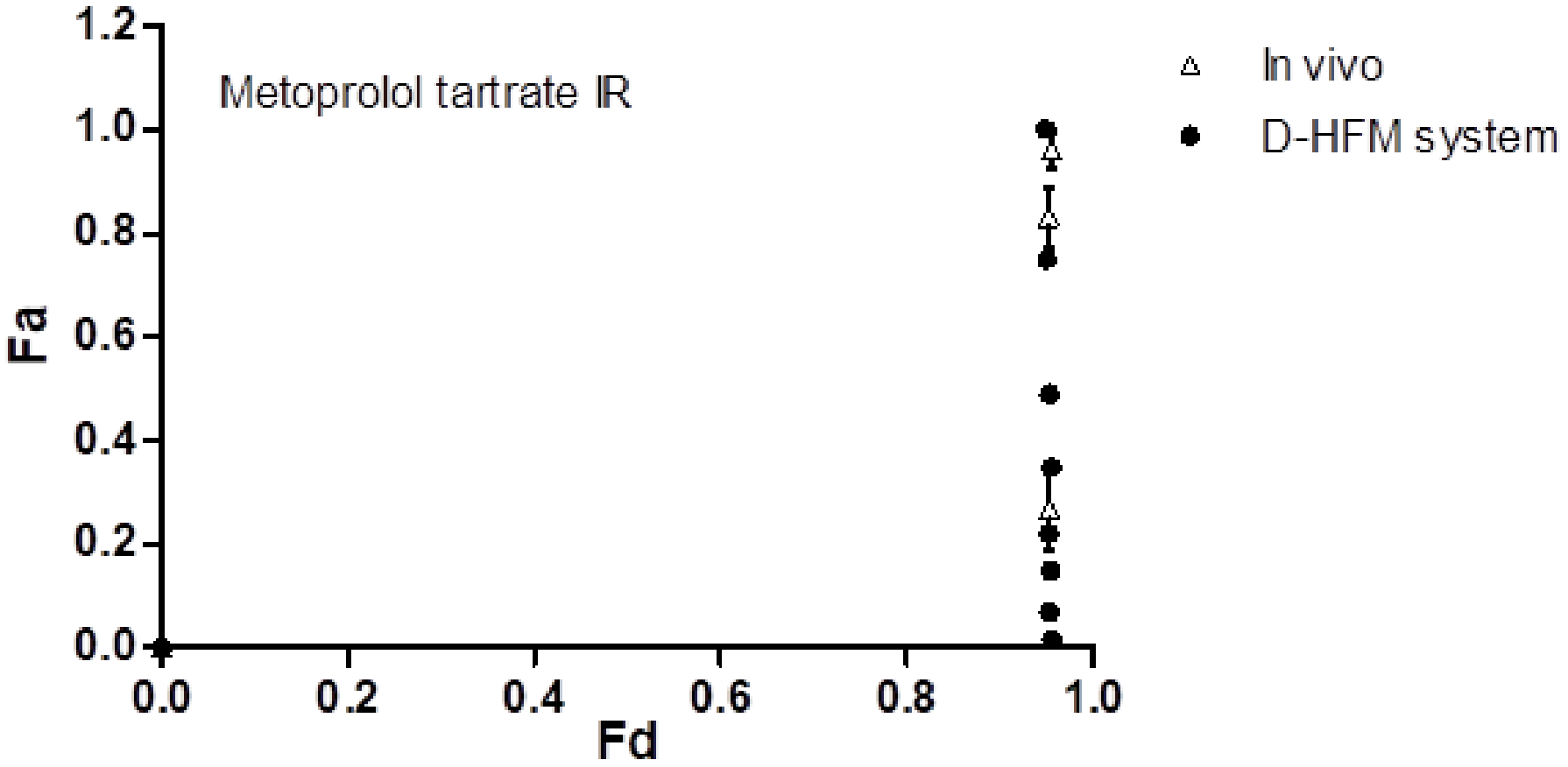
Murray JD, et al. Reduced-Resistances Model for Enhanced Drug Permeation via a Solubilizing Receiver Medium: A Mechanistic Study with Hollow Fiber Membranes. Mol Pharm. 2026 Mar 2;23(3):2036-2049.

Comparison of In Vitro versus In Vivo for Biopharmaceutics Risk Assessment

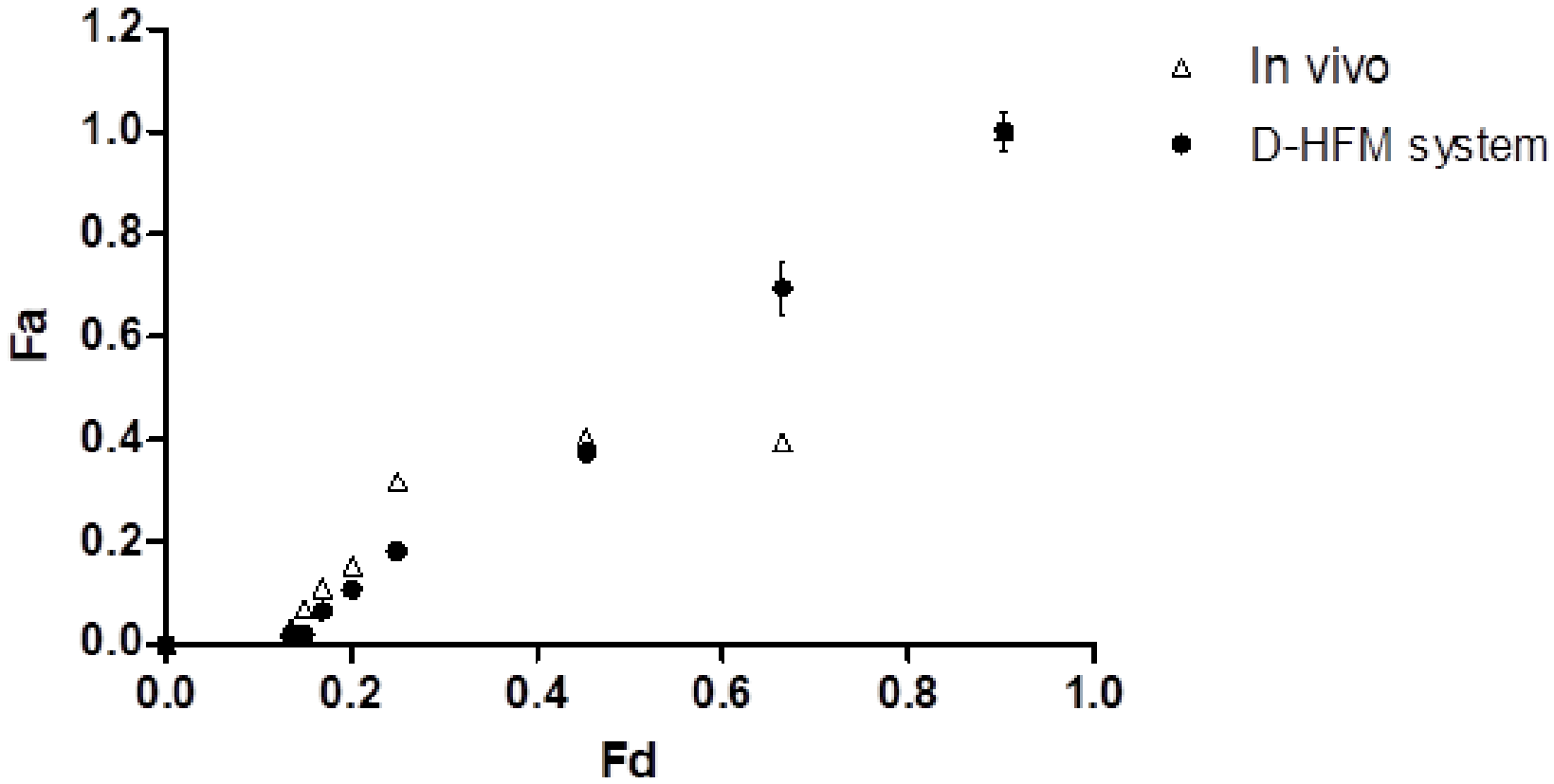
Drug product	Visual observation from in vivo Levy-Polli plot	Visual observation from in vitro D-HFM Levy-Polli plot
Metoprolol tartrate IR	permeation rate limited	permeation rate limited
Lamotrigine IR	mixed rate limited	permeation rate limited
Ranitidine HCl IR	permeation rate limited	permeation rate limited
Piroxicam IR	permeation rate limited	permeation rate limited
Metoprolol succinate ER	dissolution rate limited	dissolution rate limited

Adhikari A, Seo, PR, Polli, JE. (2022): Dissolution-Hollow Fiber Membrane (D-HFM) system to anticipate biopharmaceutics risk of tablets and capsules. DOI: 10.1016/j.xphs.2022.09.030. J Pharm Sci. 112:751-759.

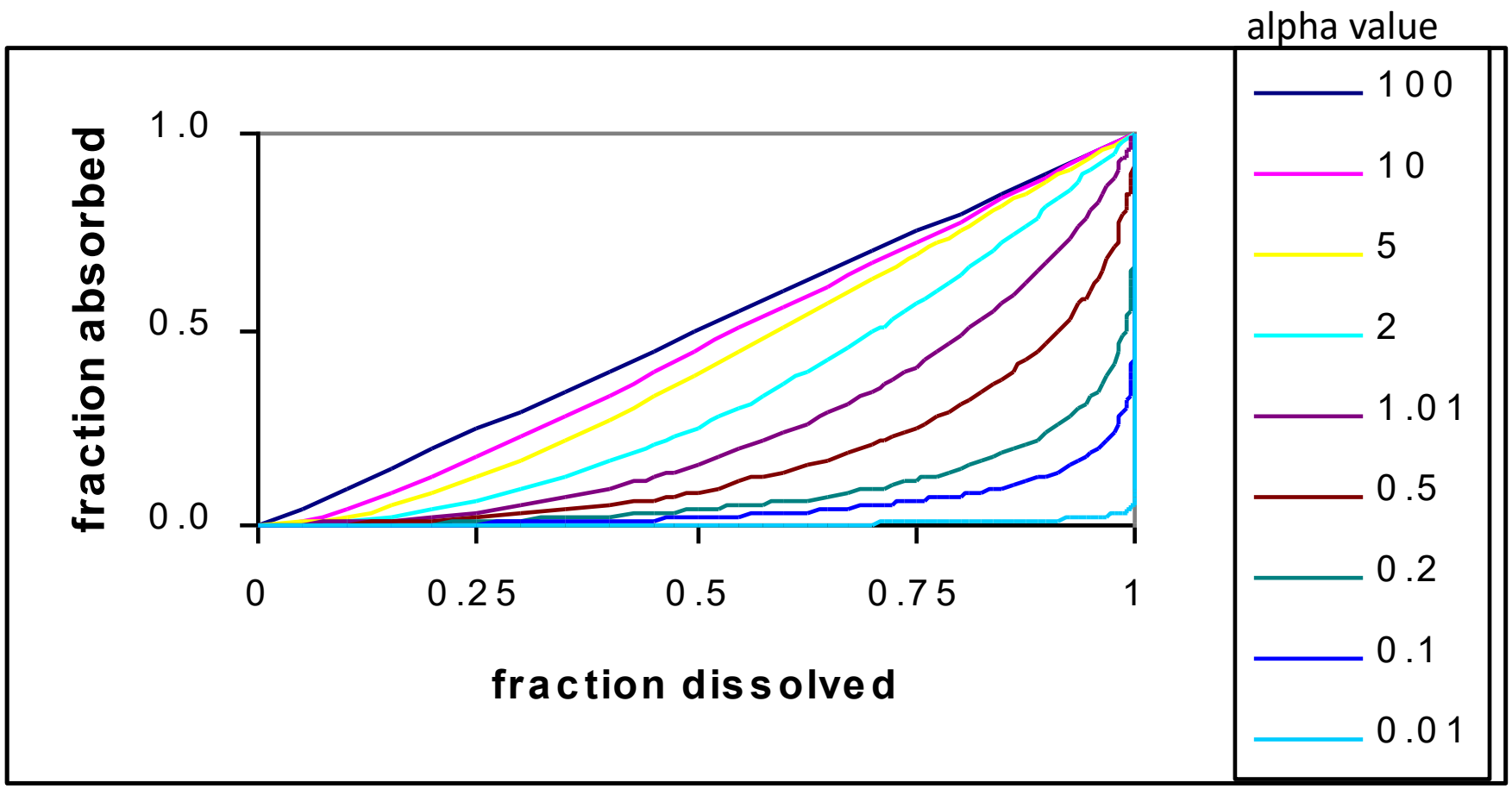
Levy-Polli plot of metoprolol IR tablet from in vivo clinical study and from in vitro D-HFM system



Levy-Polli plot of metoprolol ER tablet from in vivo clinical study and from in vitro D-HFM system



Deconvolution-based IVIVR model



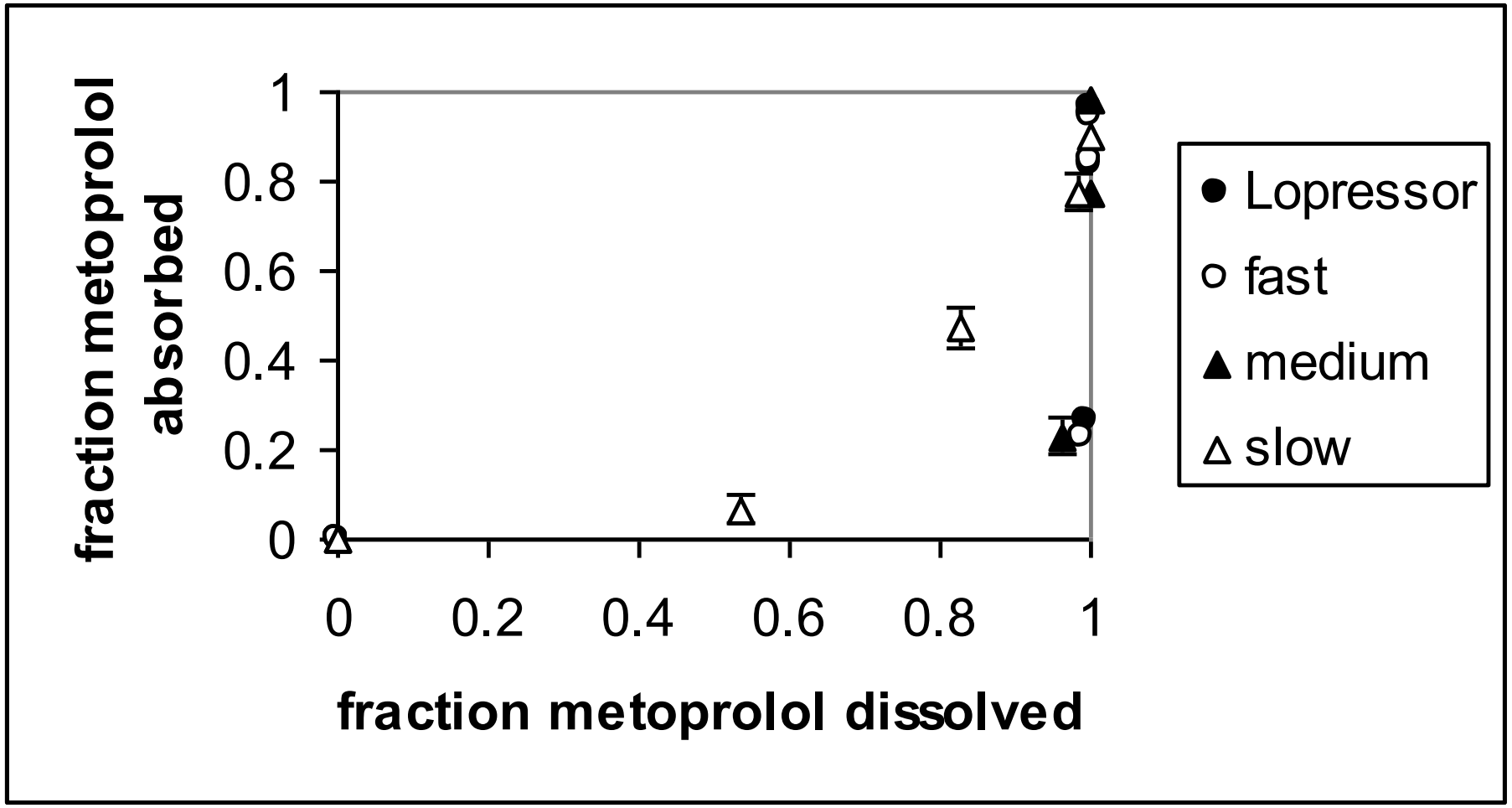
$$\alpha = \frac{k_p^{app}}{k_d}$$

Polli, J.E., Crison, J.R., and Amidon, G.L. (1996): A novel approach to the analysis of in vitro-in vivo relationships. *J. Pharm. Sci.* **85:**753-760

$$F_a = \frac{1}{f_a}\left(1 - \frac{\alpha}{\alpha - 1}\left(1 - F_d\right) + \frac{1}{\alpha - 1}\left(1 - F_d\right)^{\alpha}\right)$$

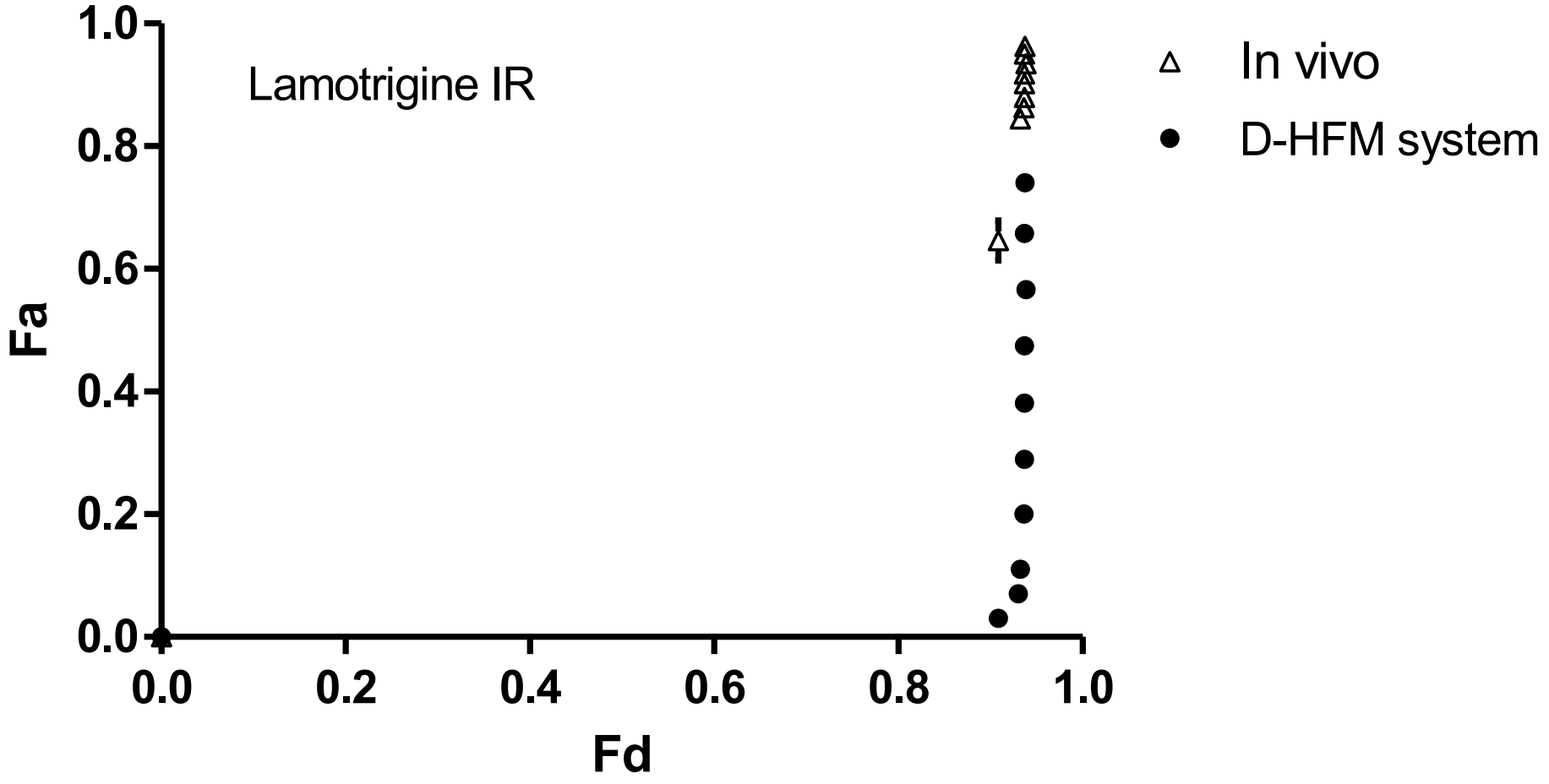
USP Level A is a special (linear) case where $f_a = 1$ and $\alpha >> 1$, such that $F_a = F_d$.

Metoprolol IR IVIVRs



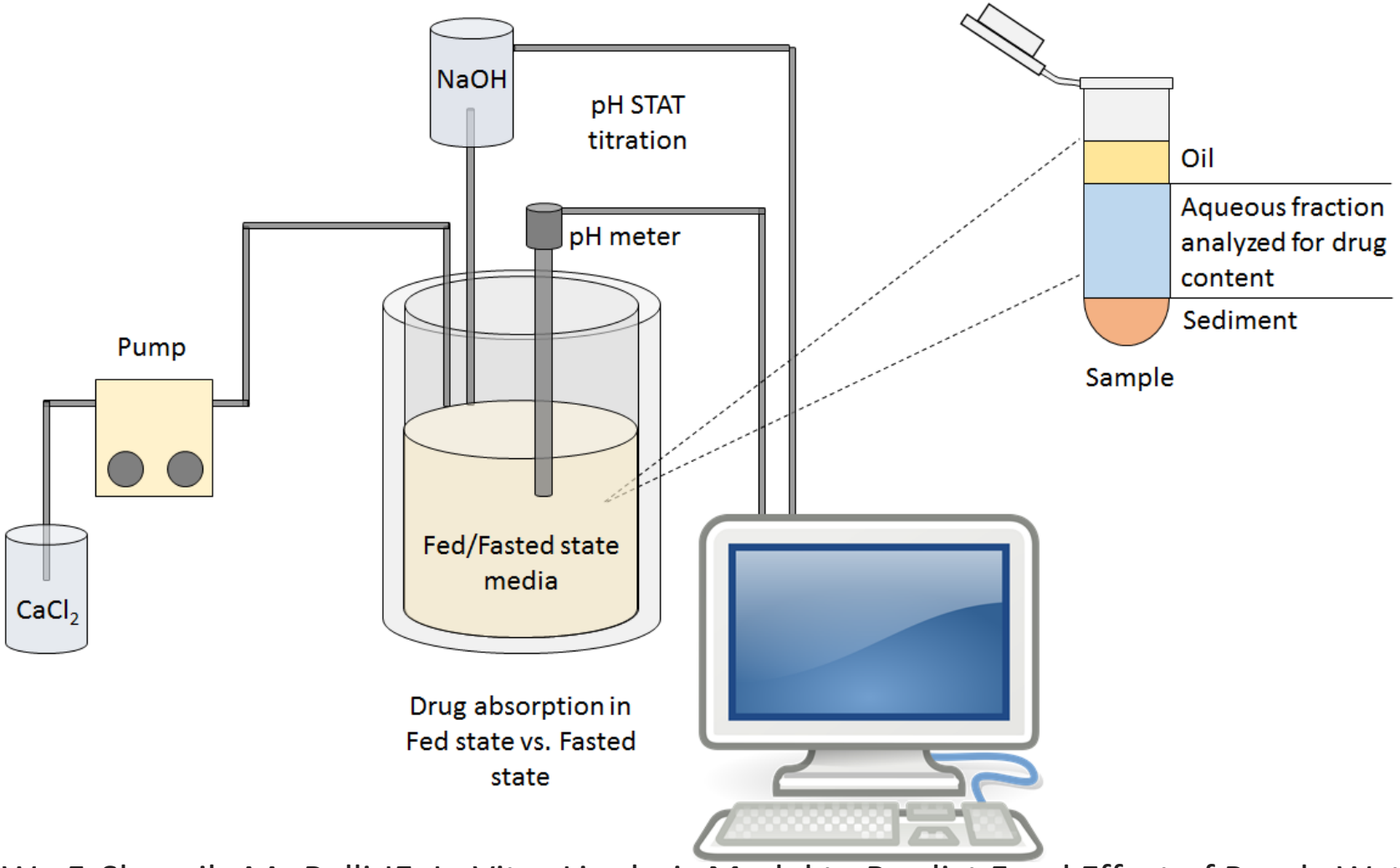
Polli, J.E., Rekhi, G.S., Augsburger. L.L., and Shah, V.P. (1997): Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. *J. Pharm. Sci*. **86**:690-700.

Levy-Polli plot of lamotrigine IR tablet from in vivo clinical study and from in vitro D-HFM system



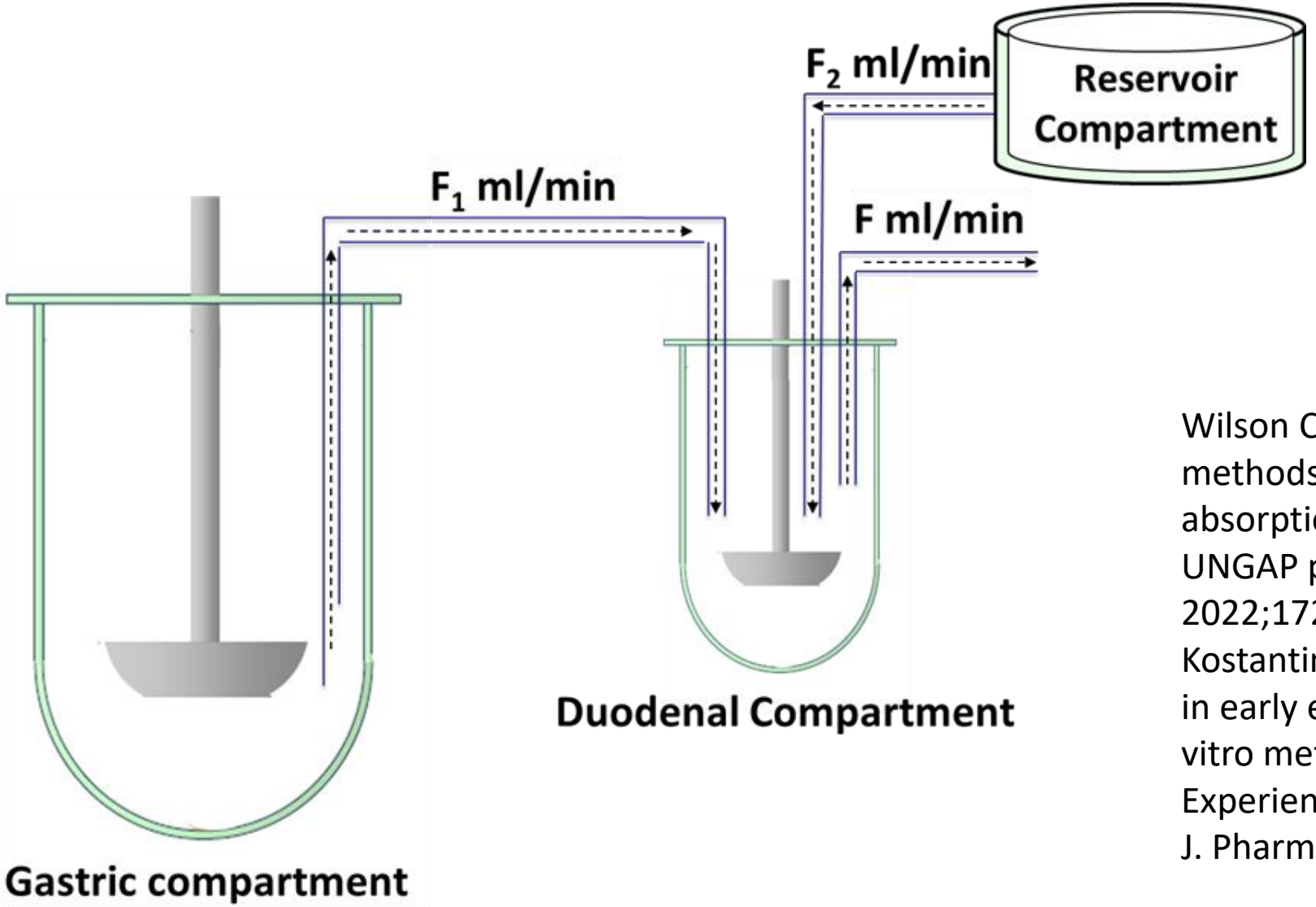
Possible to downgrade biopharmaceutics risk from medium to low for this BCS Class IIb?

In vitro lipolysis model



Patel RP, Cristofoletti R, Wu F, Shoyaib AA, Polli JE. In Vitro Lipolysis Model to Predict Food Effect of Poorly Water-Soluble Drugs Itraconazole, Rivaroxaban, and Ritonavir. J Pharm Sci. 2024 Aug;113(8):2361-2373.

BioGIT system for early exposure



Wilson CG, et al. Integration of advanced methods and models to study drug absorption and related processes: An UNGAP perspective. Eur J Pharm Sci. 2022;172:106100.
Kostantini C., et al. Screening for differences in early exposure in the fasted state with in vitro methodologies can be challenging: Experience with the BioGIT system. J. Pharm. Sci. 112:2240-2248 (2023).

Prediction of in vitro dissolution (a/k/a Predictive dissolution modeling)

- To the authors' best knowledge, in vitro dissolution modeling in pharmaceutics has mainly been used for (1) early-stage formulation development or (2) real-time release testing (RTRt) in manufacturing.
- Zaborenko N, Shi Z, Corredor CC, Smith-Goettler BM, Zhang L, Hermans A, Neu CM, Alam MA, Cohen MJ, Lu X, Xiong L, Zacour BM. First-Principles and Empirical Approaches to Predicting In Vitro Dissolution for Pharmaceutical Formulation and Process Development and for Product Release Testing. AAPS J. 2019 Feb 21;21(3):32. doi: 10.1208/s12248-019-0297-y. PMID: 30790200; PMCID: PMC6394641.

Prediction of in vitro dissolution profile (a/k/a Predictive dissolution modeling)

- Q: Why is prediction of in vitro dissolution profile a good idea, at least for medium and higher risk?
- A: Successful prediction of in vitro dissolution profile adds to product understanding.
  - Dumarey M, et al. Dissolution of Oral Solid Dosage Formulations: Surrogate Models and Real-time Release. AAPS J. 2025 Jun 27;27(5):115.
- Assumptions:
  - In vitro dissolution provides predictive insight to in vivo performance, including biodiscrimination.
  - An intent of conducting in vitro dissolution is to measure in vivo dissolution profile.
    - Use of (compositionally) biorelevant media suggests the aim to mimic in vivo dissolution.
  - Prediction of in vitro dissolution profile is more feasible (since less complex) than prediction of either in vivo dissolution profile or in vivo PK profile.
    - Less true (and much less important) for lower risk products where dissolution is not rate-limiting.

Film model for particle dissolution into surfactant solutions

$$\frac{dM}{dt} = -\frac{3D}{hr_0\rho} M_0^{\frac{1}{3}} M^{\frac{2}{3}} \left(C_s - \frac{M_0 - M}{V}\right)$$

$$\frac{dM}{dt} = -z M_0^{\frac{1}{3}} M^{\frac{2}{3}} \left(C_s - \frac{M_0 - M}{V}\right)$$

where M = mass of solid drug

M_0 = mass of total drug

C_s = solubility of drug into media

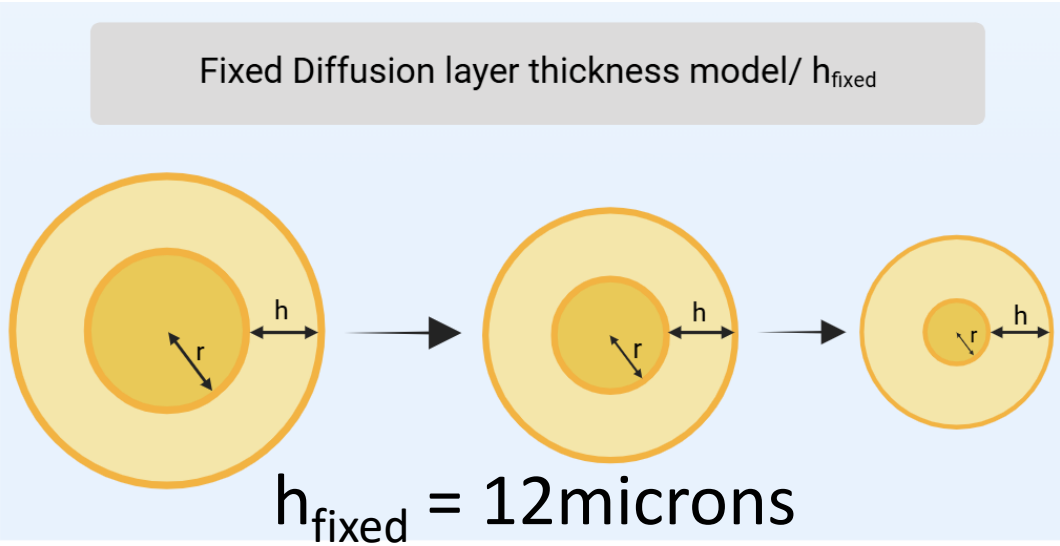
V = volume of media

D = diffusivity of micelle

r_0 = initial particle radius

ρ = density of drug

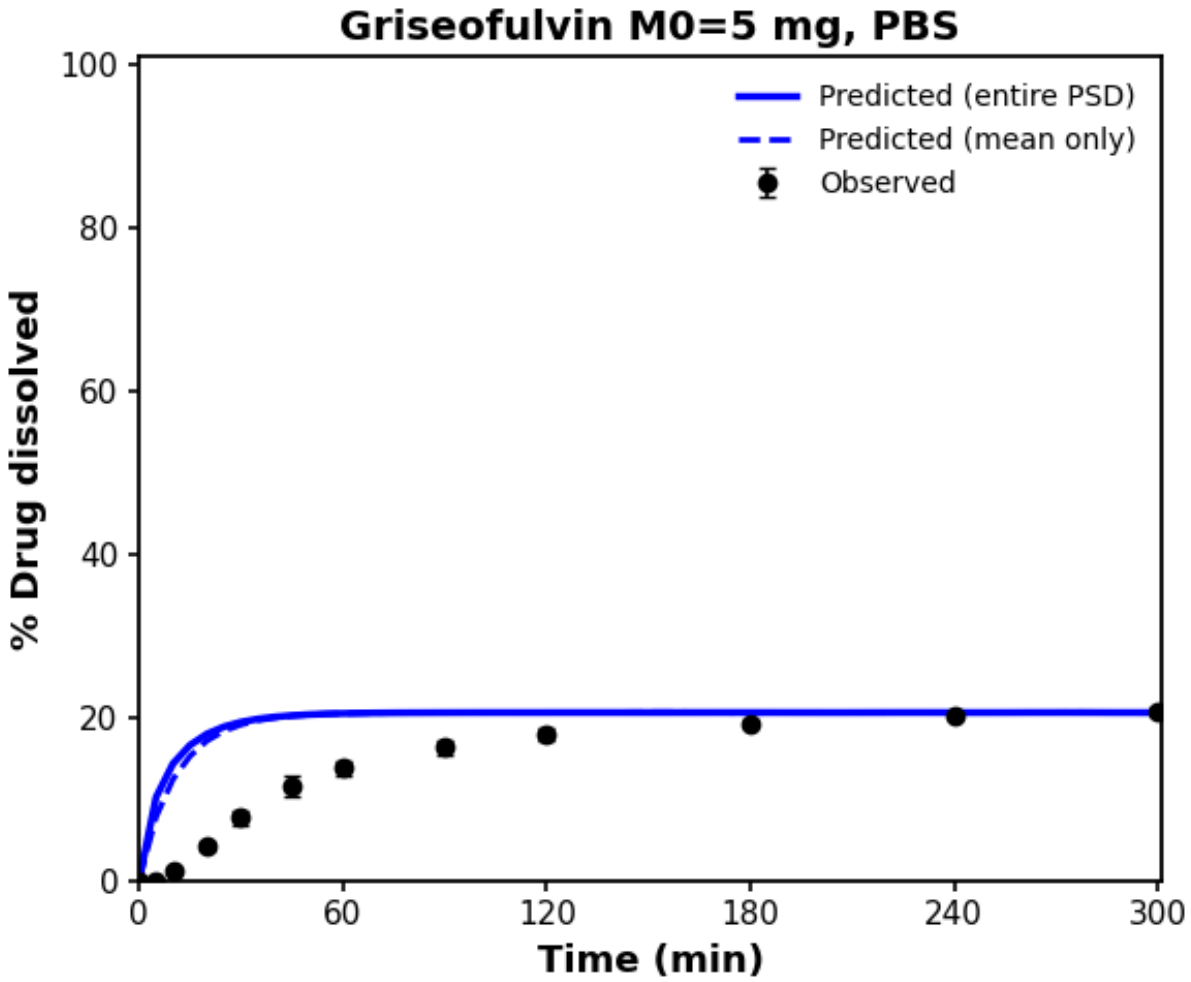
h = diffusion layer thickness

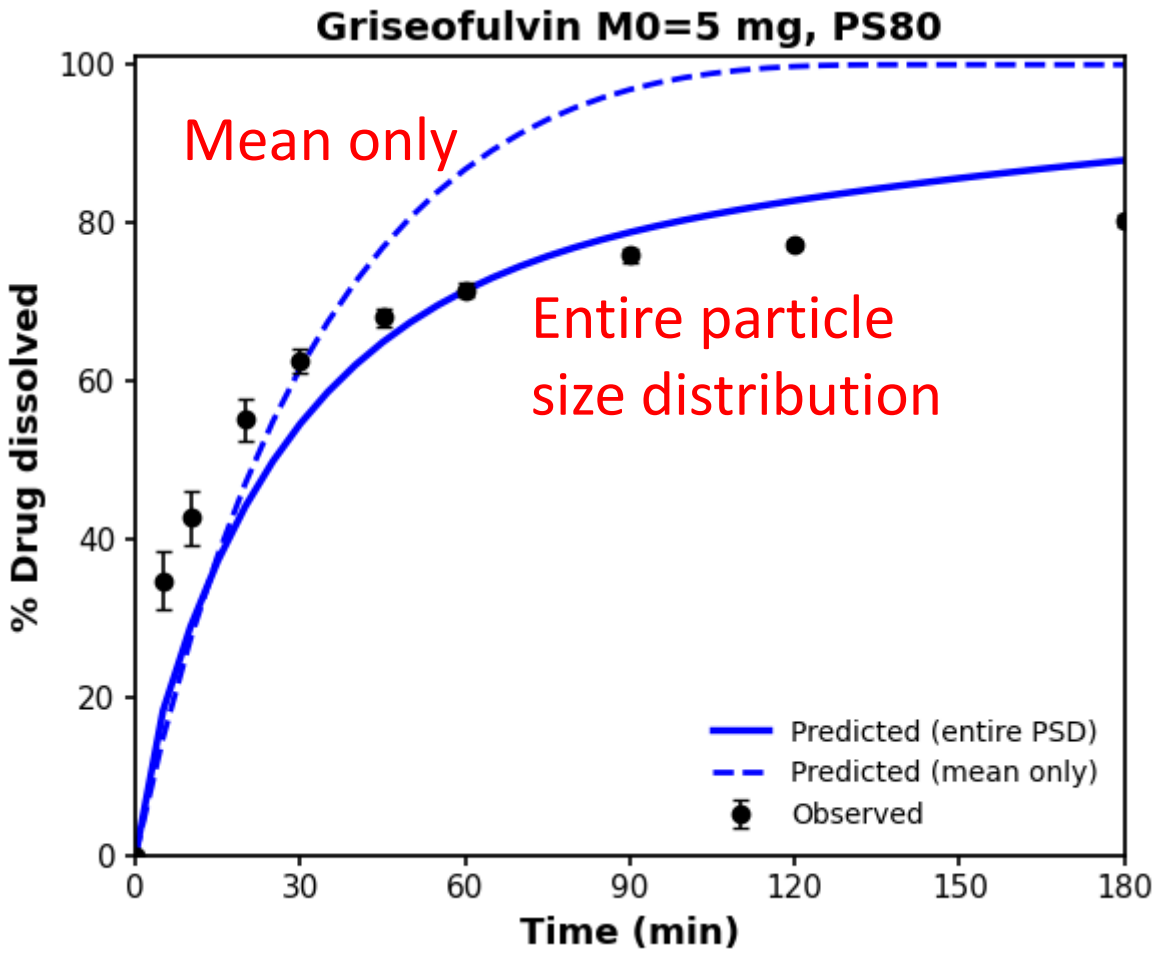


Patel RP, Nordquist EB, Polli JE. Prediction of surfactant-mediated dissolution of poorly soluble drugs from drug powder. Eur J Pharm Sci. 2025 May 1;208:107052.

Predicted particle dissolution profiles of griseofulvin with and without surfactant

Drug: 5mg powder
Media: 50mM phosphate buffer (100ml) +/- surfactant
Apparatus: USP II minipaddle
Speed: 75rpm





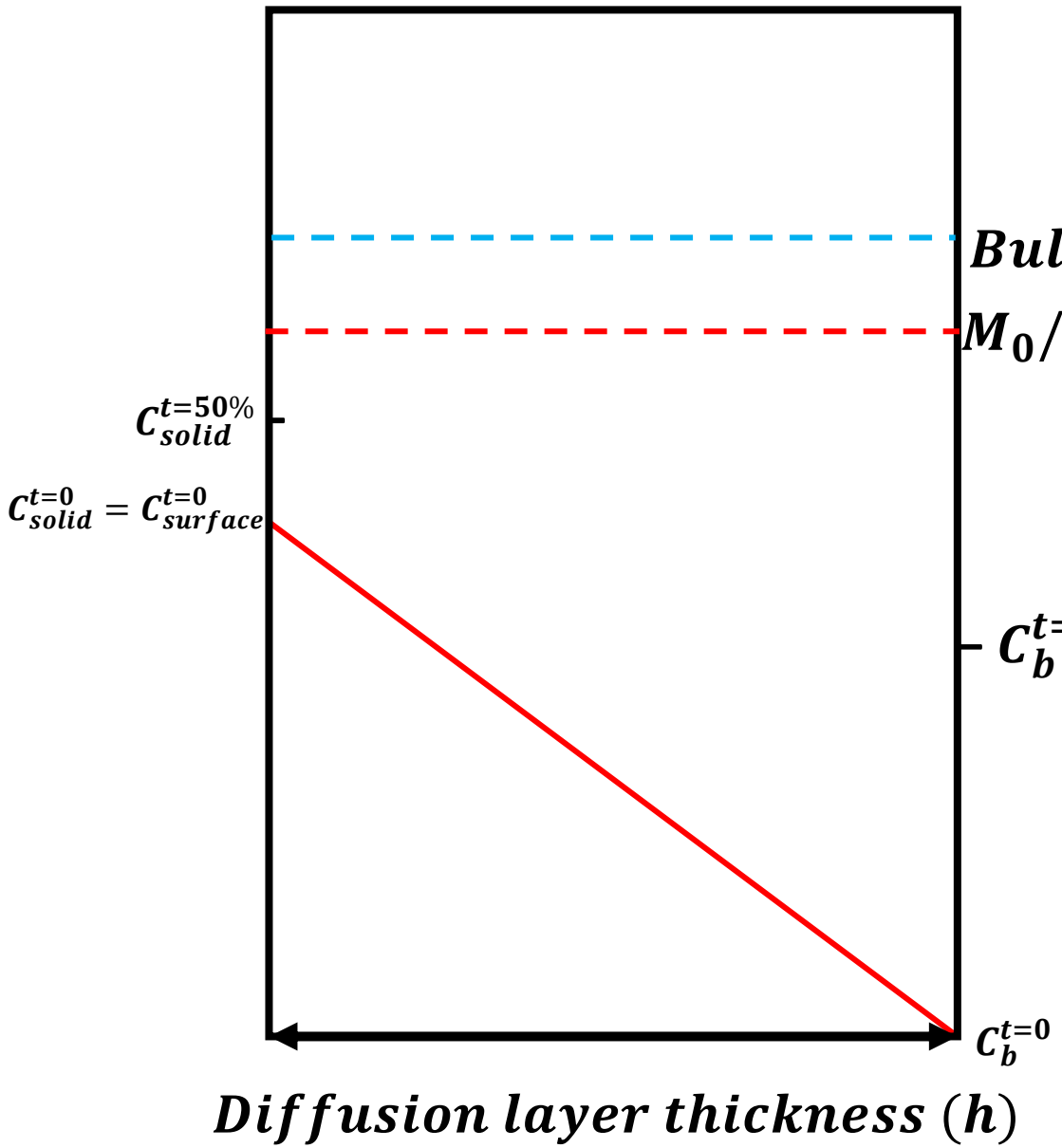
Conventional Film Model (Z-factor): $\frac{dM}{dt} = -\frac{3D}{\rho r_0 h} M_0^{\frac{1}{3}} M^{\frac{2}{3}} \left(C_s - \frac{M_0 - M}{V}\right)$

Transient pH film model (applied to particle dissolution)

- Scenario High: $\frac{dM}{dt} = -\frac{3D}{\rho r_0 h} \frac{C_{slurry}}{C_s} M_0^{\frac{1}{3}} M^{\frac{2}{3}} \left(C_s - \frac{M_0 - M}{V}\right)$
- Scenario Moderate and Low: $\frac{dM}{dt} = -\frac{3D}{\rho r_0 h} \frac{C_{slurry}}{C_b^{t=inf}} M_0^{\frac{1}{3}} M^{\frac{2}{3}} \left(C_b^{t=inf} - \frac{M_0 - M}{V}\right)$

For example, since $\frac{C_{slurry}}{C_s} < 1$, dissolution of the ionizable weak acid in Transient pH film model scenario high will be slower than conventional film model.

Transient pH Film Model for Ionizable Drug Dissolution



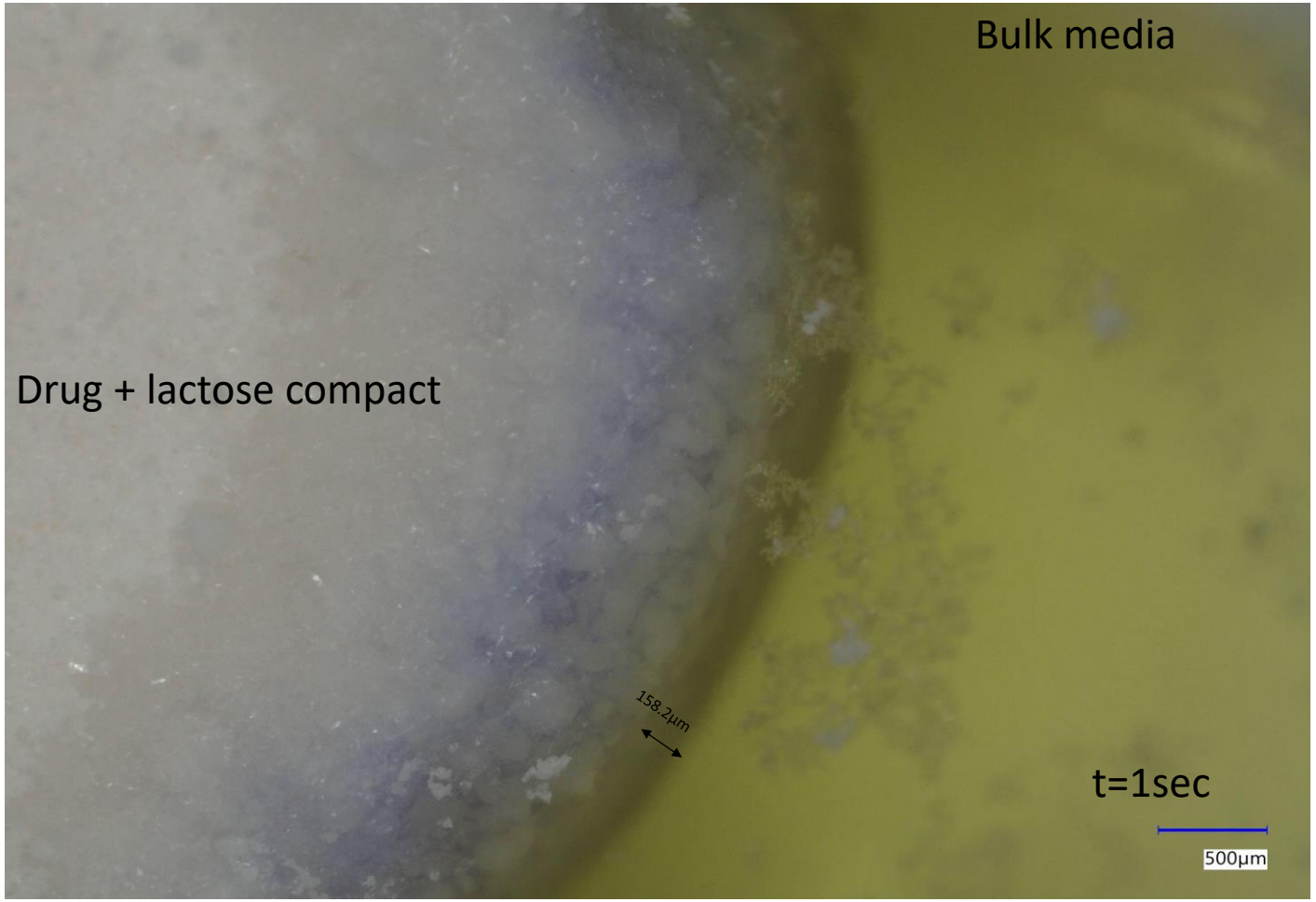
Three Different Dose Scenarios

- High: $M_0/V > C_s > C_{surface}^{t=0}$
- Moderate: $C_s > M_0/V > C_{surface}^{t=0}$ ✓
- Low: $C_s > C_{surface}^{t=0} > M_0/V$

- $C_{surface}^{t=0}$ is initial surface solubility, which is lower than Cs due to surface pH change
- Main Model Assumption: Surface solubility linearly increases as dissolution progresses

Patel RP, Polli JE. Transient pH film model for in vitro powder dissolution of weakly acidic drugs into buffer: Consideration of surface acidification and comparison to conventional film model. J Pharm Sci. 2025 Oct;114(10):103961.

Haloperidol/lactose compact dissolving in presence of 5mM phosphate buffer pH 2.9 with 0.005% BPB dye

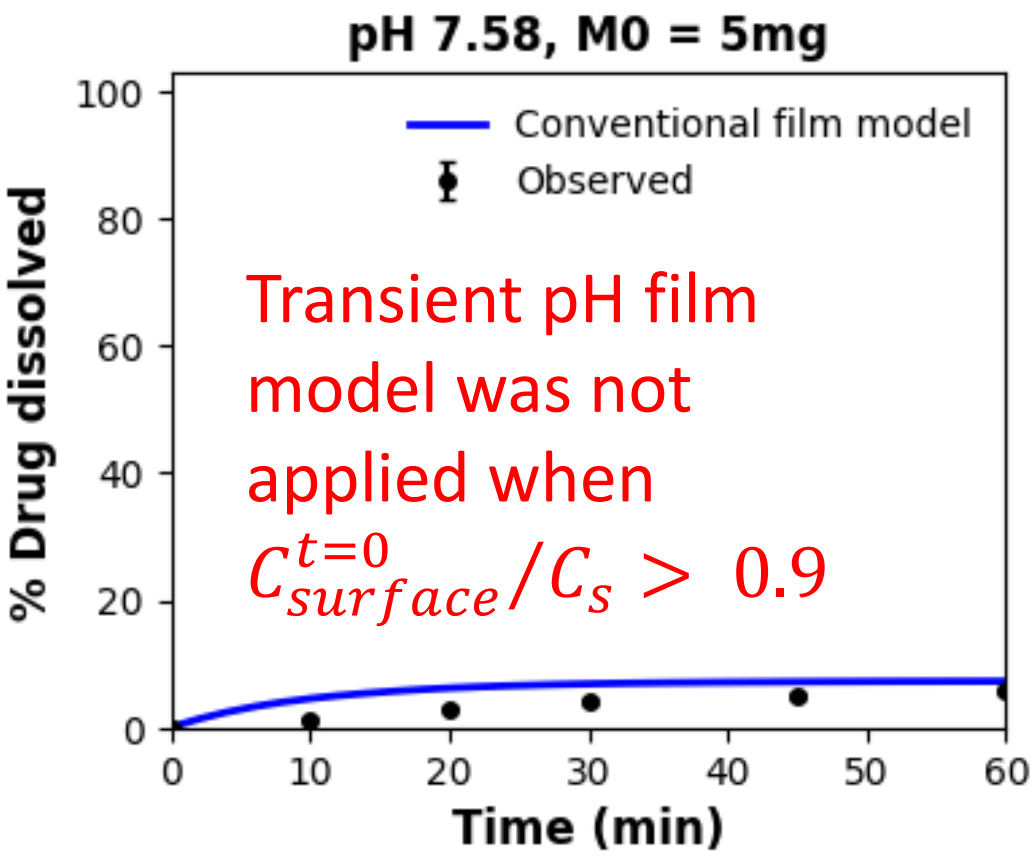


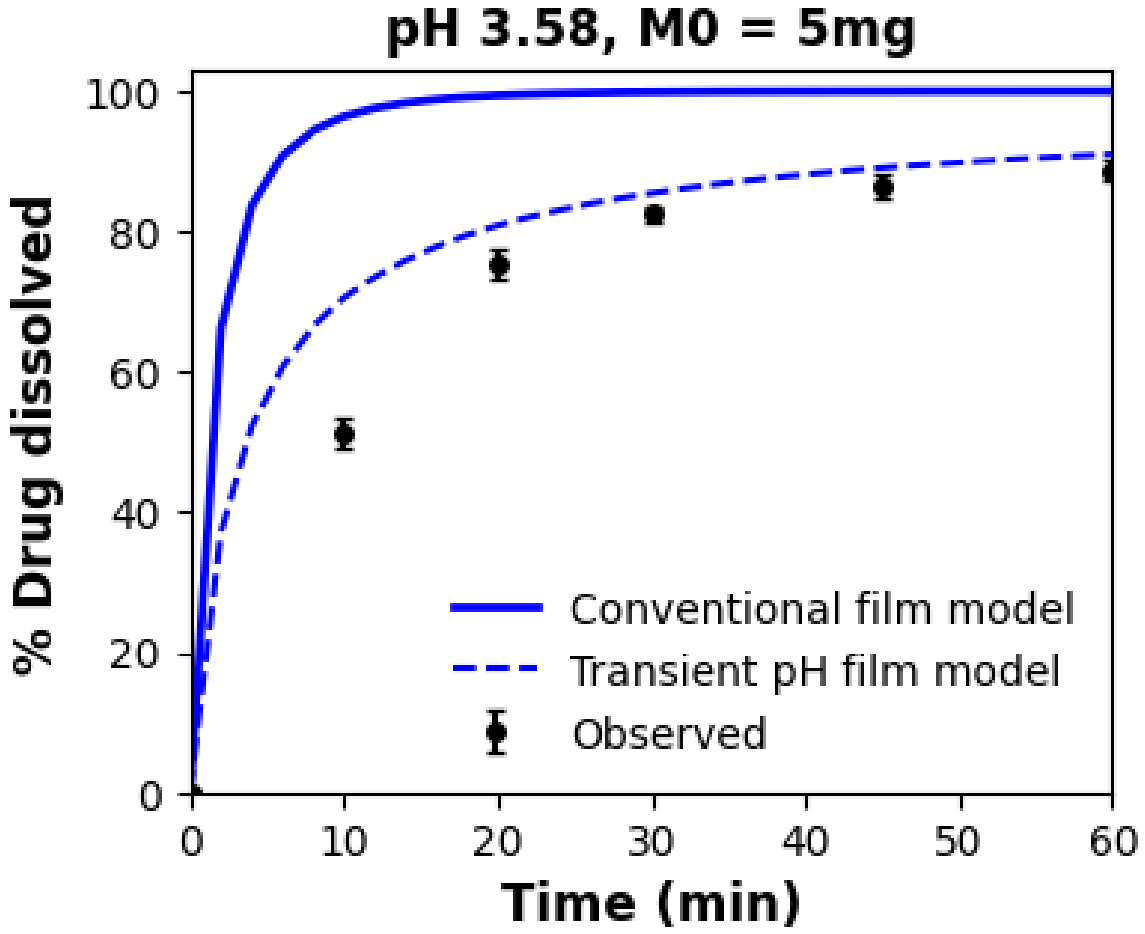
Media was yellow, reflecting pH= 2.9. Haloperidol surface immediately turned blue, reflecting rapid surface alkalinization.

A relatively more alkaline boundary layer (blue) adjacent to drug surface (pH about > 4.21) formed, approximately 160µm in width.

Patel RP, Polli JE. Transient pH film model for in vitro powder dissolution of weakly basic drugs into buffer and comparison to conventional film model. J Pharm Sci. 2026 Mar 27;115(6):104265.

Predicted particle dissolution profiles of dipyridamole (pKa= 6.4) into buffered medium





In vitro drug dissolution was more accurately predicted from the transient pH film model than the conventional film model when applied.

Drug solubility: FaHIF versus FaSSIF, and FeHIF versus FeSSIF

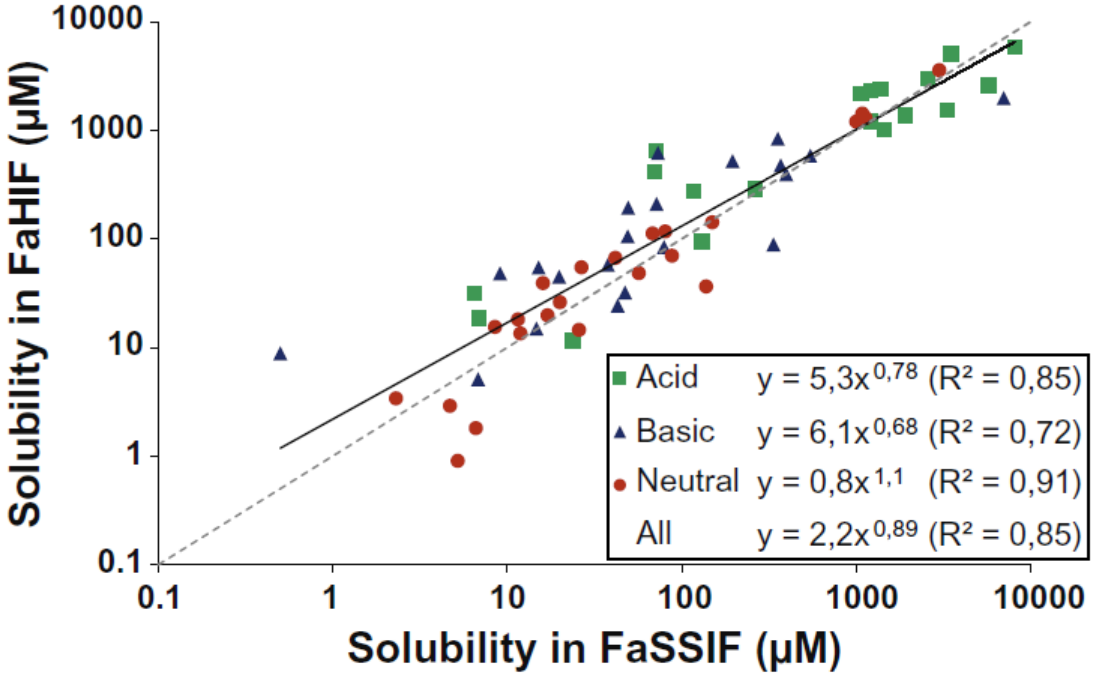


Fig. 3. Overall correlation between solubility in FaHIF and FaSSIF (based on data from Table 1). Regression equations for neutral, acidic, basic and all compounds are reported on the graph. The dotted gray line indicates the $y = x$ relation.

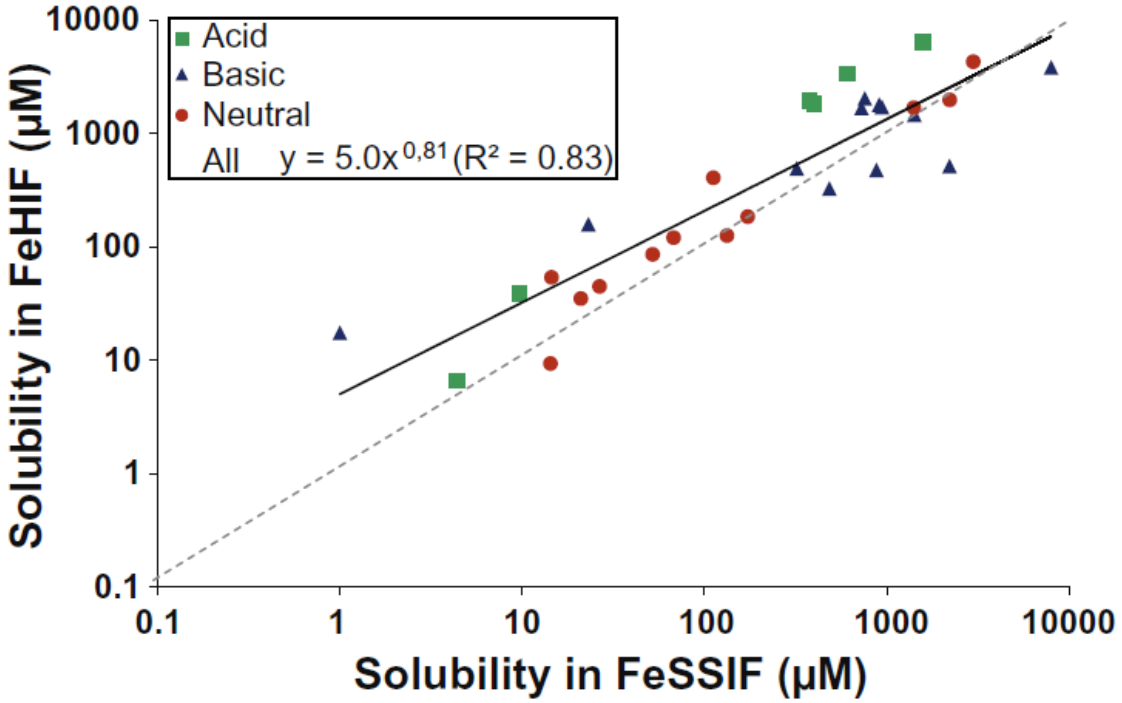
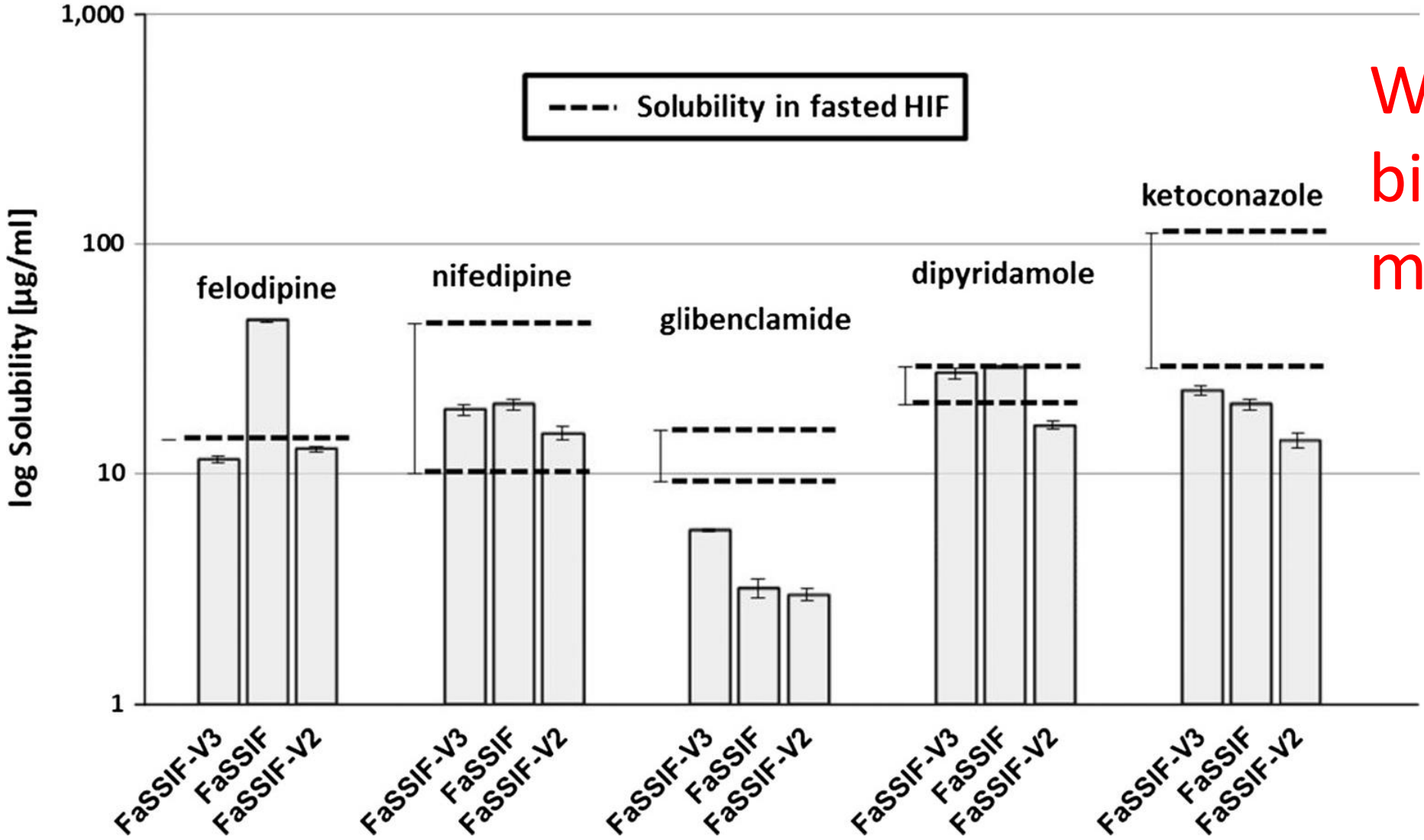


Fig. 4. Overall correlation between solubility in FeHIF and FeSSIF (based on data from Table 2, FeSSIFv1 or based on crude taurocholate). The regression equation including all compounds is reported on the graph. Due to the limited data set, no separate regressions for neutral, acidic and basic compounds are reported. The dotted gray line indicates the $y = x$ relation.

Augustijns P, et al. A review of drug solubility in human intestinal fluids: implications for the prediction of oral absorption. Eur J Pharm Sci. 2014 Jun 16;57:322-32.

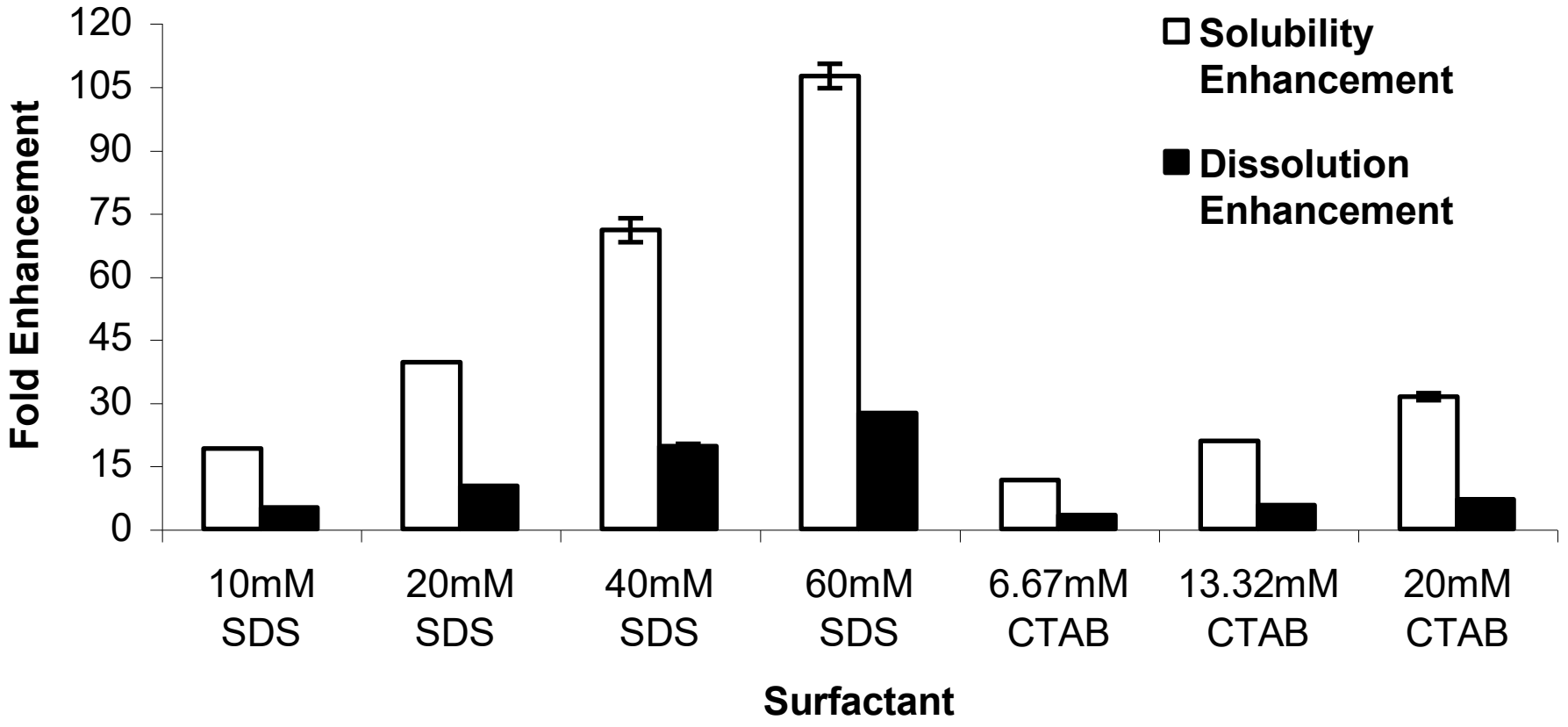
Comparison of FaSSIF-V1 versus FaSSIF-V2 (and V3)



Which biorelevant media?

Fuchs A, Leigh M, Kloefer B, Dressman JB. Advances in the design of fasted state simulating intestinal fluids: FaSSIF-V3. Eur J Pharm Biopharm. 2015 Aug;94:229-40.

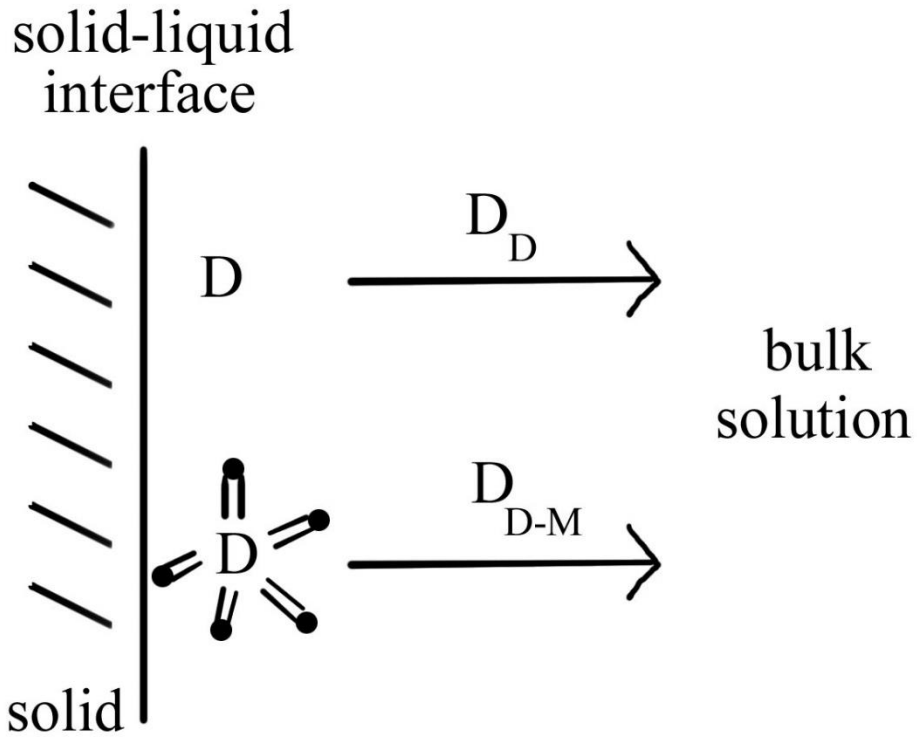
Enhancement of griseofulvin solubility and dissolution by SDS and CTAB



Dissolution enhancement is substantially less than solubility enhancement.

Balakrishnan A, Rege BD, Amidon GL, Polli JE. Surfactant-mediated dissolution: contributions of solubility enhancement and relatively low micelle diffusivity. J Pharm Sci. 2004 Aug;93(8):2064-75.

Surfactant-mediated dissolution enhancement



Intrinsic dissolution model $\phi_{intrinsic} = 1 + \frac{f_m}{f_f} \cdot \frac{D_{D-M}^{\frac{2}{3}}}{D_D^{\frac{2}{3}}}$

Film model $\phi_{film} = \left(1 + \frac{f_m}{f_f}\right) \cdot \frac{D_{eff}}{D_D}$

- ϕ is the degree of surfactant-mediated dissolution enhancement
- f_m is the fraction of drug in micelle and f_f is the fraction of free drug
- D_D and D_{D-M} are the diffusivities of free drug and drug-loaded micelles, respectively, and
- D_{eff} is effective diffusivity, where $D_{eff} = f_f \cdot D_D + f_m \cdot D_{D-M}$

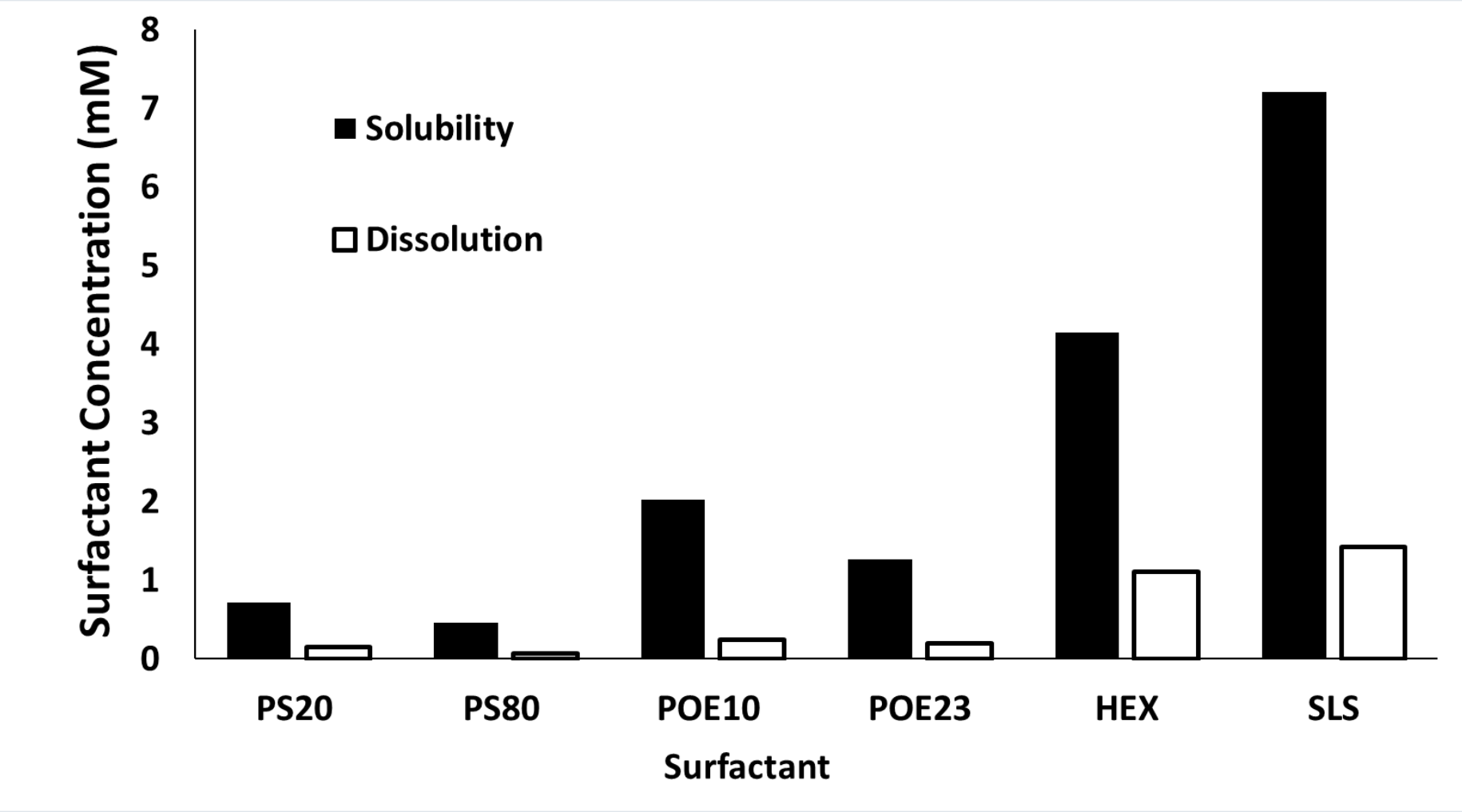
Balakrishnan A, Rege BD, Amidon GL, Polli JE. Surfactant-mediated dissolution: contributions of solubility enhancement and relatively low micelle diffusivity. J Pharm Sci. 2004 Aug;93(8):2064-75.

Oktay AN, Polli JE. Efficiency of single pharmaceutical surfactants to mimic intestinal biorelevant media solubilization and dissolution of etravirine: Comparison of intrinsic and film dissolution models. Eur J Pharm Sci. 2024 May 1;196:106746.

Etravirine-loaded micelle radius and diffusivity values. D_D of free etravirine = $103x10^{-7}$ cm^2/s.

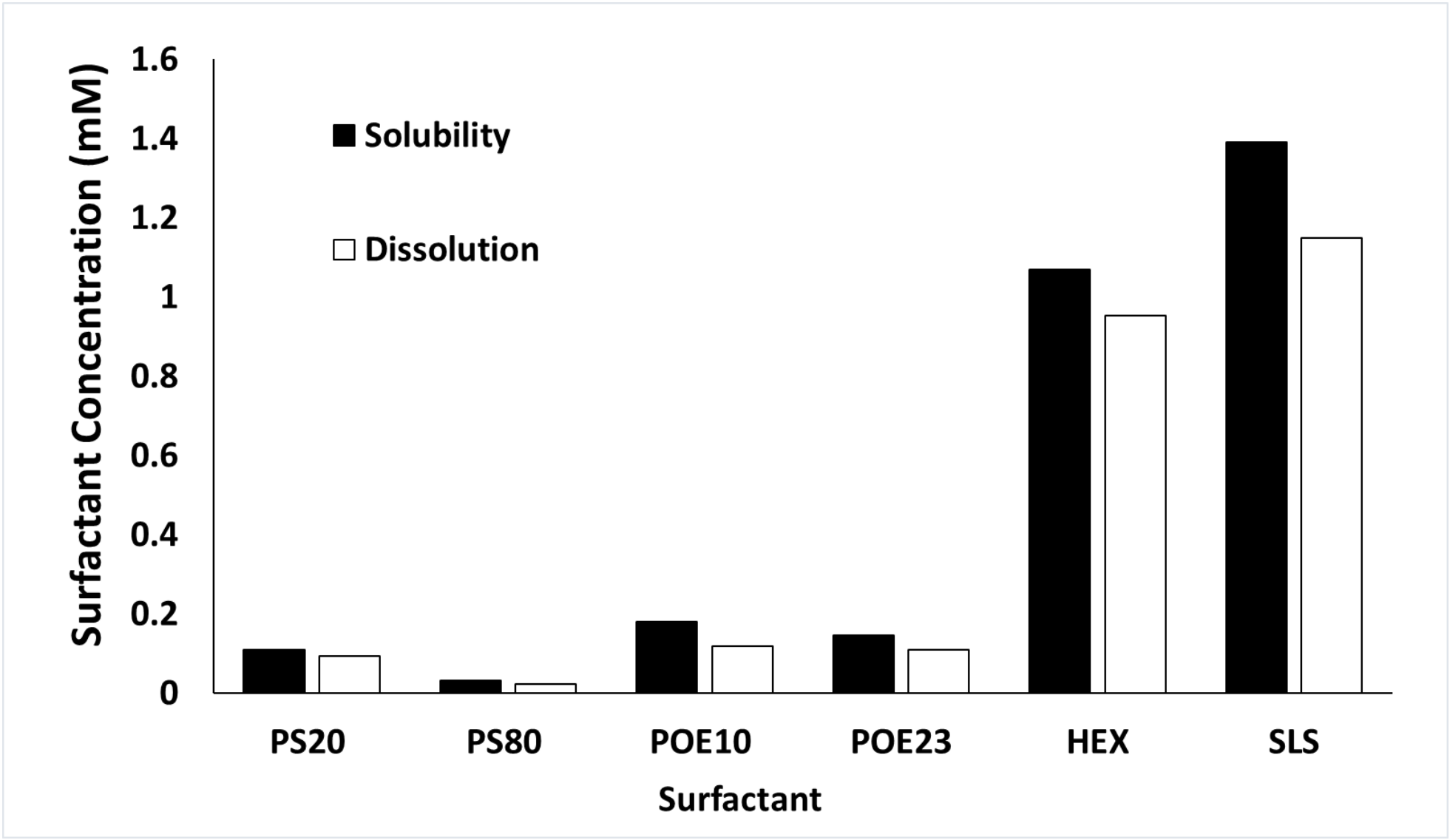
Media (2%)	Micelle radius (nm)	D_{D-M} $x10^7$ (cm^2/s)	D_{eff} $x10^7$ (cm^2/s)
PS20	5.44±0.15	4.73±0.13	5.22±0.13
PS80	6.11±0.19	4.15±0.13	4.52±0.12
POE10	4.20±0.06	6.57±0.09	7.30±0.09
POE23	5.32±0.02	6.02±0.023	6.88±0.02
HEX	2.90±0.19	9.39±0.64	10.1±0.06
SLS	2.11±0.07	10.4±0.3	11.4±0.3
FeSSIF-V2	46.8±0.1	0.578±0.001	12.0±0.001
FaSSIF-V2	23.6±0.1	1.30±0.007	75.2±0.002

How much surfactant needed to mimic FeSSIF-V2 for etravirine?



Oktay AN, Polli JE. Efficiency of single pharmaceutical surfactants to mimic intestinal biorelevant media solubilization and dissolution of etravirine: Comparison of intrinsic and film dissolution models. Eur J Pharm Sci. 2024 May 1;196:106746.

How much surfactant needed to mimic FaSSIF-V2 for etravirine?

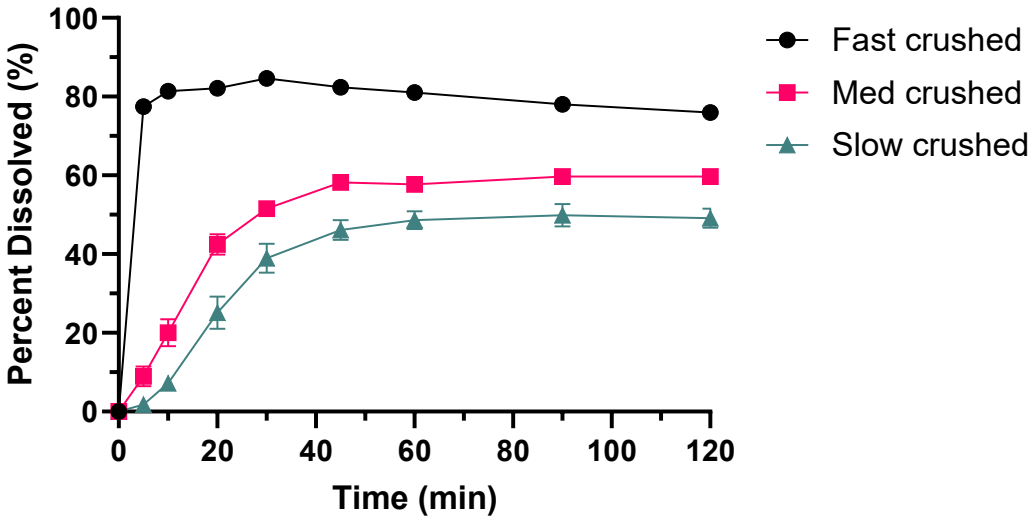


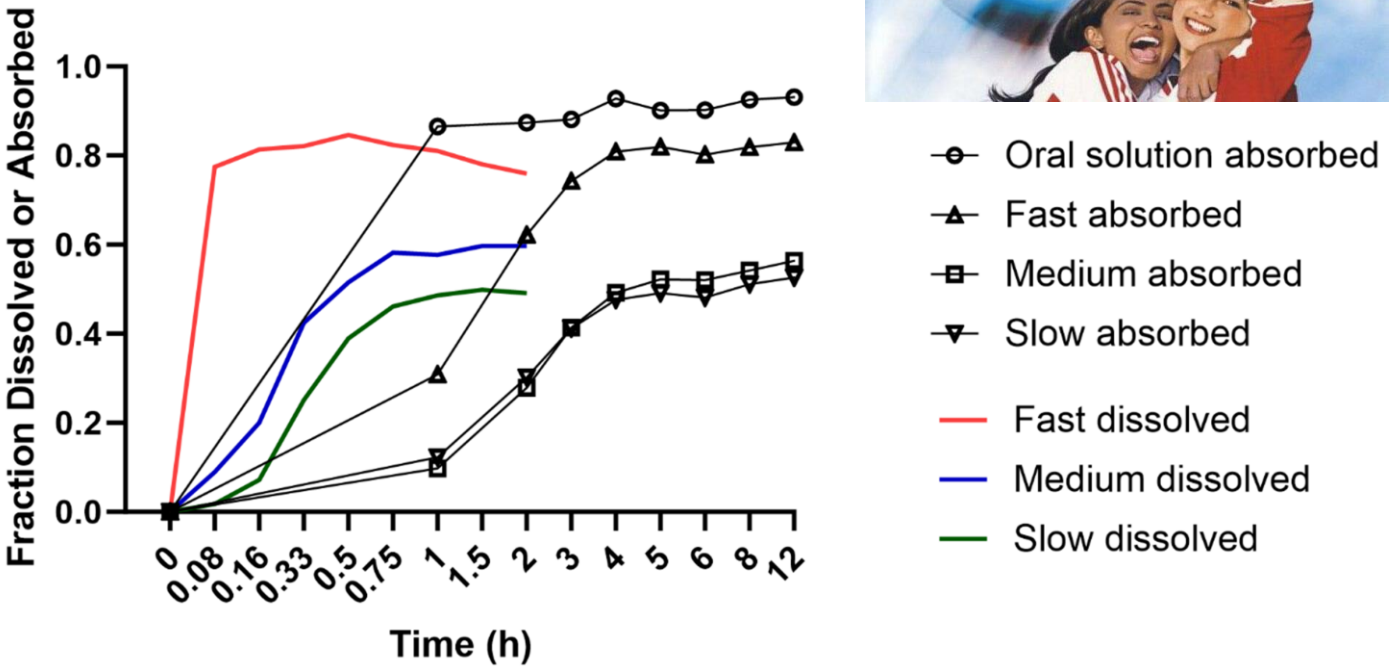
Itraconazole ASD Tablets: IVIVC Findings

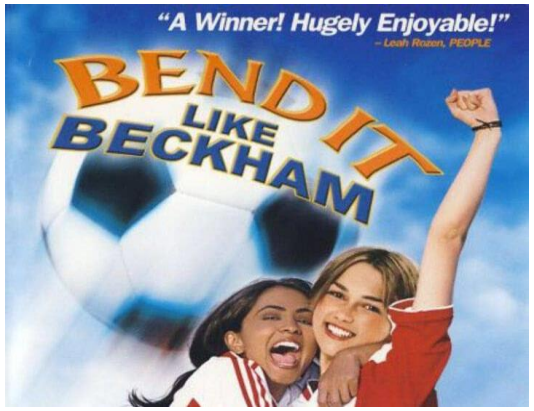
- FDA Level A IVIVC was successfully achieved
- Largest contributor was polymer grade
  - HPMCAS-L provided faster and higher dissolution
- Modest impact of slug and tablet compaction pressure and disintegrant amount (HPMCAS-M)
- In vivo Medium and Slow tab PK parameters were closer than initially expected based upon traditional in vitro USP vessel testing
  - In vitro trituration of tablets provided improved dissolution profile w/r/t IVIVC and reflected in vivo pulverization
  - "An identified obstacle to non-compendial methods is the uncertainty of global regulatory acceptance of such methods."
    - Raines K, et al. (2023): Drug Dissolution in Oral Drug Absorption: Workshop Report. AAPS J. 25:103. https:// doi. org/ 10. 1208/s12248- 023- 00865-8.

Coutinho AL, Adhikari A, Krug S, Kane M, Hollenbeck RG, Hoag SW, Polli JE. In Vitro-In Vivo Correlation Of Amorphous Solid Dispersion Enabled Itraconazole Tablets. Pharm Res. 2025 Mar;42(3):485-502.

Loo-Riegelman Informs Target Dissolution Profile



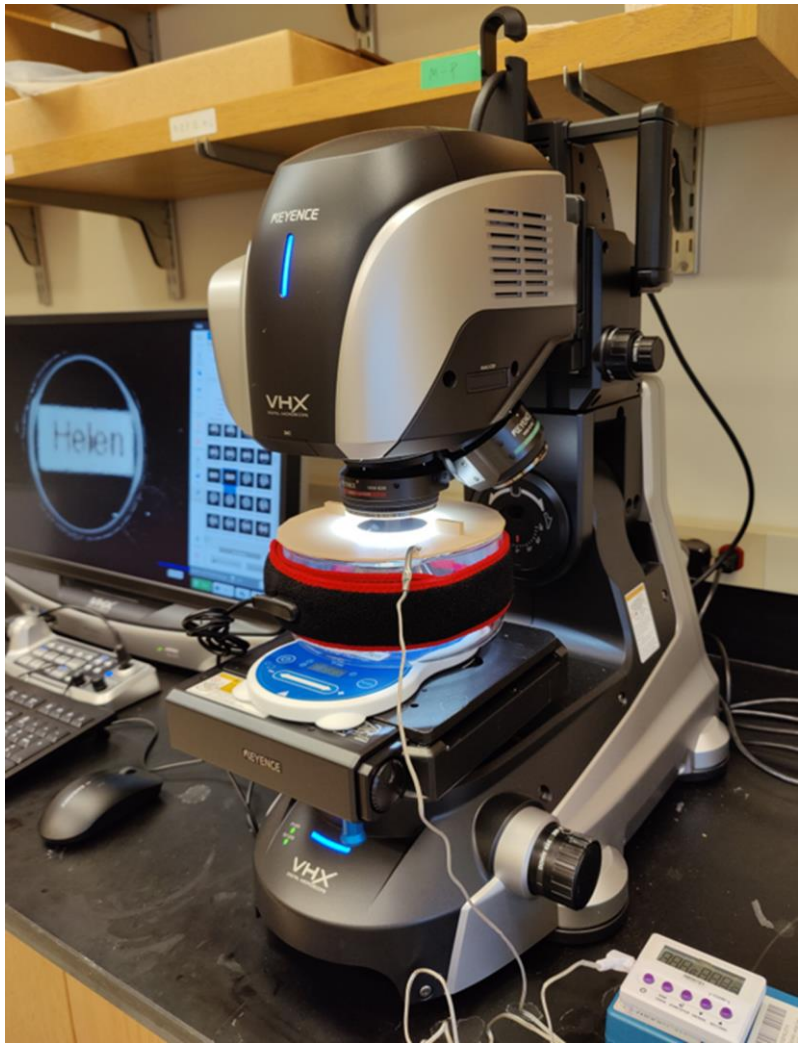




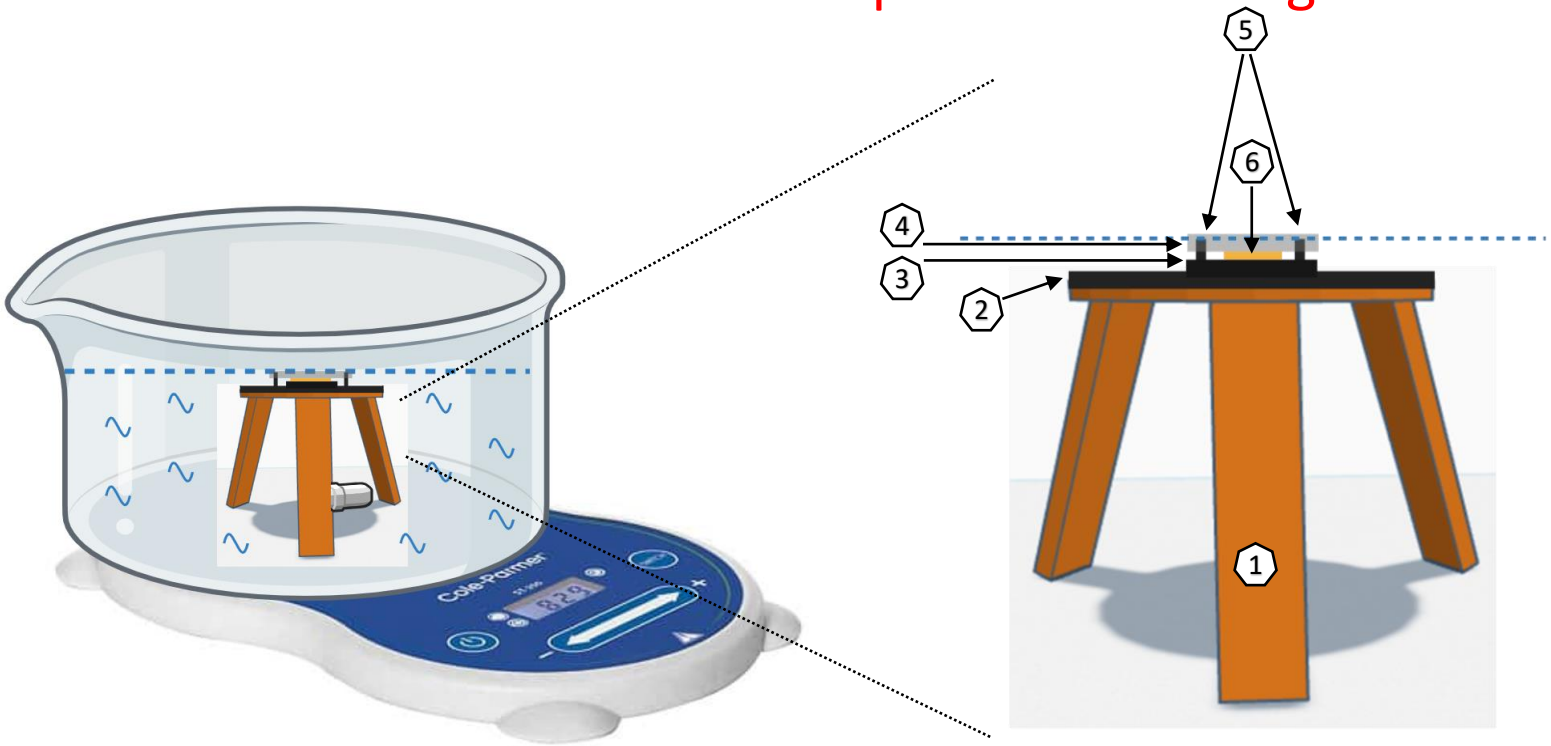
- USP II apparatus at 50 rpm
- 900 mL USP SIF pH 6.4
- Tables were individually crushed and passed through sieve US mesh #14 (1400 micron)

F2 Values	
Fast vs Med	19.9
Slow vs Med	46.3

Microscope-enabled Disc Dissolution System (MeDDiS)



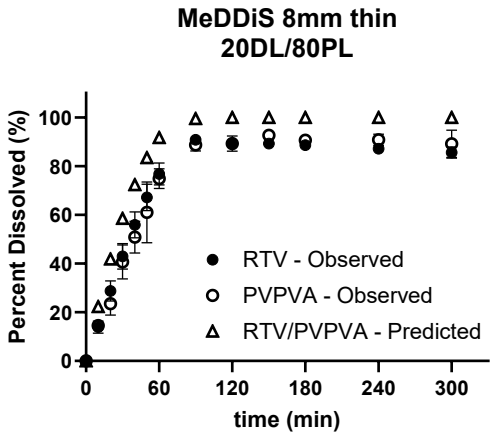
ASD disc fabricated via vacuum compression molding

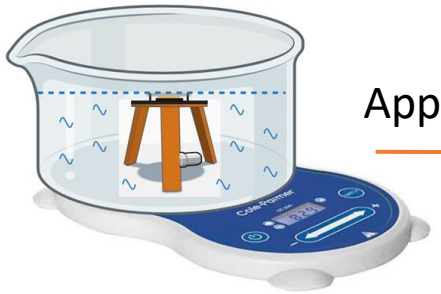


- The sandwich design: **glass plate : ASD disc : glass plate**
  - Allows only medium exposure and penetration from the side of the ASD disc and not from the disc top or bottom.

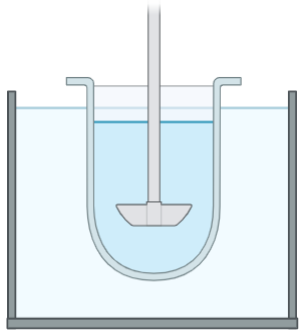
Men S, Polli JE. Microscope-enabled disc dissolution system: Concordance between drug and polymer dissolution from an amorphous solid dispersion disc and visual disc degradation. J Pharm Sci. 2024 Dec;113(12):3586-3598.

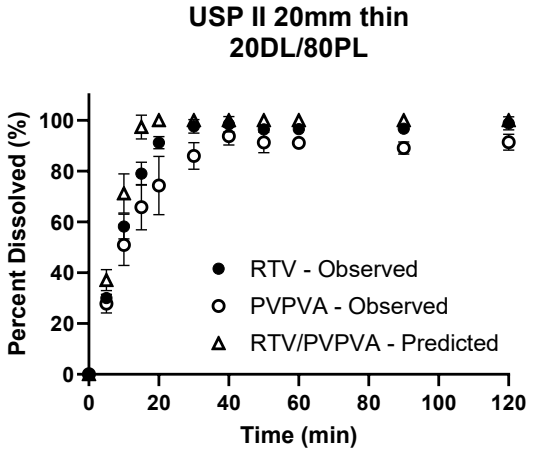
Solvent Penetration Rate (dd/dt) Predicts Drug Release



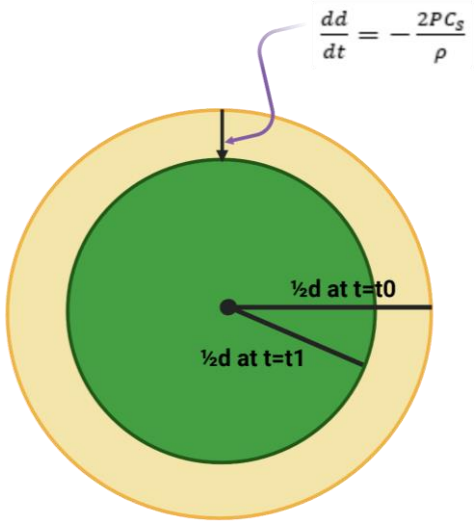


Applied measured dd/dt

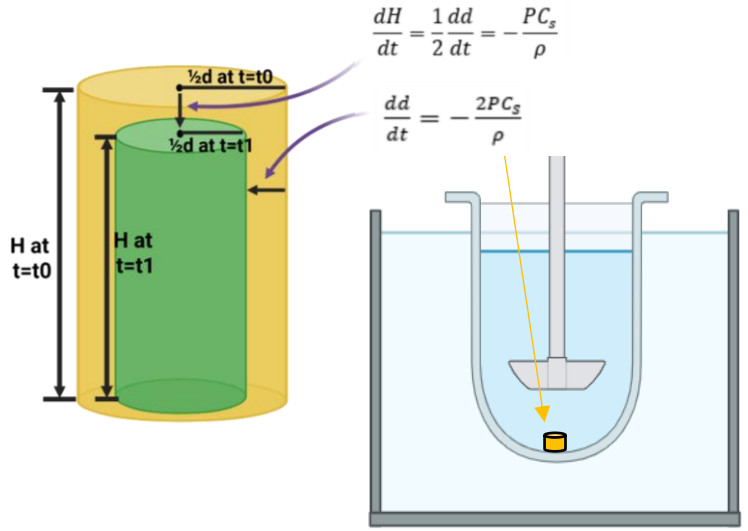




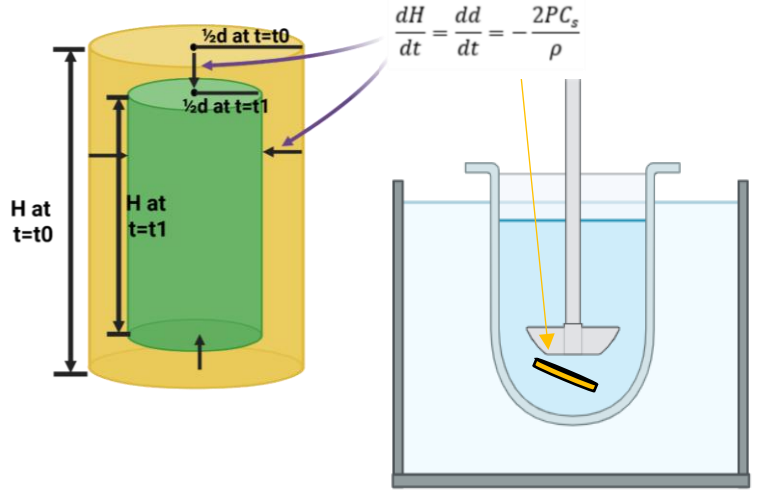
Disc Side Model



Sunken Disc Model



Total Disc Model



Ref: Shuaiqian Men, Yuly Chiang Yu, and James E. Polli. *Molecular Pharmaceutics* 2026 23 (3), 1905-1928.

Laboratory and data analysis tools

- Deconvolution and dissolution/permeation apparatus
  - Elucidating rate limiting step
- Additional promising tools: BioGIT system and lipolysis
- Prediction of in vitro dissolution
  - Surfactant systems
  - Transient pH film model
- Biorelevant media
  - Impact of low micelle diffusivity
  - Mimic solubility in biorelevant media or dissolution in biorelevant?
- ASD IVIVC: in vitro trituration of tablets to mimic in vivo
- Predicting ASD dissolution via solvent penetration rate model

Thank you!

- Prior and current graduate students and post-doctoral fellows
- FDA collaborators