Prediction of Oral Drug Absorption and Biopharmaceutic Risk Using a Dissolution-Hollow Fiber Membrane (D-HFM) System: An overview of an example project with M-CERSI and FDA

James E. Polli

University of Maryland, Baltimore

jpolli@rx.umaryland.edu

Topics

- Characterize a dissolution-hollow fiber membrane (D-HFM) system and compare its resulting in vitro drug permeation constants K_p' to in vivo clinical permeation constants k_p for four drugs in various BCS classes
  - Adhikari A, Seo, PR, Polli, JE. (2022): Characterization of dissolution-permeation system using hollow fiber membrane module and utility to predict in vivo drug permeation across BCS classes. DOI: 10.1016/j.xphs.2022.07.002. J Pharm Sci. 111:3015-87.
- Predict the in vivo human absorption profile and biopharmaceutic performance of five drug products using the D-HFM system
  - Adhikari A, Seo, PR, Polli, JE.: (2023): 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.

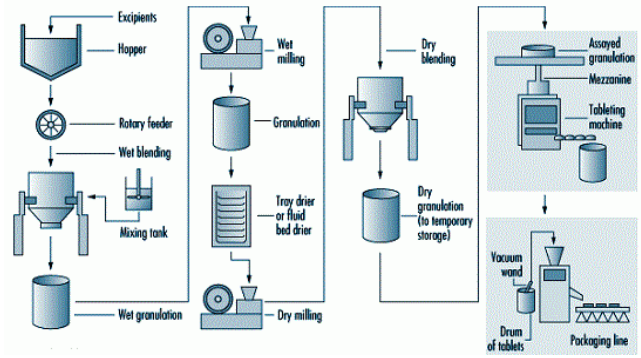
Acknowledgement and Disclaimer

- FDA grant U01FD005946 for University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI).
- https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis

- The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on the behalf of the U.S. Food and Drug Administration.
- JEP is a member of the Scientific Advisory Board of SimulationsPlus.

Chemistry, Manufacturing, and Controls (CMC)

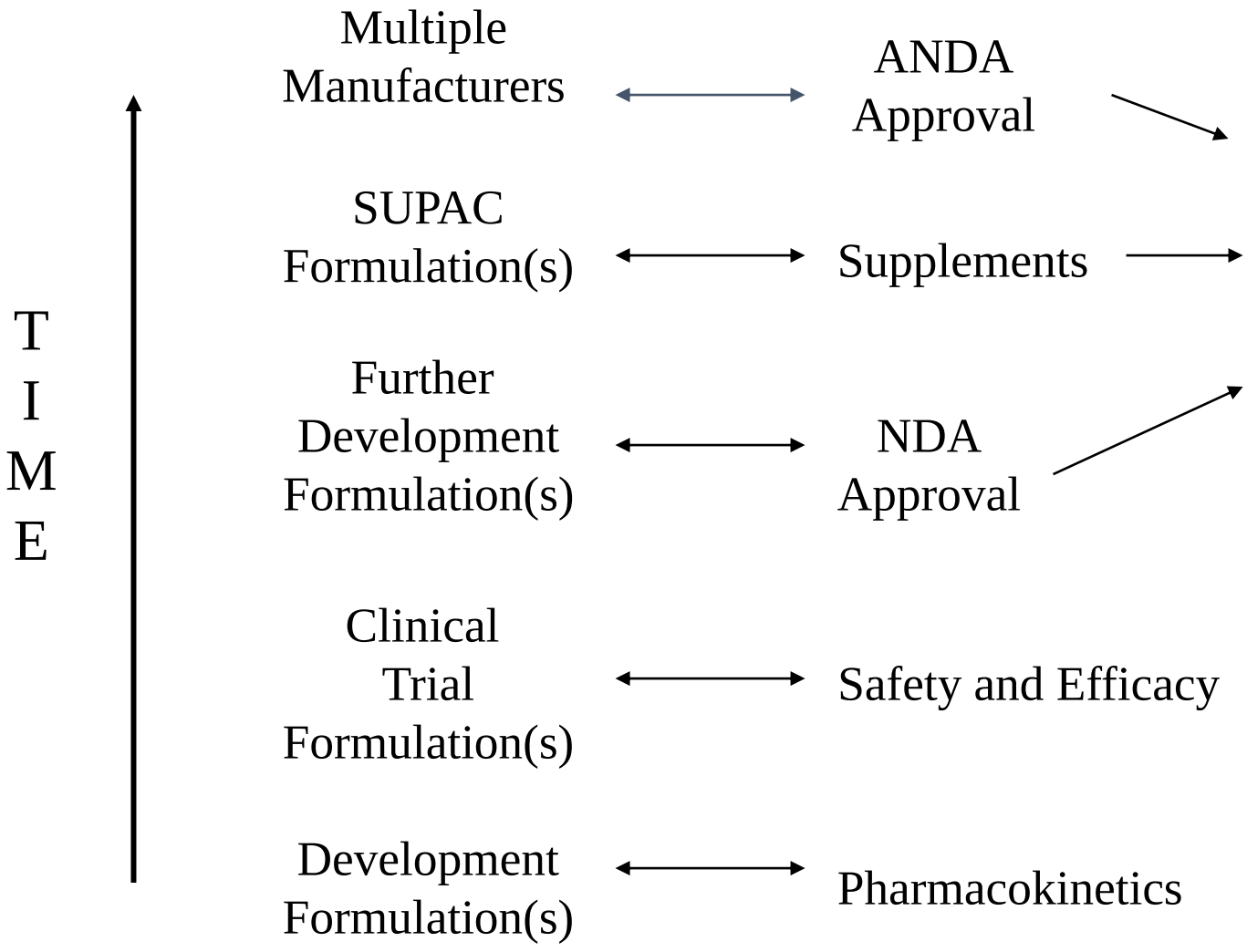
- a/k/a Quality (or sometimes non-clinical)
- Concerns both the drug product and the manufacturing facility
- Integral part of any pharmaceutical product application to FDA
- Applicable to the entire product lifecycle
- Drug product
  - Manufacturing process, quality control and release testing, and specifications and stability
- Manufacturing facility
  - Design, qualification, operation, and maintenance



Key points: Product understanding is important.

Tablets and capsules do not directly come from a written prescription.

Chemistry, Manufacturing, and Controls (CMC) lifecycle



NDA = new drug application
ANDA = abbreviated new drug application
SUPAC = scale-up and post-approval change

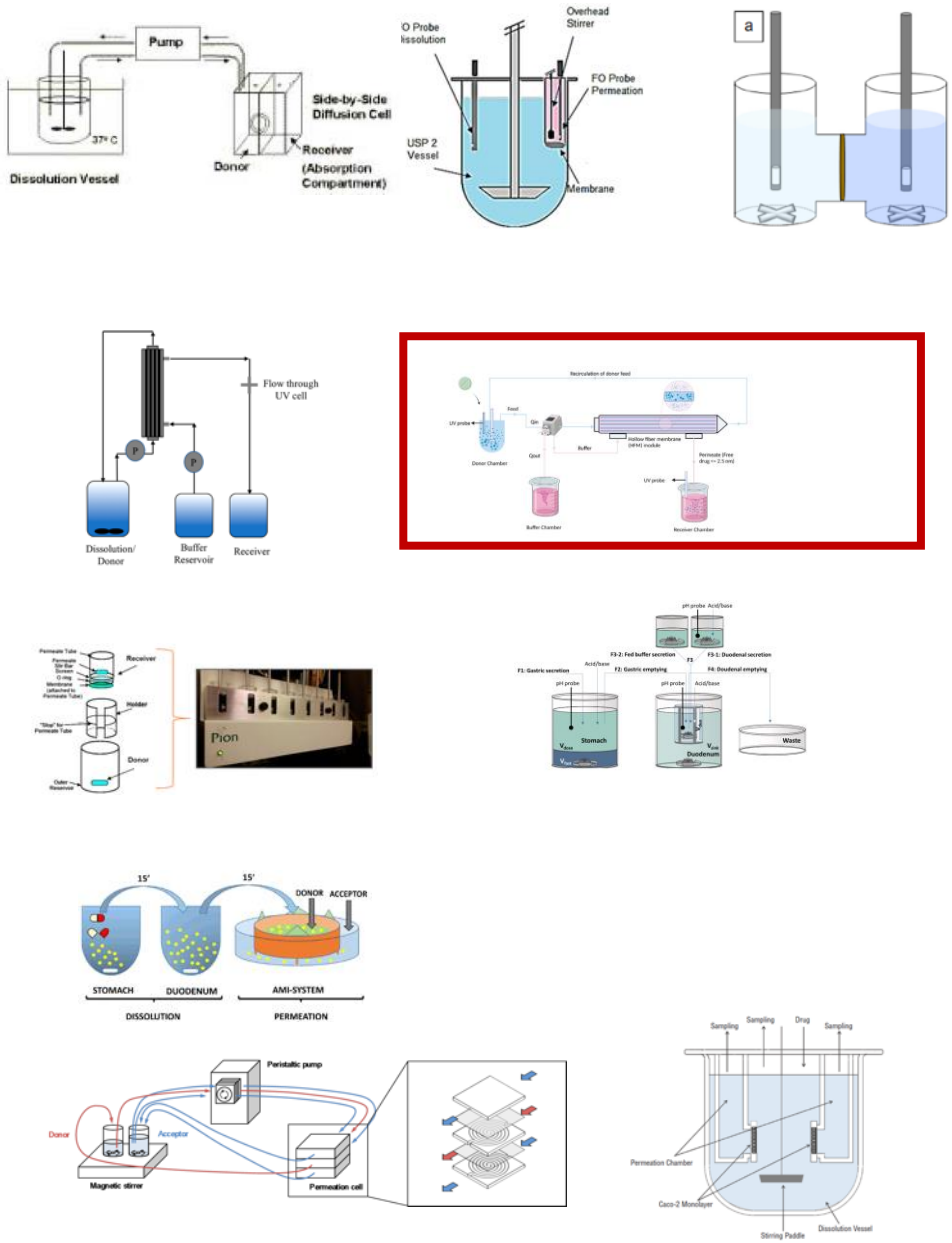
Key point: Changes happen. There is a frequent need to assess ongoing product similarity over many years.

Oral drug absorption from tablets and capsules

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

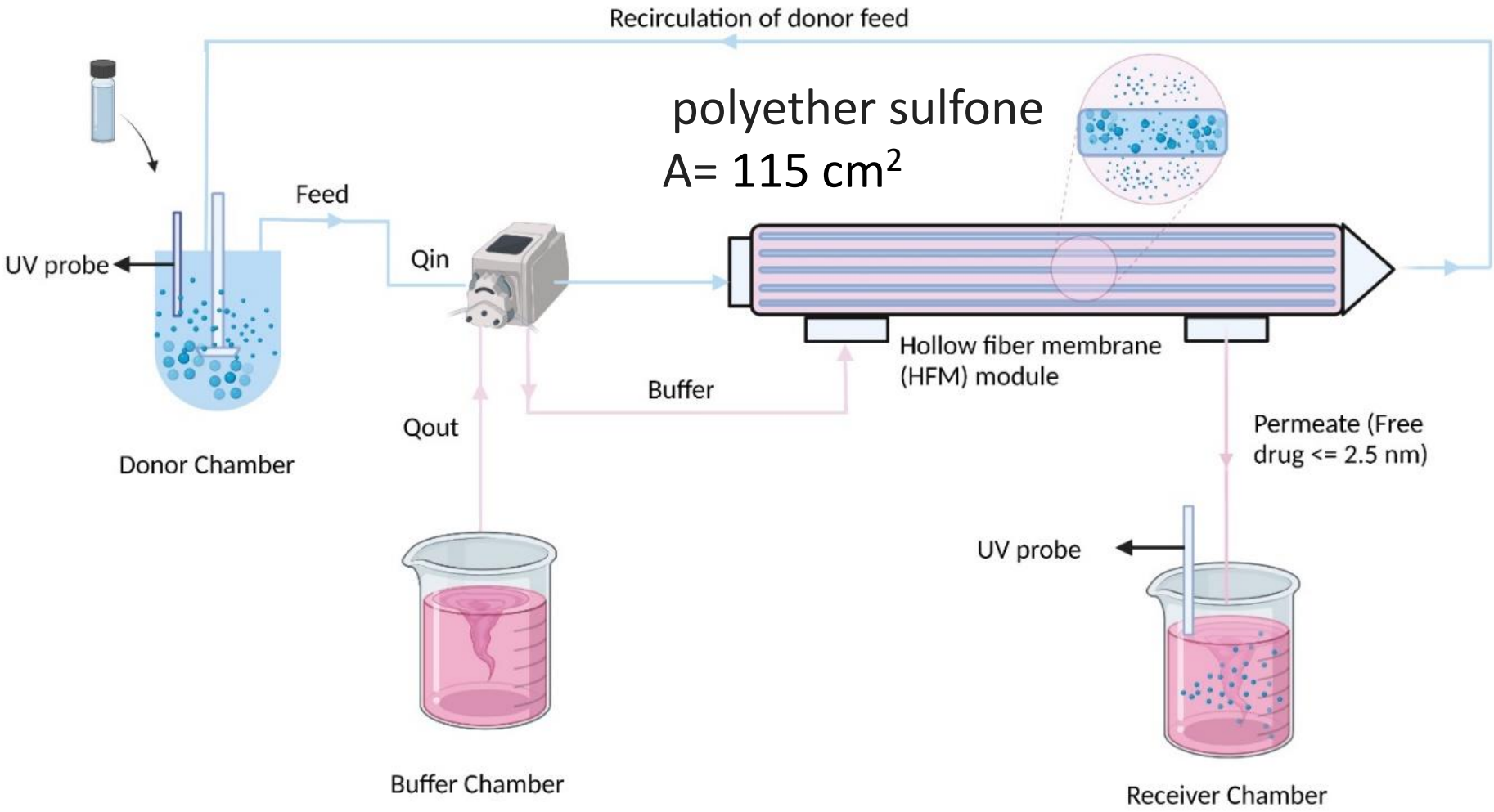
- An identified obstacle to non-compendial methods is the uncertainty of global regulatory acceptance of such methods.
  - K. Raines et al. (2023): Drug Dissolution in Oral Drug Absorption: Workshop Report. In press in AAPS Journal.

Setup	Reference	Barrier	A [cm^2]	V_{Donor} [mL]	A/V [cm^{-1}]	Sample	Diss/Perm set-up
Diss/Perm	*Ginski et al. 1999a,b*	Caco-2 *(AAPS Pharmsci; IJP)*	1.00	300	**0.003**	Complete dosage form	Continuous
MacroFLUX™	*Borbás et al. 2018*	Lipid-soaked filter (PAMPA)	3.80	1062	**0.004**	Complete dosage form	Continuous
Microflux ™	*Tsinmann et al. 2018*	Lipid-soaked filter (PAMPA)	1.54	20	**0.08**	Down-scaled formulation	Continuous
Hollow fiber module	*Hate et al. 2019*	Dialysis principle	100	50	**2.00**	Complete dosage form, solution	Continuous
Diamod®	*Moens et al., 2023*	Dialysis membrane	65	30	**2**	Complete dosage form	Continuous
TIM Tiny TIM	*Mármol et al., 2022*	Hollow fiber dialysis		55-300	**n/a**	Complete dosage form	Continuous
Vertical membrane flux cell	*Stewart et al. 2017*	Lipid-soaked filter (PAMPA)	4.90	5	**0.98**	Drug substance	Continuous
AMI-system	*Berben et al. 2018*	Dialysis membrane	4.91	0.7	**7.38**	Complete dosage form	Dis-continuous
PermeaLoop™	*Sironi et al. 2018*	Dialysis membrane / Permeapad	27.6	20	**1.38**	Downscaled formulation	Continuous
Permeapad® Plate; Plain Plate	*Jacobsen et al 2019*	Dialysis membrane / Permeapad	0.2	0.15-0.4	**1.33-0.5**	Downscaled dosage form	Continuous



Adapted from Annette Bauer-Brandl

Illustration of dissolution-hollow fiber membrane (D-HFM) system



Summary

- Characterize a dissolution-hollow fiber membrane (D-HFM) system
- Mixing tank (MT) model for D-HFM with recirculation and change in volume

$$M_{in} = M_{in}^{t=0} e^{-\frac{\left(AP_{app} - Cl_D^{loss}\right)}{V_{in}^{t=0} - Cl_D^{loss}\, t} t}$$

- Favorable Area/Volume ratio
- In vitro K_p' was close to in vivo k_p for four drugs in various BCS classes
- HFM module has potential to incorporate drug permeation into the in vitro assessment of in vivo tablet and capsule performance

Area/Volume ratio

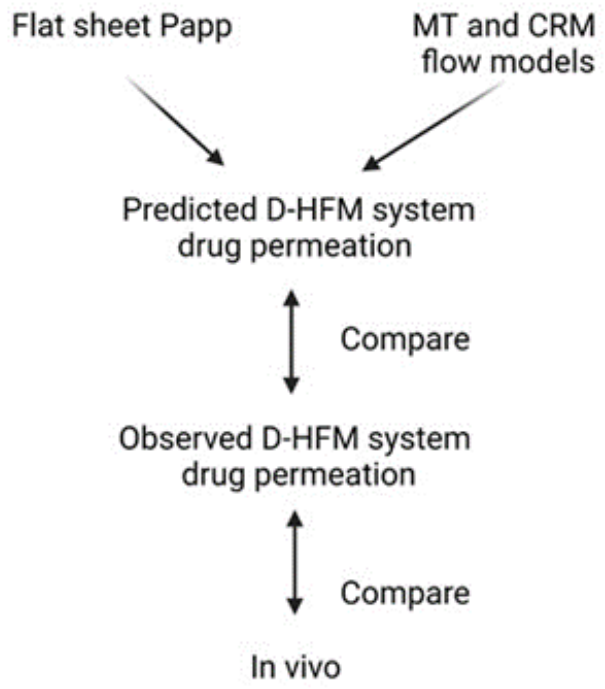
- Area of HFM = 115 cm^2
- A/V ratio of D-HFM = 1.15 cm^{-1} if V=100ml
- In vivo human A/V ratios have been estimated to be 11 cm^{-1} , 2.2 cm^{-1} and 1.9 cm^{-1}
- To estimate in vitro $K_p^{'} = \left(\frac{A}{V}\right)_{system} \times P_{app}$

- To identify a more desirable in vitro A/V ratio,

$$\left(\frac{A}{V}\right)_{target} = \frac{k_p}{P_{app}}$$

Experimental studies and model predictions in dissolution-hollow fiber membrane (D-HFM) system development

Panel A



Panel B

Side by side diffusion studies (microFlux)
- Membrane permeability (across flat sheet)
- Drug permeation profile

Model predictions using MT and CRM flow models
-Predicted drug permeation profile across D-HFM system using flat sheet permeability
- Donor flow rate and donor volume sensitivity study

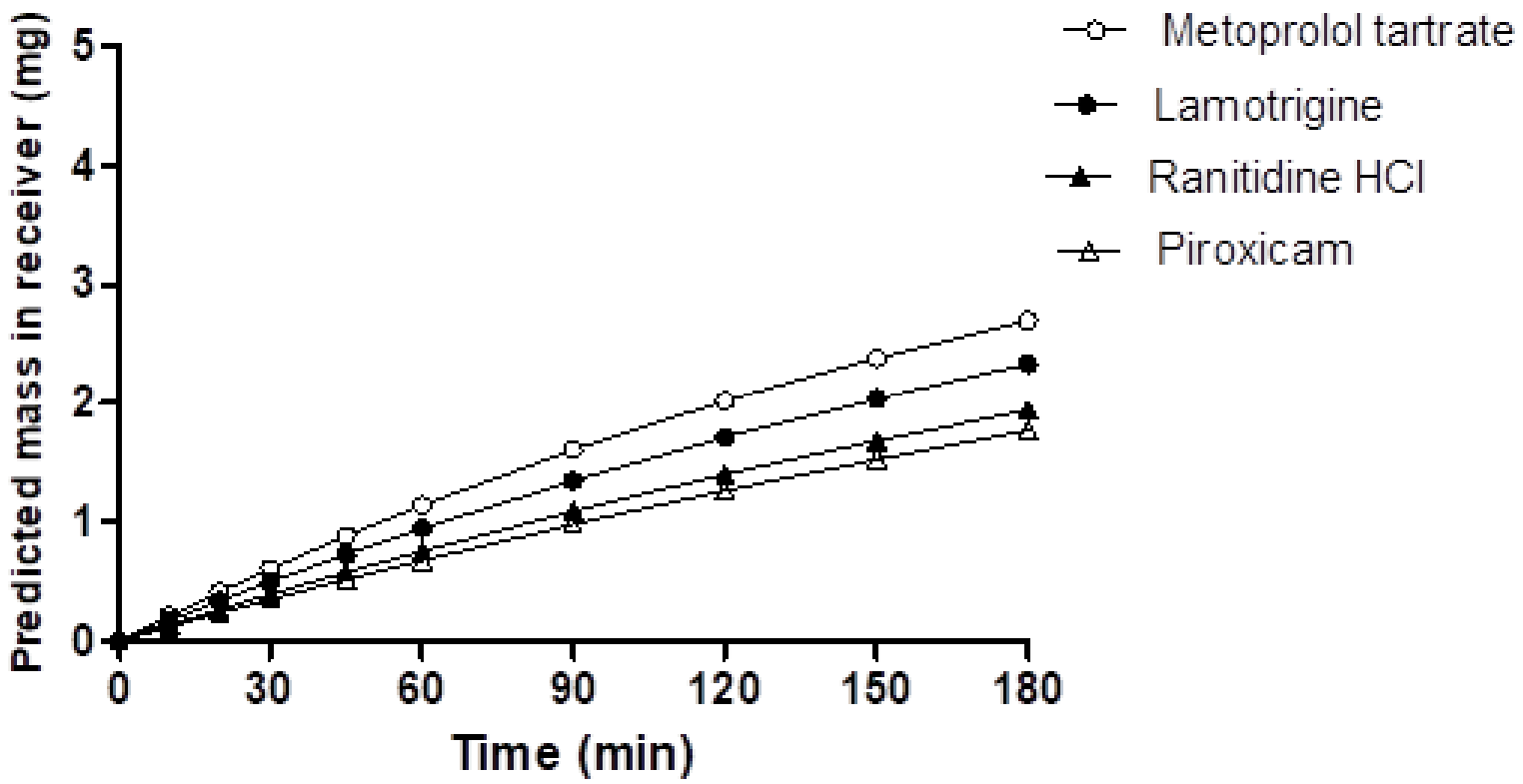
D-HFM permeation studies
-Flow rate sensitivity study using metoprolol tartrate
-D-HFM permeation studies with metoprolol tartrate, lamotrigine, piroxicam, and rantidine HCl
    - Drug permeation profile
    - Membrane permeability (across HFM module; hollow fibers)

Comparison of observed and predicted D-HFM system performance
-Drug permeation profile
-Membrane permeability

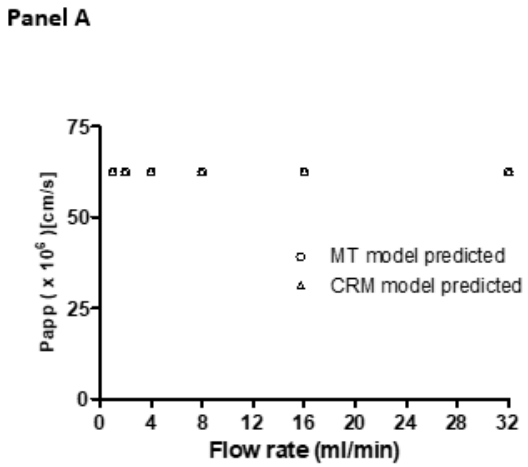
Comparison of observed HFM Kp' to in vivo Kp

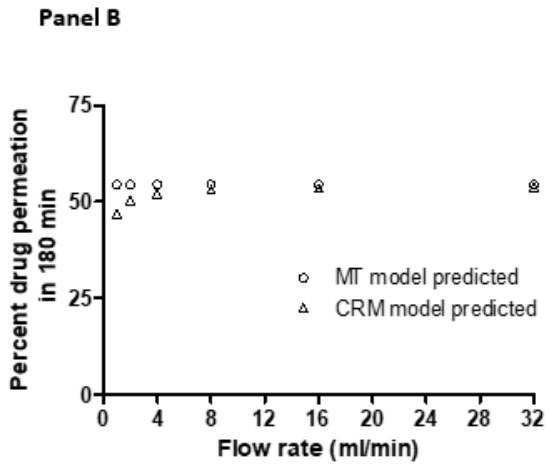
Predicted drug permeation profile in D-HFM system using MT model

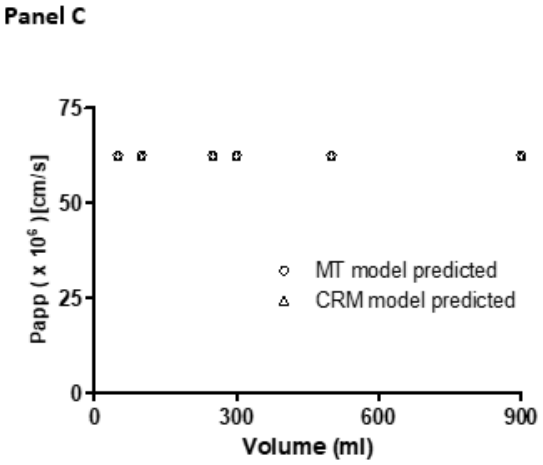
Total donor drug mass was 5 mg. A= 1.15 cm^{-1}. V = 100ml.

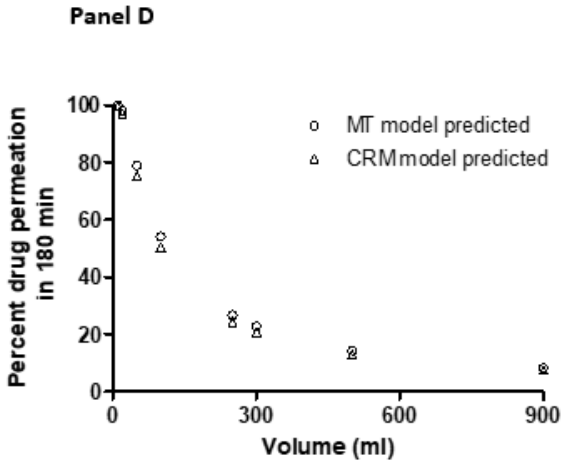


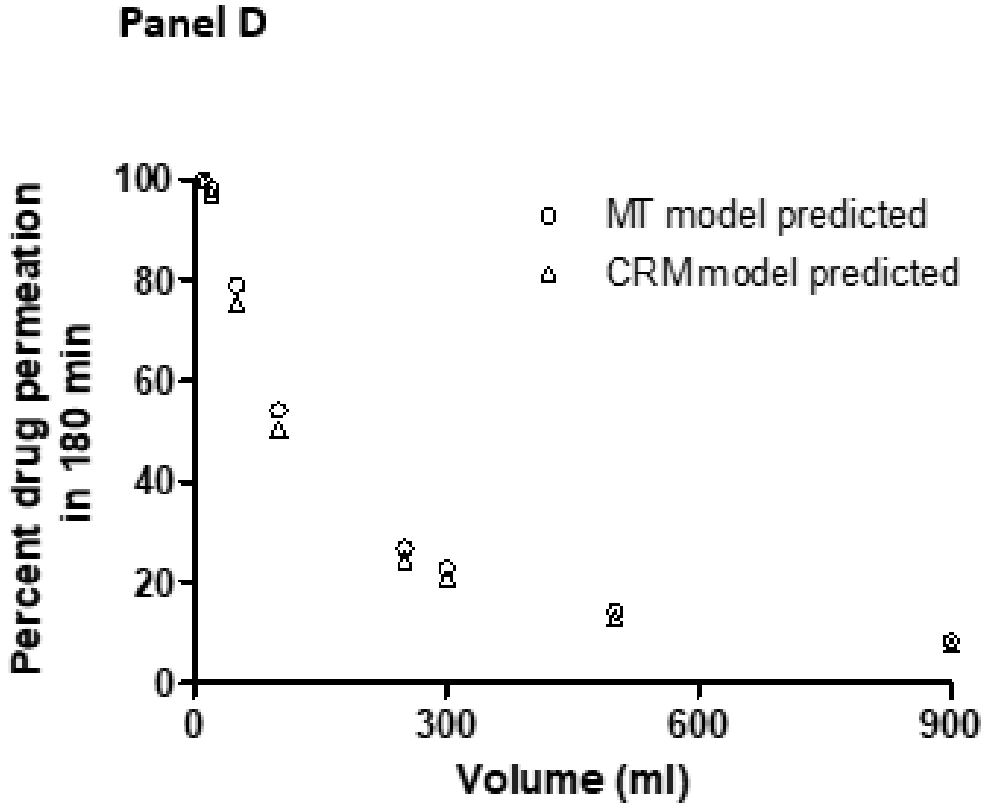
Donor flow rate and donor volume sensitivity study using MT and CRM flow in D-HFM system





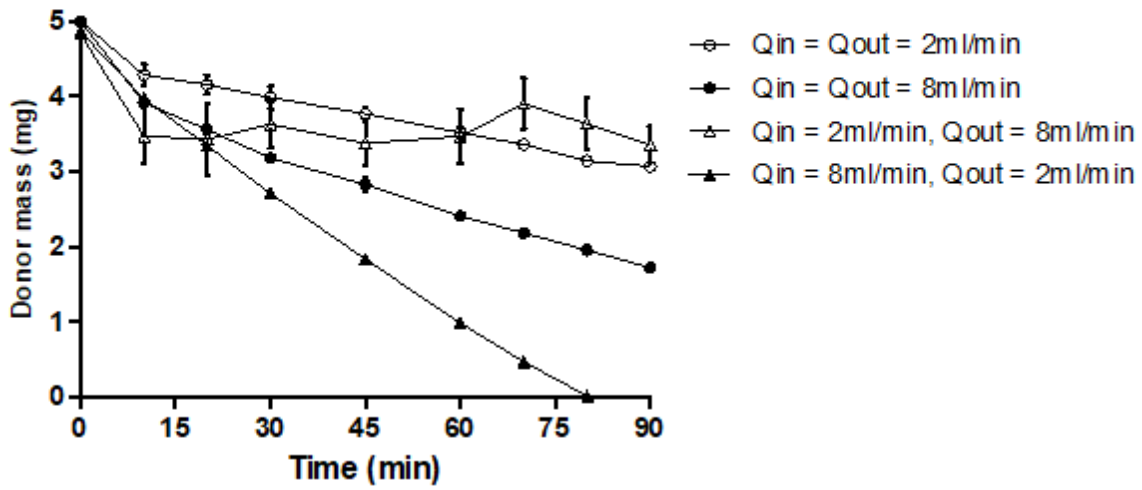




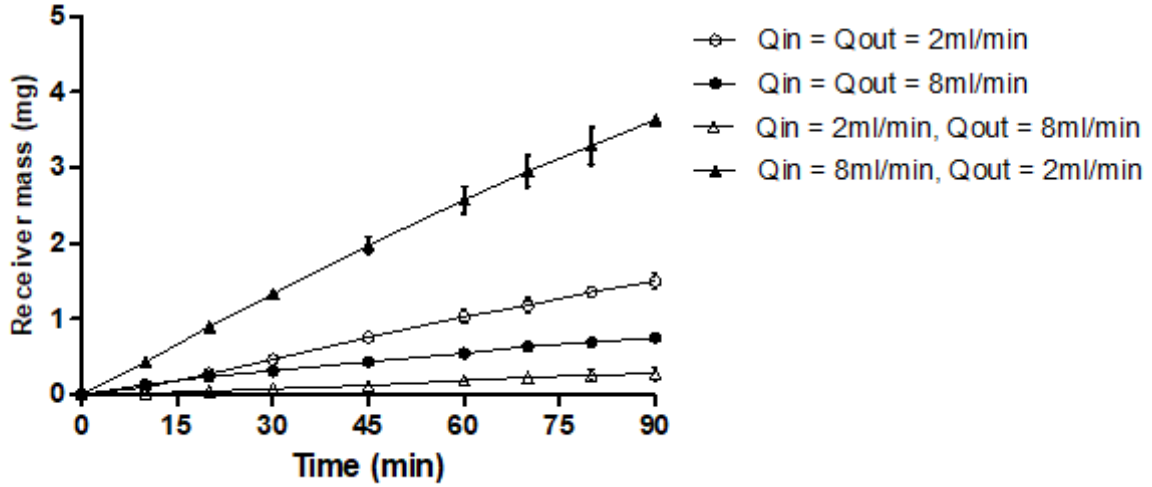


Flow rate sensitivity study using metoprolol tartrate in D-HFM system

Panel A



Panel B

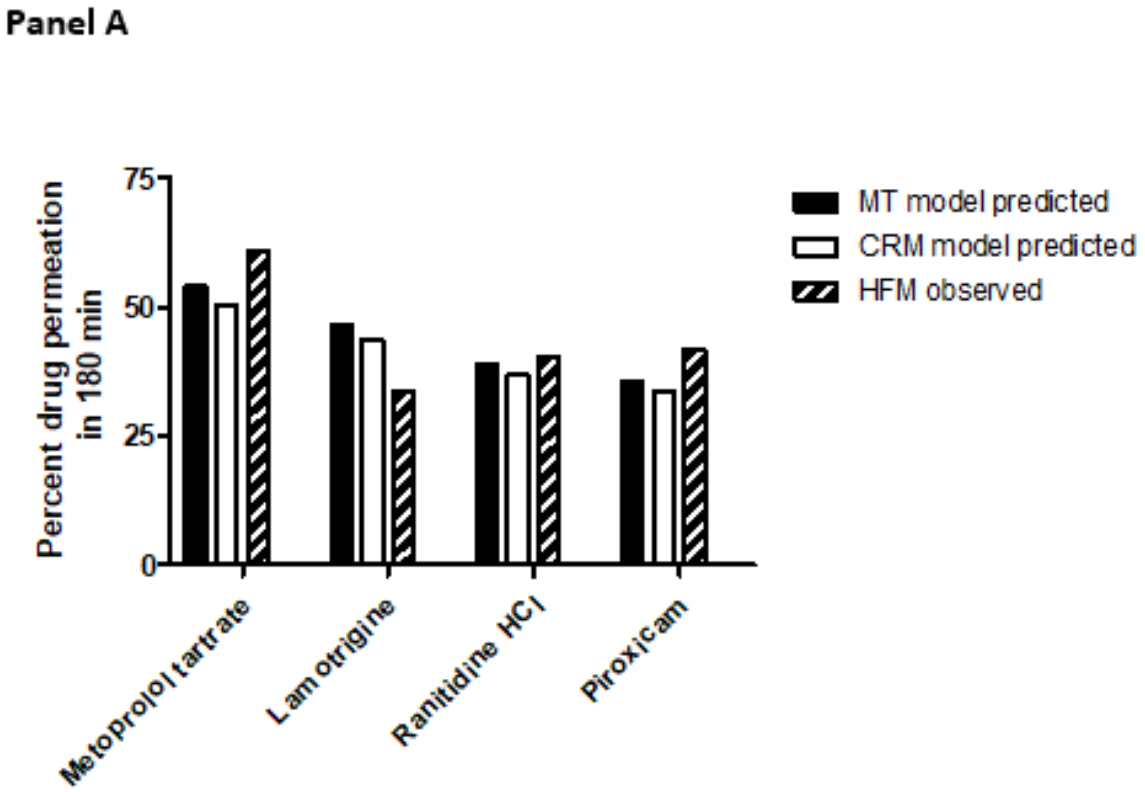


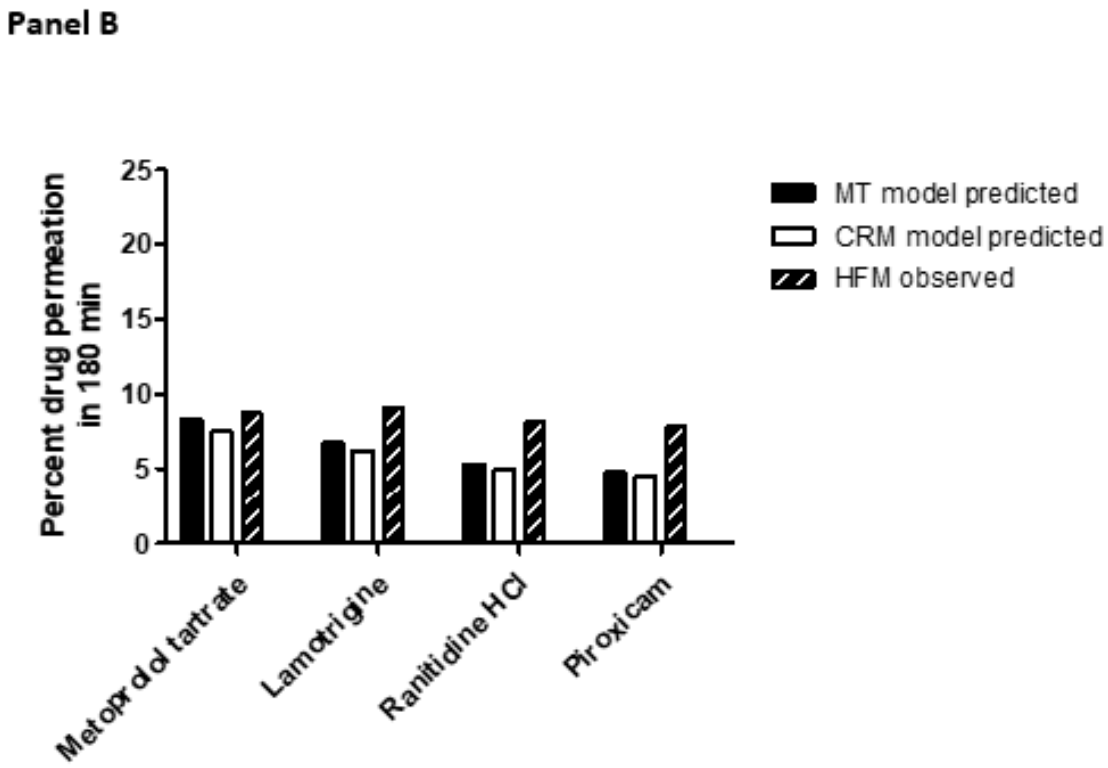
Selected Qin = Qout = 2ml/min. Larger hydrostatic pressure effects at higher flow rates.

Comparison of predicted and observed percent drug permeation in 180 min

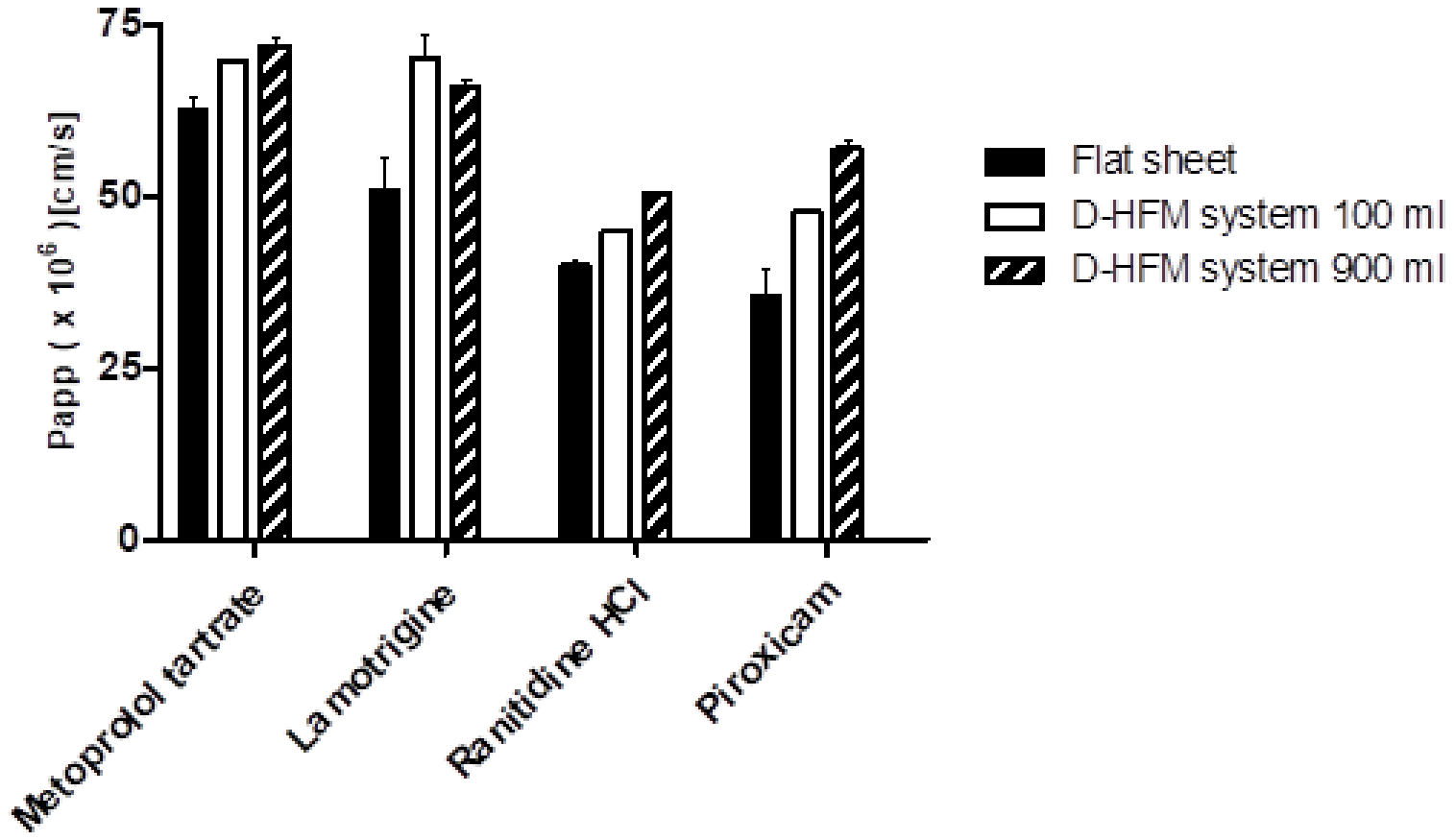
donor volume = 100 ml

donor volume = 900 ml

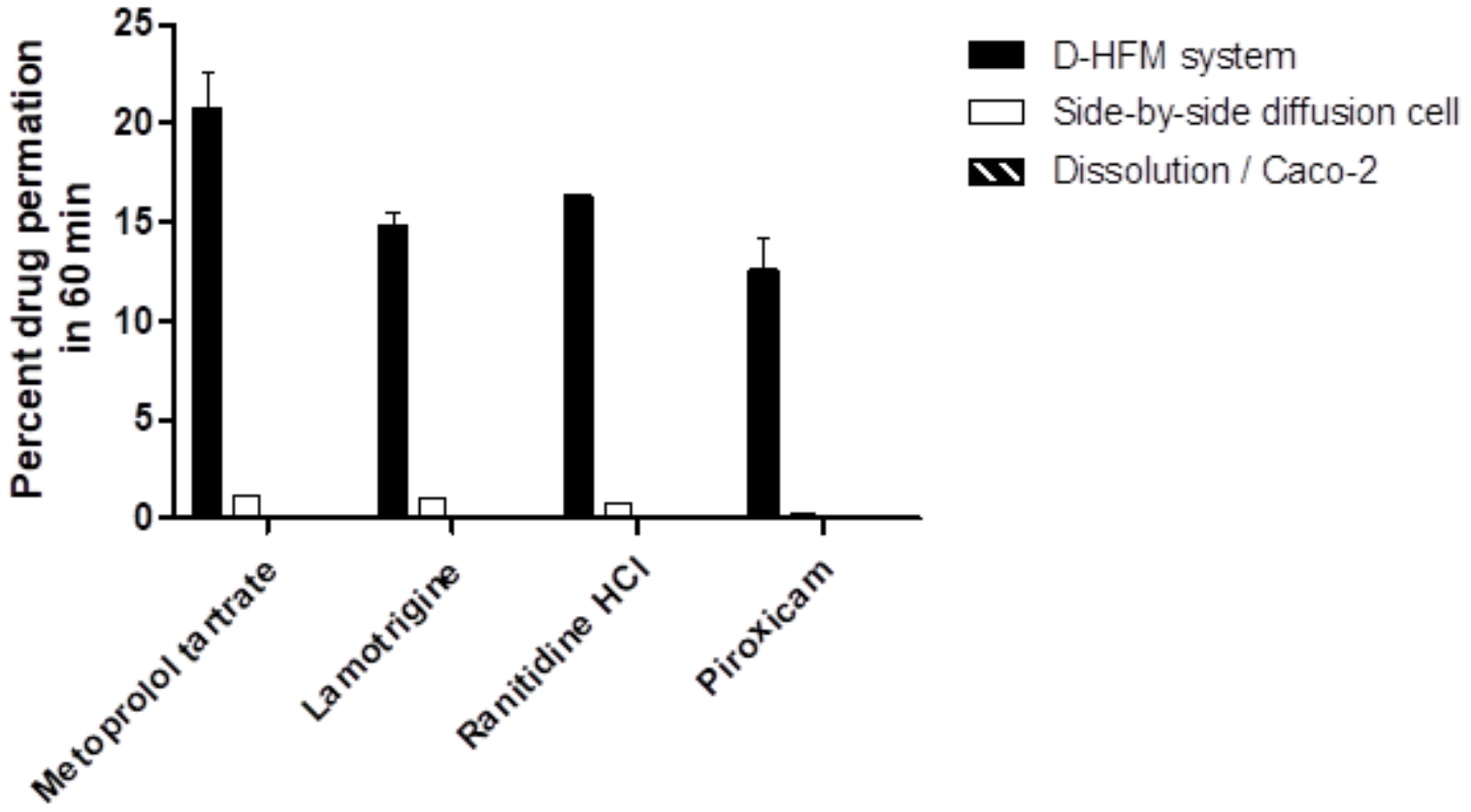




Comparison of flat sheet and HFM membrane permeability



Comparison of observed drug permeated in 60 min from various in vitro models



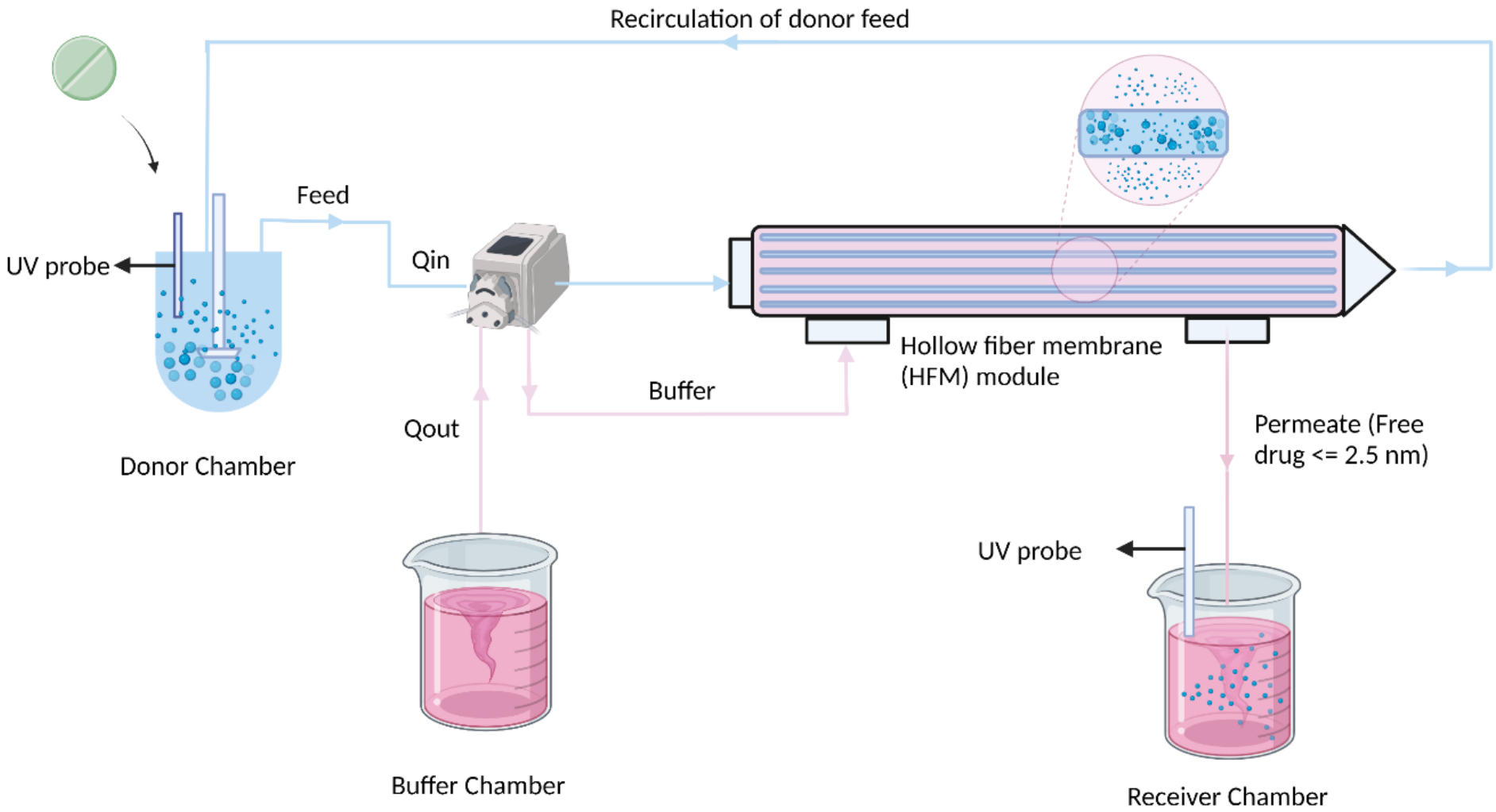
Comparison of observed in vivo clinical permeation constant k_p with in vitro permeation constant $K_p^{'}$ from various in vitro models

Drugs	In vivo clinical permeation constant $[k_p$ (hr^{-1})]	In vitro permeation constant based on D-HFM system $[K_p^{'}$ (hr^{-1})]	In vitro permeation constant based on side-by-side diffusion cell $[K_p^{'}$ (hr^{-1})]	In vitro permeation constant based on dissolution/Caco-2 system $[K_p^{'}$ (hr^{-1})]
Metoprolol tartrate	**0.609**	**0.288 – 0.033**	0.017	0.0003
Lamotrigine	**4.93**	**0.289 – 0.0302**	0.014	0.001
Ranitidine HCl	**0.225**	**0.186 – 0.0231**	0.011	0.000006
Piroxicam	**9.00**	**0.197 – 0.0261**	0.0098	0.0007

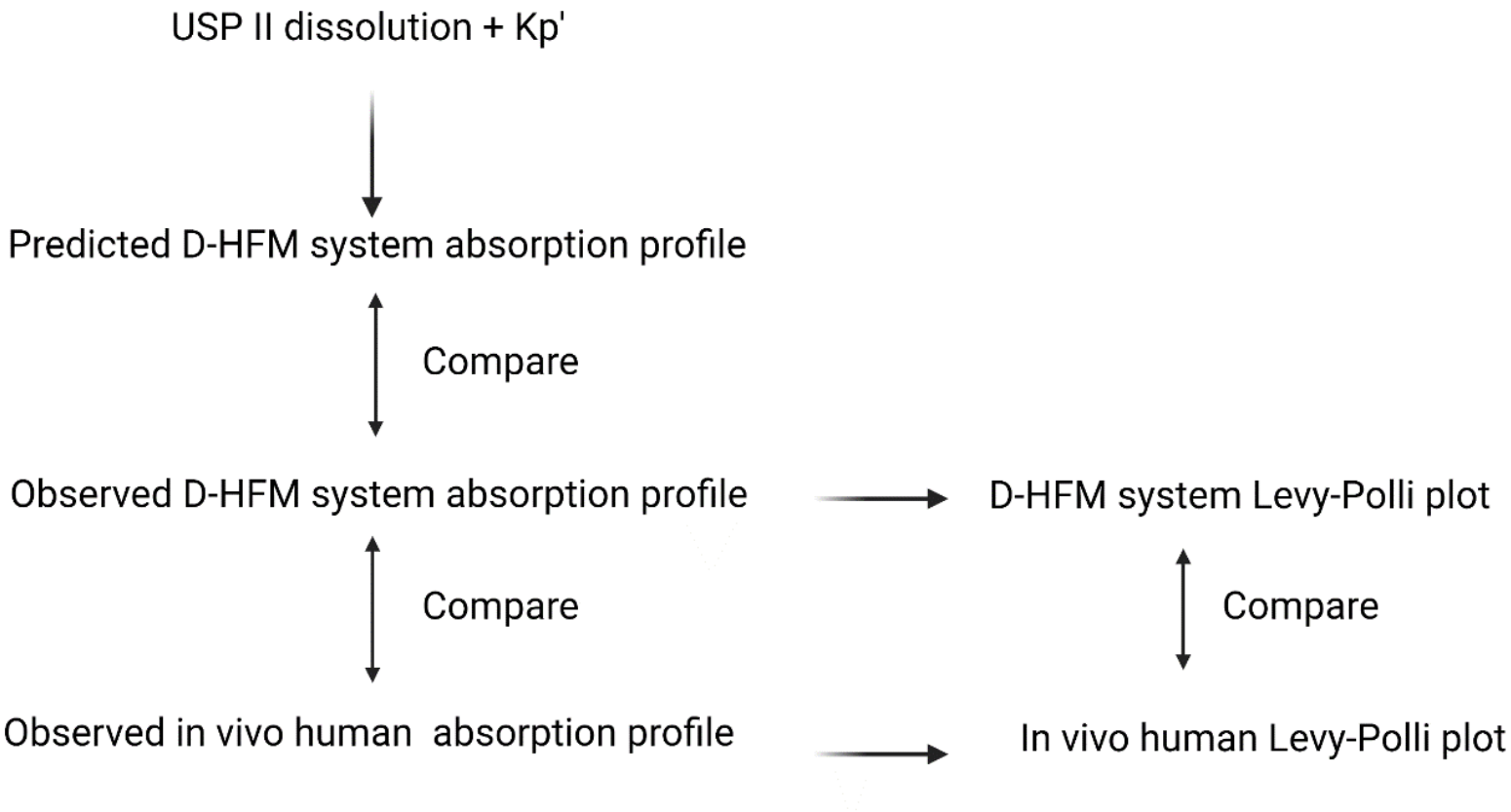
Topics

- Characterize a dissolution-hollow fiber membrane (D-HFM) system and compare its resulting in vitro drug permeation constants K_p' to in vivo clinical permeation constants k_p for four drugs in various BCS classes
  - Adhikari A, Seo, PR, Polli, JE. (2022): Characterization of dissolution-permeation system using hollow fiber membrane module and utility to predict in vivo drug permeation across BCS classes. DOI: 10.1016/j.xphs.2022.07.002. J Pharm Sci. In press.
- Predict the in vivo human absorption profile and biopharmaceutic performance of five drug products using the D-HFM system
  - Adhikari A, Seo, PR, Polli, JE.: Dissolution-Hollow Fiber Membrane (D-HFM) system to anticipate biopharmaceutics risk of tablets and capsules. Submitted.

Illustration of dissolution-hollow fiber membrane (D-HFM) system



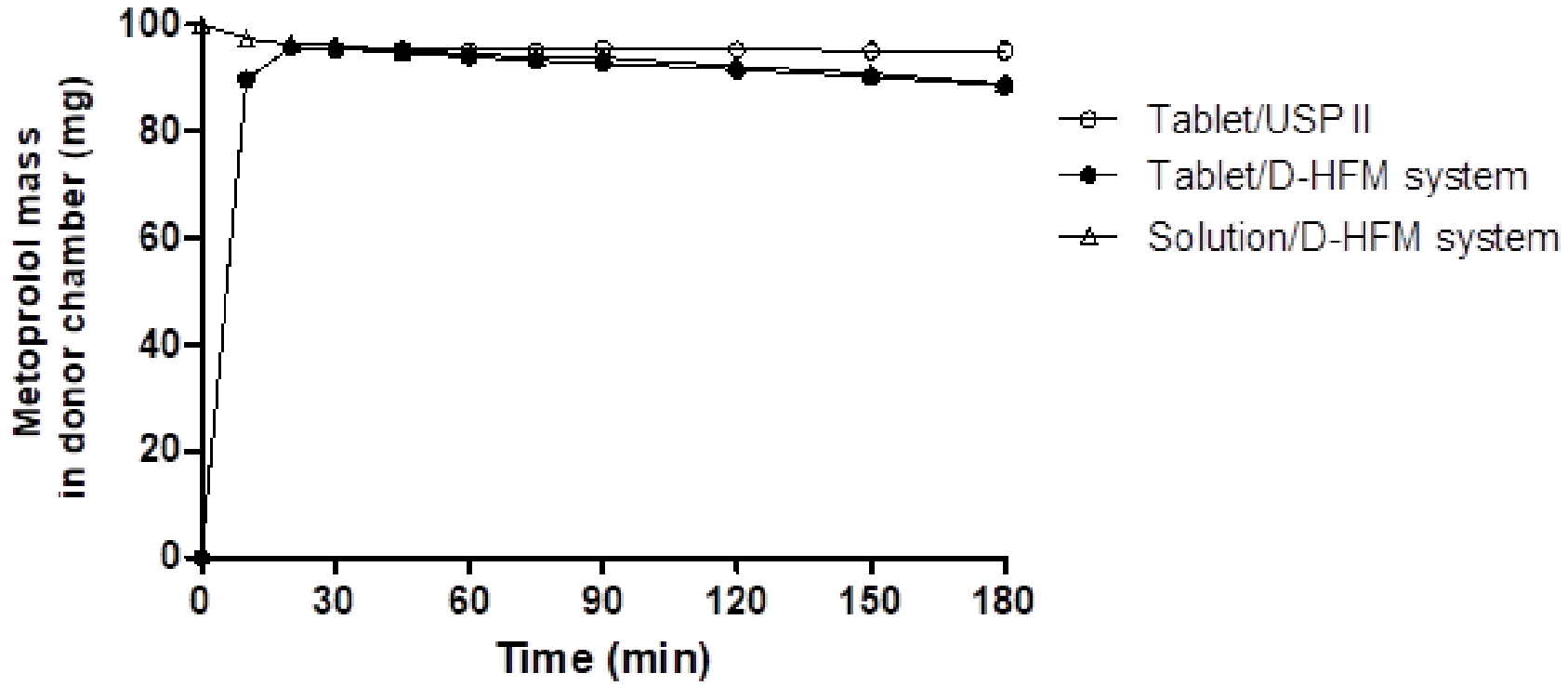
Scope and flow of tablet and capsule studies



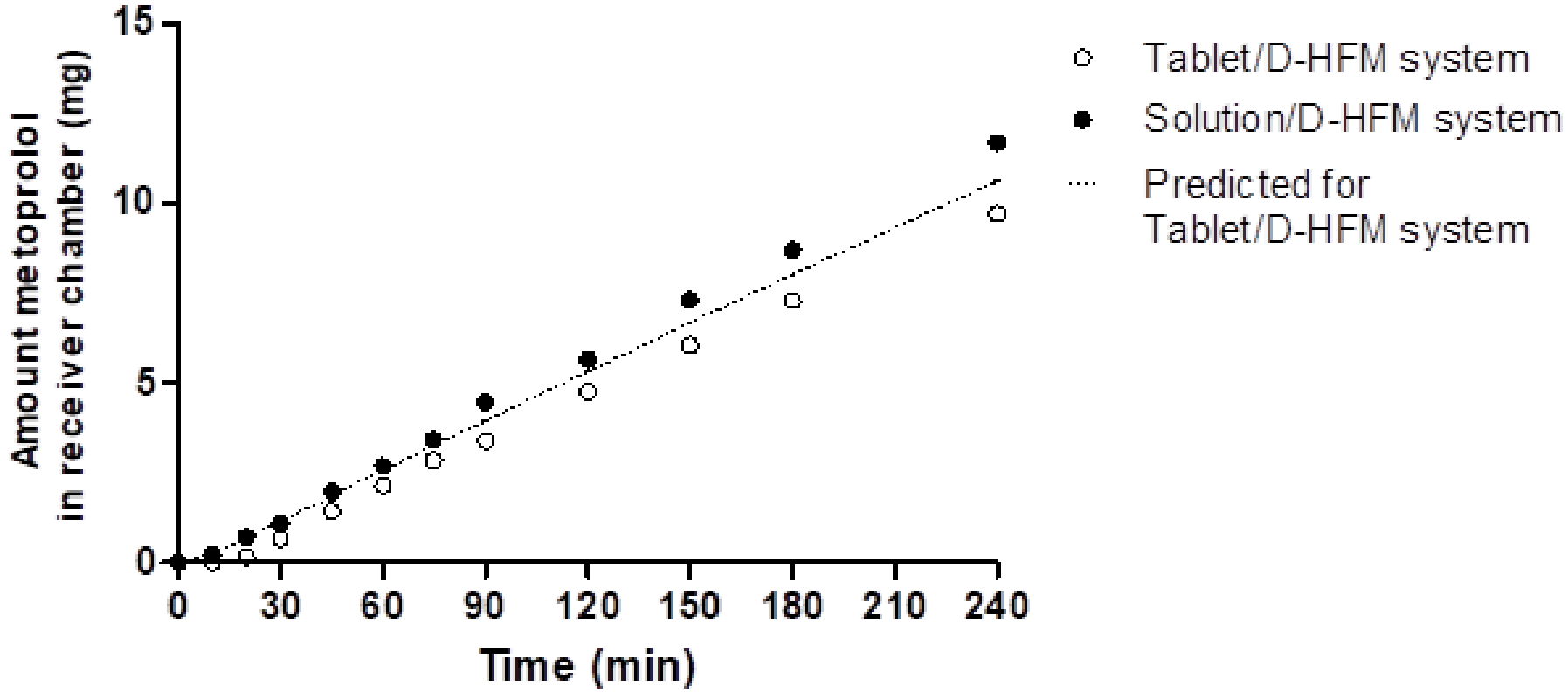
Summary

- Predicted and observed absorption profiles in D-HFM system showed close agreement for each solid oral dosage form
- Levy-Polli plots from D-HFM system successfully predicted the four IR products to be low biopharmaceutic risk
- Levy-Polli plots from D-HFM system successfully predicted metoprolol ER product to be high biopharmaceutic risk due to dissolution rate limited absorption
- In vitro D-HFM system has utility to predict in vivo biopharmaceutics risk of tablet and capsule performance

Mass dissolved in donor in USP II vessel and D-HFM system for metoprolol IR tablet and solution



Predicted and observed absorption profiles into receiver chamber in D-HFM system for metoprolol IR tablet

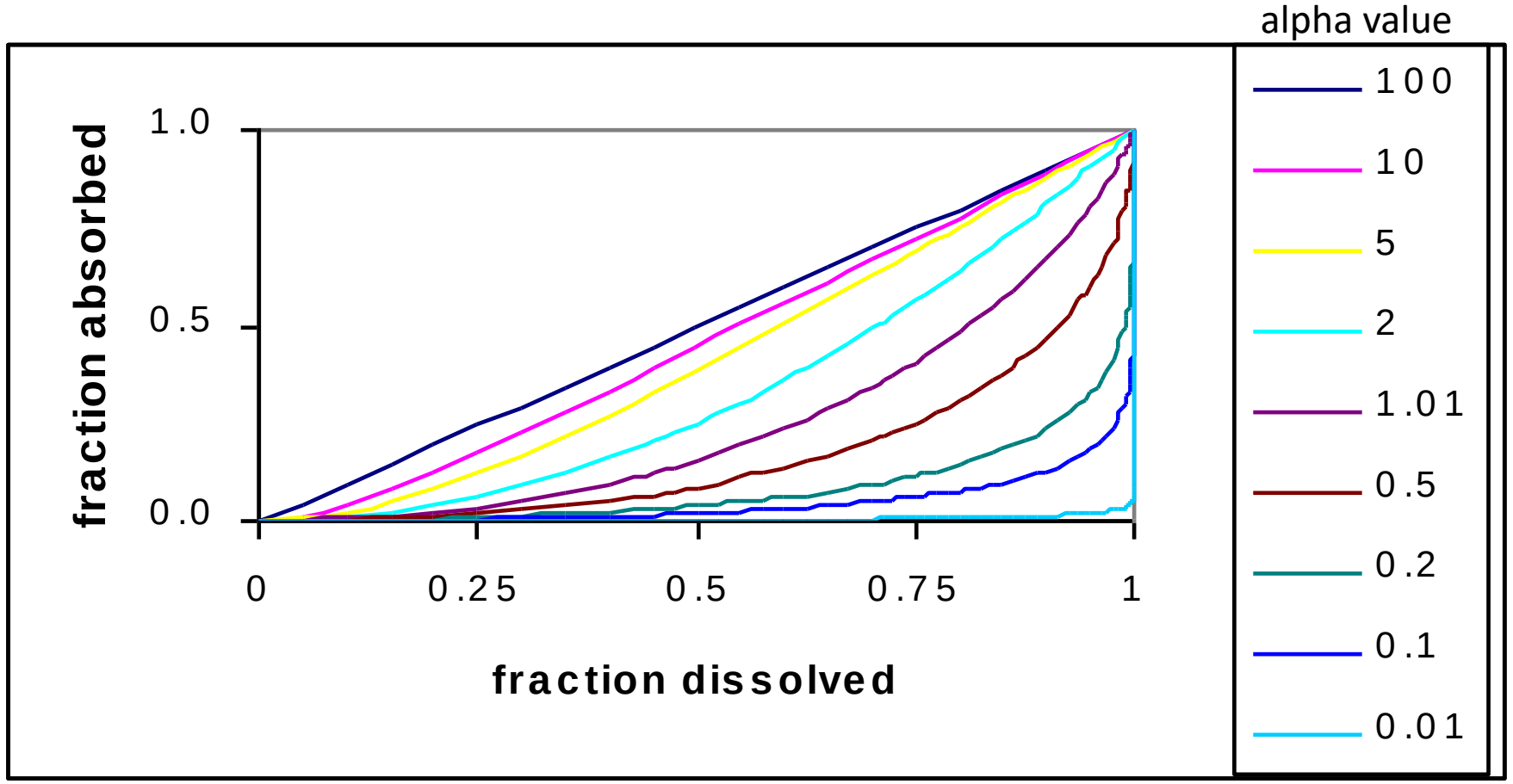


Deconvolution-based IVIVC model

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

- F_a is the fraction of the total amount of drug absorbed at time *t*,
- f_a is the fraction of the dose absorbed at *t* = infinity,
- alpha is the ratio of the first-order apparent permeation rate coefficient (k_p^{app}) to the first-order dissolution rate coefficient (k_d), and
- F_d is the fraction of drug dose dissolved at time *t*.
- 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

Theoretical IVIVRs



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

Correlation

- “degree of relationship between two random variables”

Kachigan, S.K. *Multivariate Statistical Analysis*; Radius Press, New York, 1991.

Levy plot of aspirin

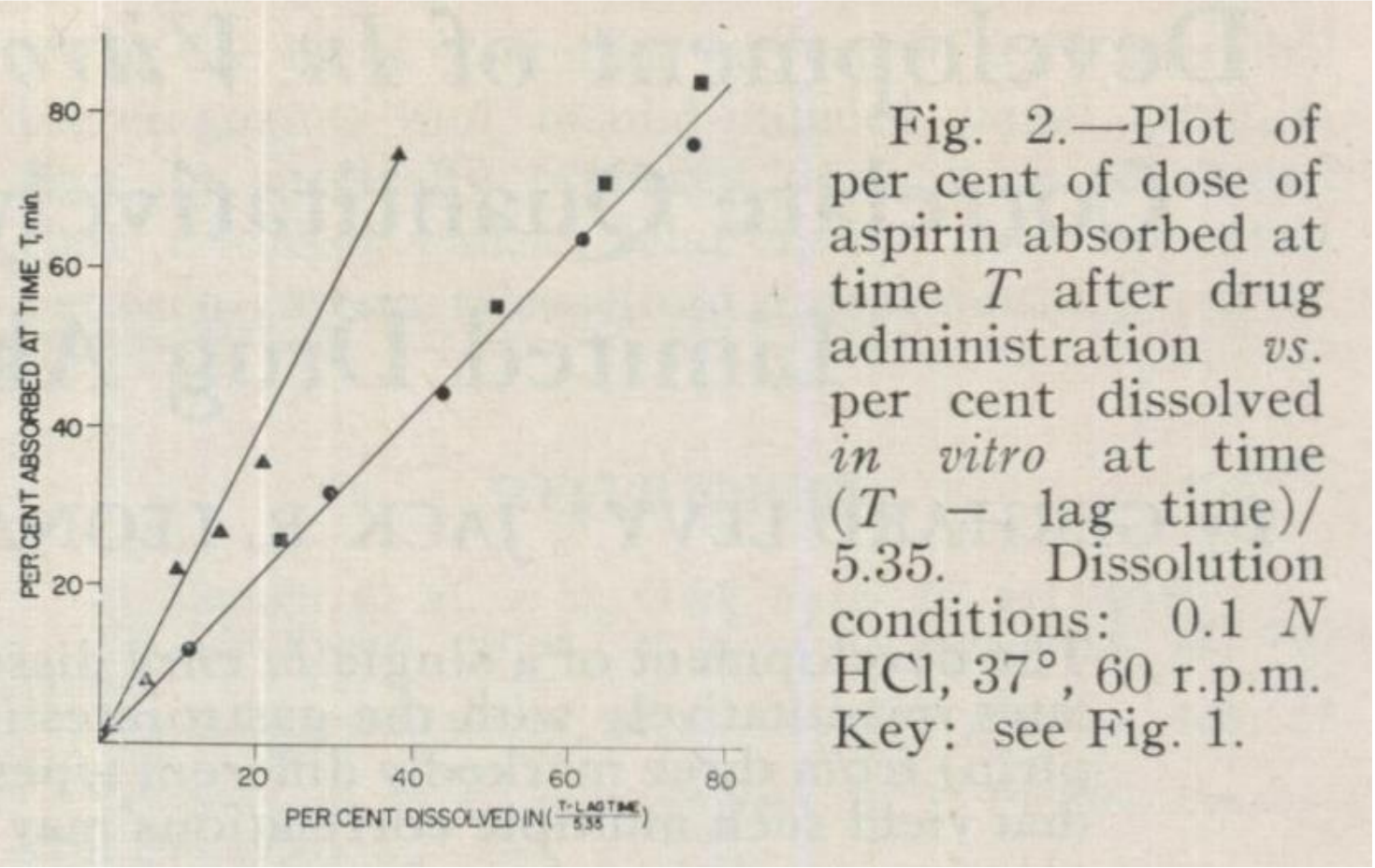
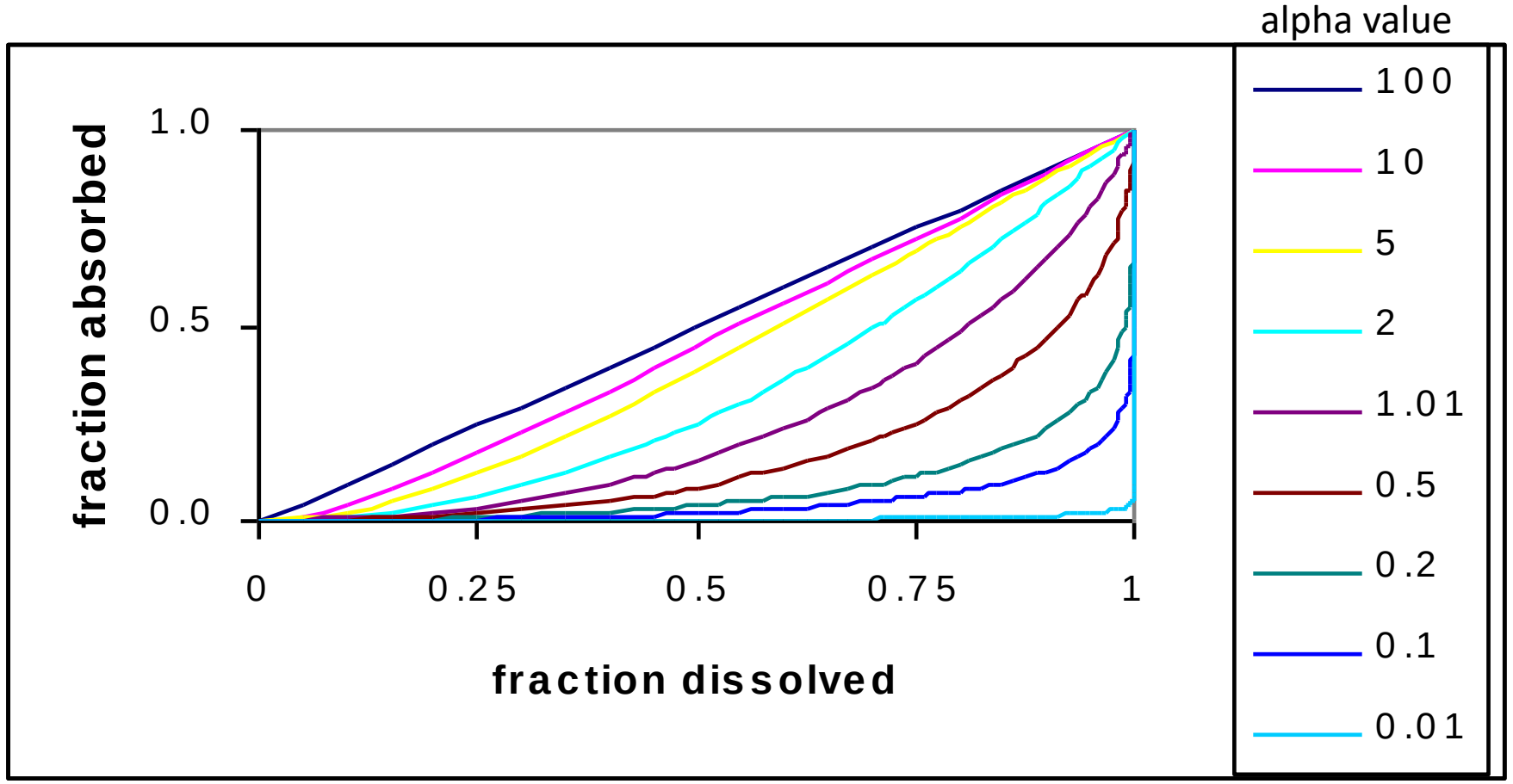


Fig. 2.—Plot of per cent of dose of aspirin absorbed at time T after drug administration *vs.* per cent dissolved *in vitro* at time (T − lag time)/5.35. Dissolution conditions: 0.1 N HCl, 37°, 60 r.p.m. Key: see Fig. 1.

Fig. 1.—Absorption of 0.65 Gm. of aspirin from solution (○), from tablets containing alkaline additives (■), plain tablets (●), and microencapsulated particles (▲). Average of 12 subjects.

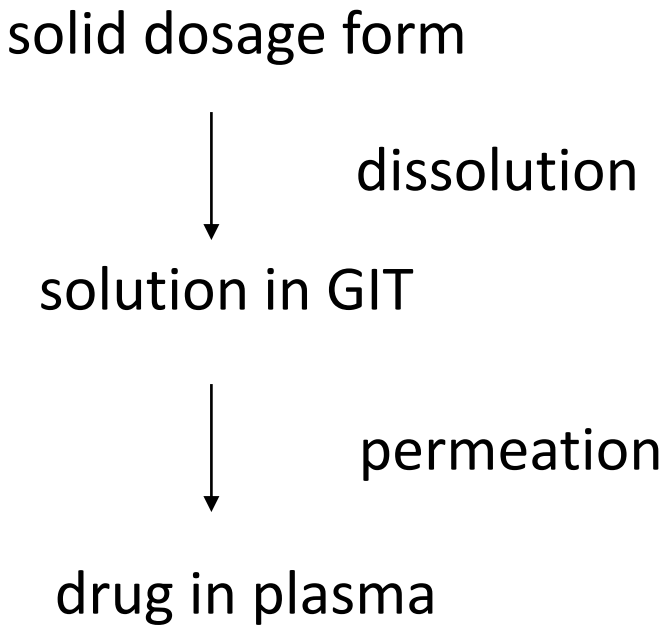
Gerhard Levy, Jack R. Leonards, Josephine A. Procknal (1965): Development of in vitro dissolution tests which correlate quantitatively with dissolution rate-limited drug absorption in man. J Pharm Sci 54:1719-1722.

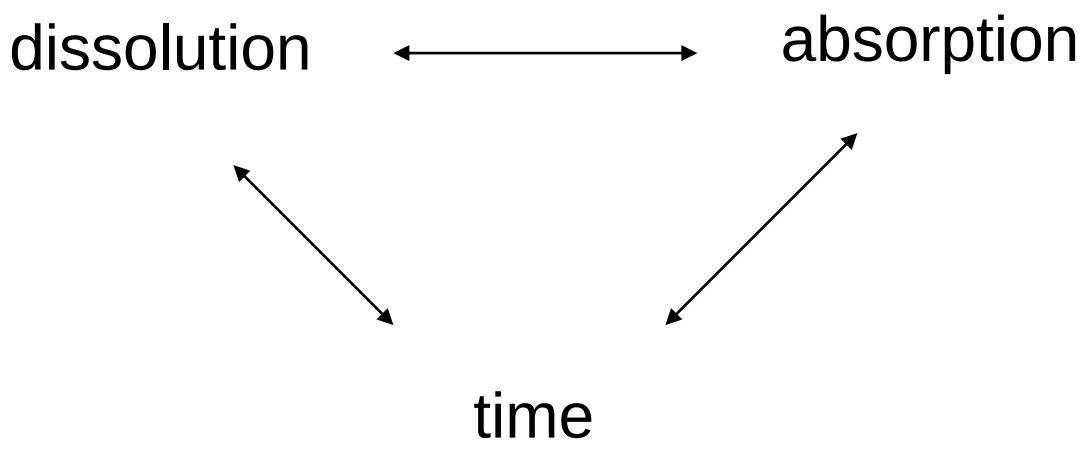
Theoretical IVIVRs



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

Model Development





Model Assumptions

- Only dissolution and permeation
  - first-order dissolution (k_d)
    - $F_d^{\text{in vitro}} = F_d^{\text{in vivo}} = F_d$
  - first-order permeation (k_p)

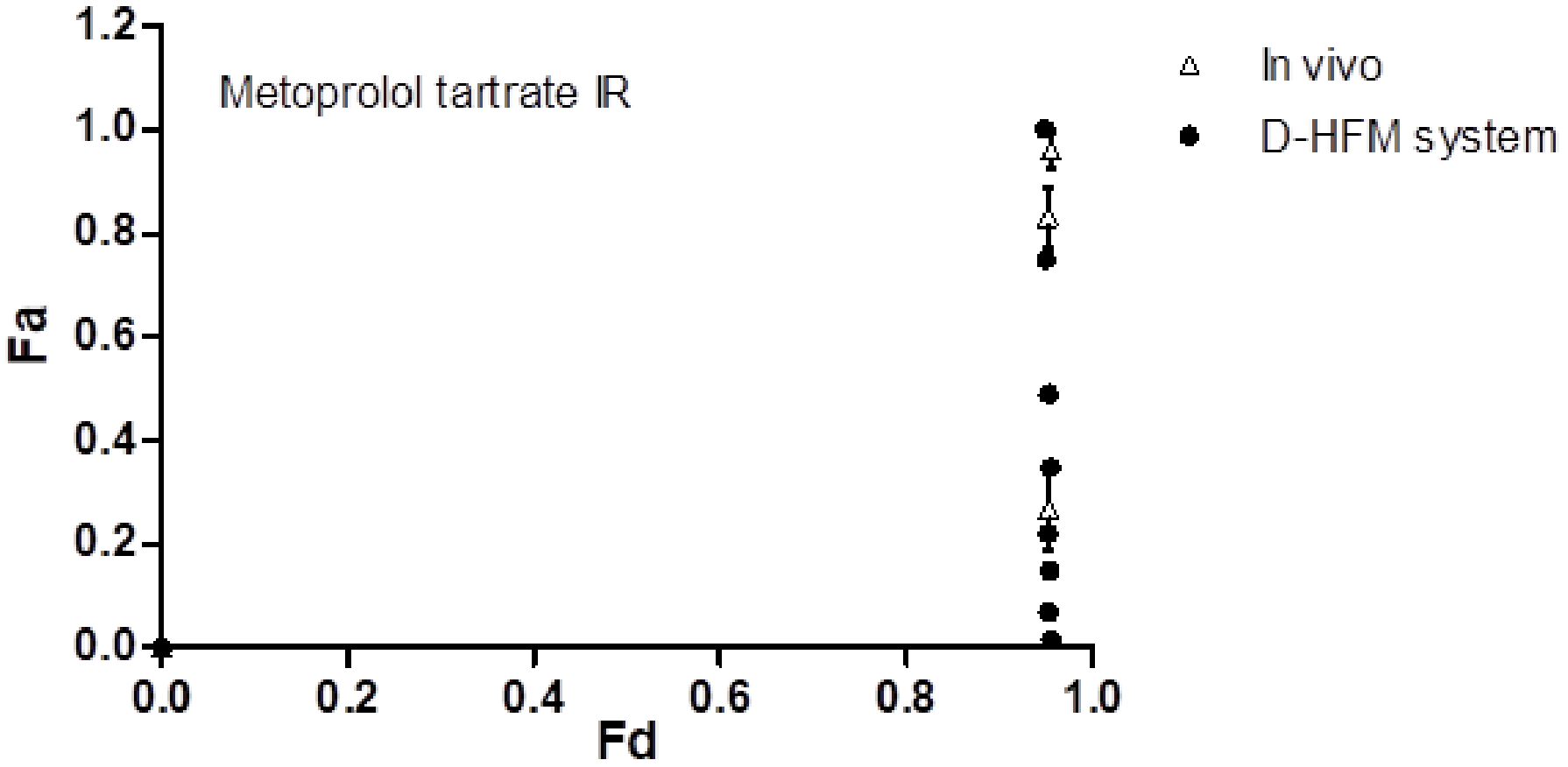
- Assumptions in the determination of F_a

Alpha

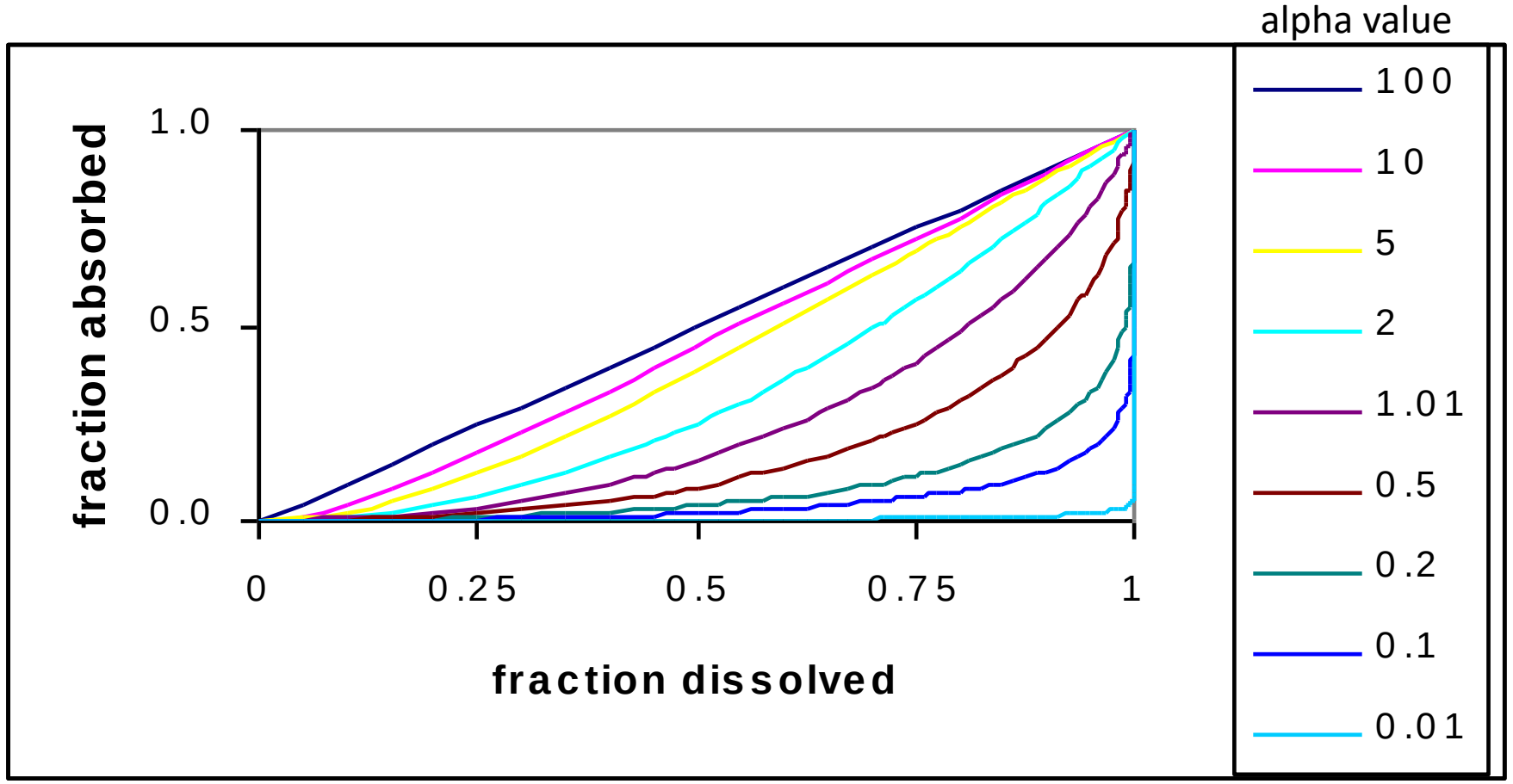
$$\alpha = \frac{k_p^{app}}{k_d}$$

- large alpha: dissolution rate-limited absorption
- small alpha: permeation rate-limited absorption
- alpha = 1: mixed rate-limited absorption

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

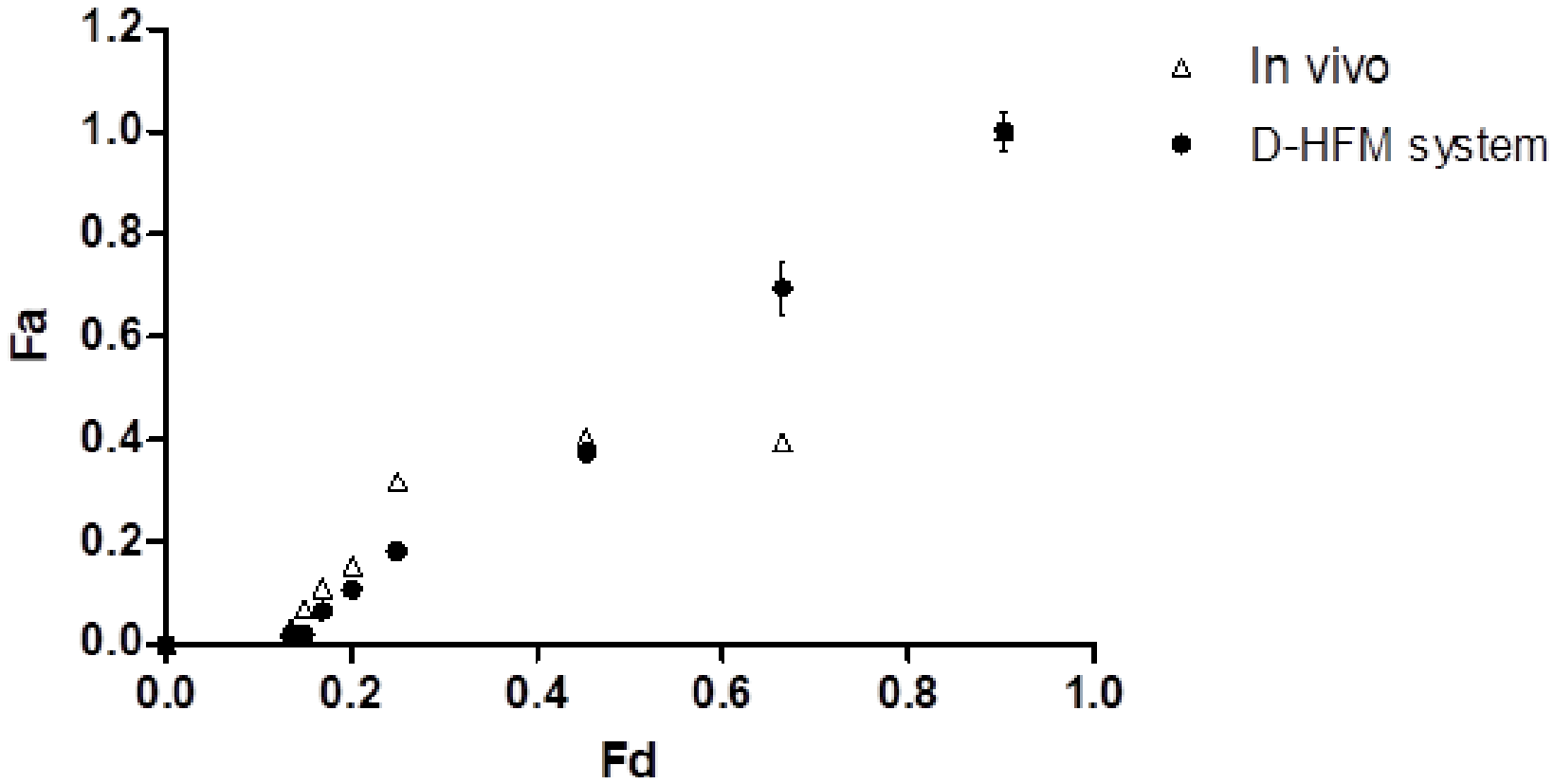


Theoretical IVIVRs



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

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



Topics

- Characterize a dissolution-hollow fiber membrane (D-HFM) system and compare its resulting in vitro drug permeation constants K_p' to in vivo clinical permeation constants k_p for four drugs in various BCS classes
  - Adhikari A, Seo, PR, Polli, JE. (2022): Characterization of dissolution-permeation system using hollow fiber membrane module and utility to predict in vivo drug permeation across BCS classes. DOI: 10.1016/j.xphs.2022.07.002. J Pharm Sci. In press.
- Predict the in vivo human absorption profile and biopharmaceutic performance of five drug products using the D-HFM system
  - Adhikari A, Seo, PR, Polli, JE.: Dissolution-Hollow Fiber Membrane (D-HFM) system to anticipate biopharmaceutics risk of tablets and capsules. Submitted.

Additional references

- 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.
- 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.
- Polli, J.E. and Ginski, M.J. (1998): Human drug absorption kinetics and comparison to Caco-2 monolayer permeabilities. Pharm. Res. 15:47-52.
- Ginski, M.J., Taneja, R., and Polli, J.E. (1999): Prediction of dissolution-absorption relationships from a continuous dissolution/Caco-2 system. AAPSPharmSci 1(2): [serial on the internet]. June 3, 1999; Approx. size: 76k + 156k in images. Available from: http://www.pharmsci.org/journal.

Thank you!

- Questions?

USP Level A

- USP Level A is a special (linear) case of

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

where f_a = 1 and α >>1, such that $F_a = F_d$.

Categories of IVIVC/IVIVR

- Convolution (FDA Level A) AAA
- Deconvolution AA
- Deconvolution (but only linear) A
  - USP Level A
- Summary parameters B
- Point estimates C
- Rank order D

Polli, J.E. “Analysis of In Vitro - In Vivo Data”. In Amidon, G.L., Robinson, J.R., and Williams, R.L. (eds.), *Scientific Foundation and Applications for the Biopharmaceutics Classification System and In Vitro - In Vivo Correlations*; *AAPS Press*: Alexandria, VA, 1997, pp. 335-352.

Selection of IVIVC Approach

interested in drug absorption

Level AA (deconvolution-based)

interested in overall pharmacokinetics

Level AAA (convolution-based)

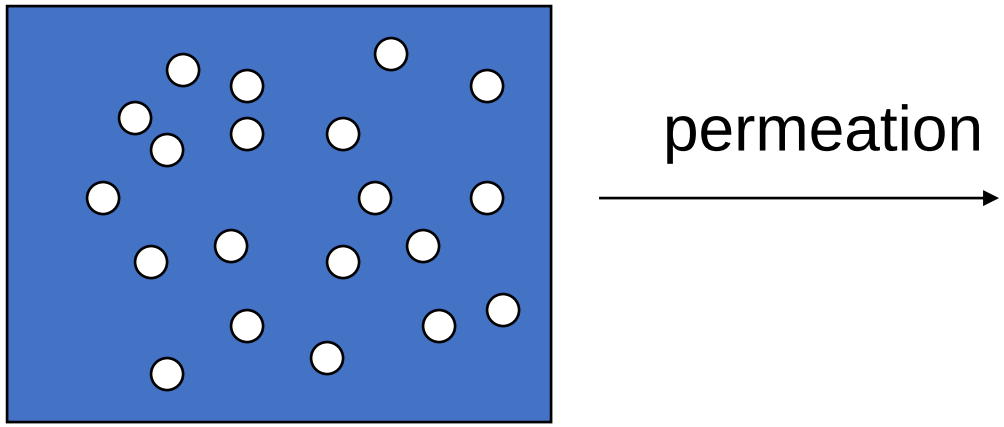
Reasons for Unsuccessful “In Vitro - In Vivo Correlation”

- inadequate “IVIVR” model
  - in vivo dissolution not rate limiting
- in vitro dissolution did not replicate in vivo dissolution
  - dissolution is being used as a QC tool
- challenges with in vivo study design/conditions
  - variability/power
  - drug PK

Obervations from Historical “Straight Line” Correlations

- Need dissolution to be rate-controlling
- Generally require the same mechanism in order to observe the same “correlation” pattern
- Different mechanism generally result in different “correlation” pattern

Effect of Incomplete Absorption due to Low Permeability



- Plasma data over-estimates absorption kinetics, since it does not “see” unabsorbed drug.
- Polli, J.E. and Ginski, M.J. (1998): Human drug absorption kinetics and comparison to Caco-2 monolayer permeabilities. *Pharm. Res.* **15**:47-52.