PBPK-based and Traditional IVIVC as Complementary Tools to Quality by Design in the Biopharmaceutics Space

David Good

4th FDA/PQRI Conference on Advancing Product Quality
Enabling Patient Focused Modeling and Simulation for Oral Products
April 10th 2019
Rockville, MD

Bristol-Myers Squibb

Outline

- Background
  - History
  - Applications
    - Formulation Development
    - Regulatory
  - Categories
- Development, Physiological, and In Vitro Considerations
- Case Studies
- Summary

In Vitro – In Vivo Correlation (IVIVC)

Working definition:

- *"A predictive mathematical treatment describing the relationship between an in vitro property of a dosage form (e.g., the rate or extent of drug release) and a relevant in vivo response (e.g., plasma concentration-time data)"*

FDA Guidance for Industry Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In VivoCorrelations (1997)*

In Vitro - In Vivo Correlations

- History
  - 1987: “science and technology at the time did not permit consistently meaningful IVIVC for ER dosage forms – IVIVCs should be a future objective.” (*ASCPT/DIA/APS/FDA – sponsored workshop*)
    - Dissolution testing useful for process control, stability, minor formulation changes and manufacturing site changes.
  - 1988: established classification of IVIVC into levels A, B, and C (*USP Stimuli Article*).
  - 1990: “….development of an IVIVC was an important objective on a product-by-product basis.” (*ASCPT/DIA/APS/FDA – sponsored workshop*)
  - 1993: “….dissolution may be used as a sensitive, reliable, and reproducible surrogate for bioequivalence testing.” (*USP/AAPS/FDA – sponsored workshop*)
  - 1997: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (FDA Guidance, Sept. 1997).

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, FDA Guidance Sept. 1997

Applications and Value of Establishing IVIVC

IVIVC can be used for many purposes:

- Applied as surrogate for human bioequivalence trials
  - Establish a safe space for key product quality attributes
  - Biowaivers for changes in the manufacturing or composition of a drug product
    - See *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale and Postapproval changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence, Guidance*
  - To reduce regulatory burden (IVIVC in lieu of additional in vivo experiments)
  - How do I develop my formulation to produce an in vitro dissolution rate that will achieve bioequivalence?
- Dissolution method development and specification setting
  - Which in vitro method best correlates with a deconvoluted in vivo profile?
  - Determine dissolution safe space (profile of all lots in the upper and lower limits of BE)

PBPK as Tool for QbD Implementation

Connects the drug substance properties (pK_a, solubility, permeability, lipophilicity) and formulation properties (particle size distribution, drug particle density) with drug products in vivo behavior (PK profiles)

"Mechanism-based modeling approaches, particularly those used during the formulation development stage, can be of great help for development .... Drug applicants are encouraged to adopt such approaches to guide formulation development and set product specifications."

"Predictive biopharmaceutical models also have great potential uses in CMC review. For example, when there is a large difference in particle size distribution... a predictive absorption model could be employed to identify the risks in having a significant difference in particle size distribution. Another important application is to define biorelevant dissolution specifications"

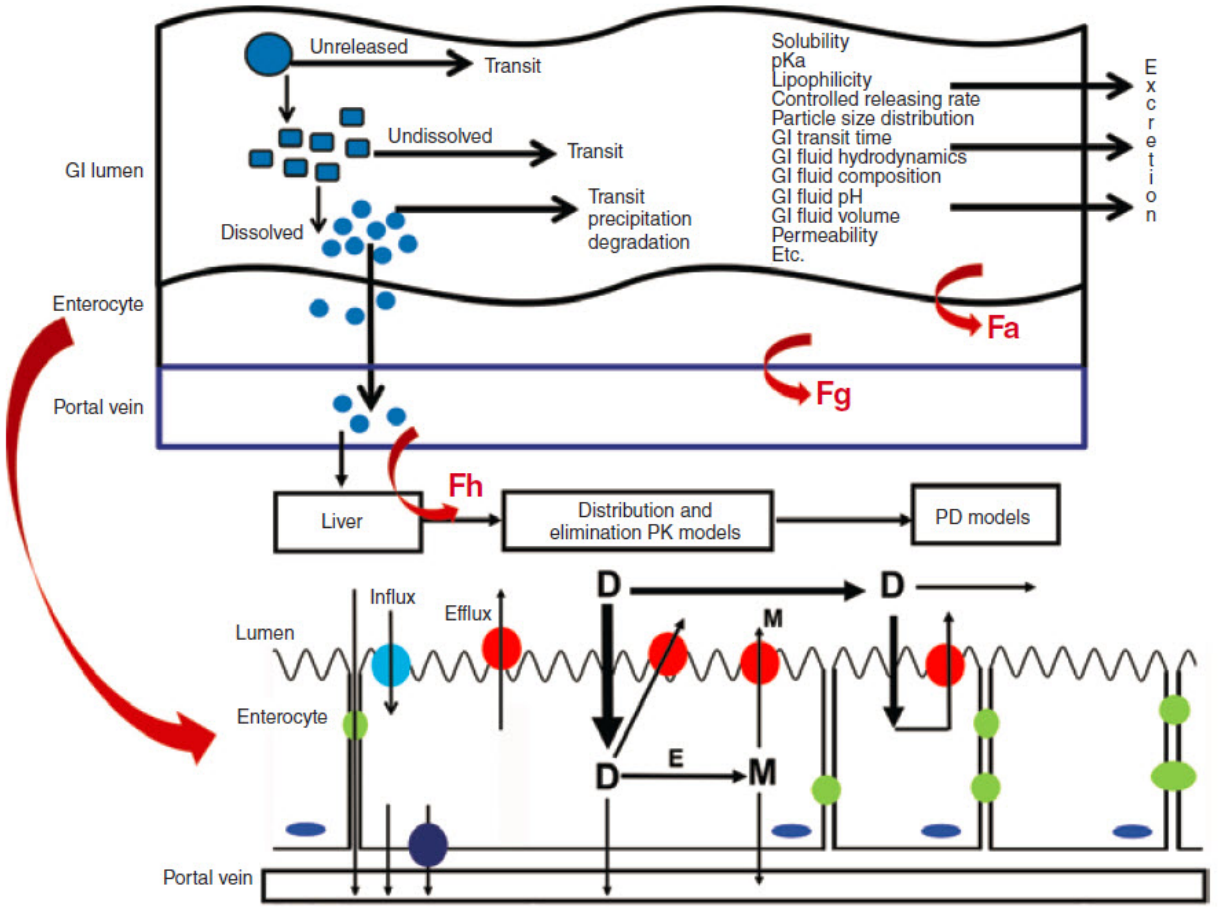


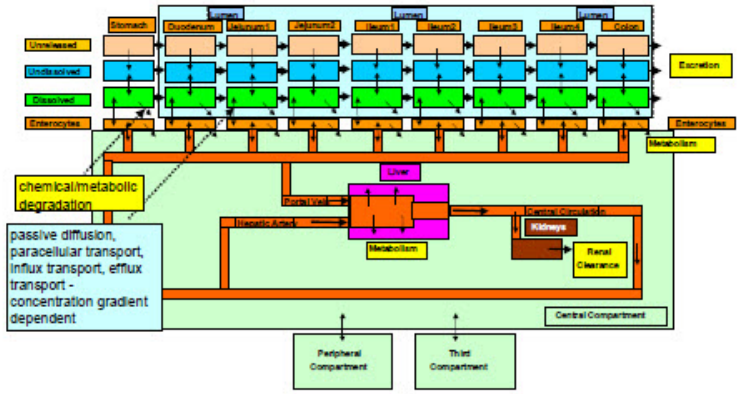
Figure 1 Schematic describing the absorption process of oral solid dosage forms and factors affecting oral absorption. D, drug; E, enzymes; Fa, fraction of drug absorption from the gastrointestinal tract; Fg, fraction of drug that escapes the gut extraction; Fh, fraction of drug that escapes the liver extraction; GI, gastrointestinal; M, metabolites; PD, pharmacodynamics; PK, pharmacokinetics.

X Zhang and RA Lionberger (FDA Office of Generic Drugs)
Clinical pharmacology & Therapeutics | VOLUME 95 NUMBER 5 | MAY 2014

Bristol-Myers Squibb

PBPK: Next step for IVIVC development and biowaivers

PBPK



Classic IVIVC

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

Based on physiological understanding modelling and first principle modelling

Take into account how other absorption factors influences effect of dissolution

Based on empirical mathematical models

Assumes dissolution proportional to absorption

Apply similar criteria for validation prior to use for biowaivers

⇒ ***Greater confidence in IPD/PBPK based biowaivers***

⇒ ***Possibility for biowaivers for all type of products, not only controlled release***

Bristol-Myers Squibb

PBPK: Next step for IVIVC development and biowaivers

PBPK based IVIVC already recognised in Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, 2014

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

30 November 2014
EMA/CHMP/EWP/280/96
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms
(EMA/CPMP/EWP/280/96 Corr1)

Draft Agreed by Pharmacokinetics Working Party	October 2012
Adoption by CHMP for release for consultation	21 February 2013
End of consultation (deadline for comments)	15 September 2013
Agreed by Working Party	22 October 2014
Adoption by Committee	30 November 2014
Date for coming into effect	1 June 2015

This guideline replaces Guideline on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation (EMA/CPMP/EWP/280/96 Corr1)

Keywords	Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics, oral, intramuscular and subcutaneous

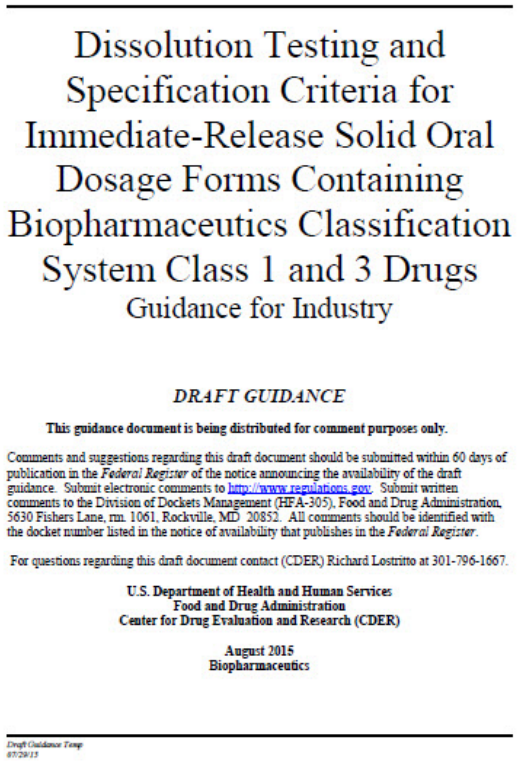
Excerpt from 3. IVIVC development and validation

Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based. One stage approaches include convolution-based and differential equation-based methods and use of physiologically-based pharmacokinetic (PBPK) models.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177884.pdf

Bristol-Myers Squibb

"Applicants may consider further supporting their proposed dissolution specifications with appropriate simulations in addition to dissolution performance data."



Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Richard Lostritto at 301-796-1667.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2015
Biopharmaceutics

Draft Guidance Temp
07/20/15

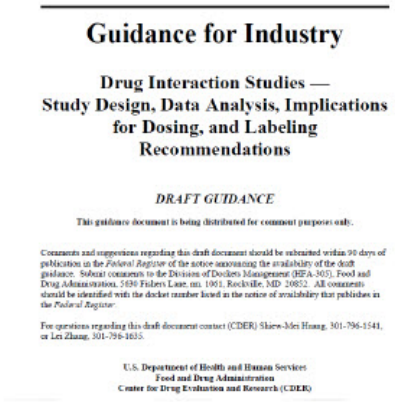
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1 Corr.*
Committee for Human Medicinal Products (CHMP)

Guideline on the Investigation of Drug Interactions

Final

Discussion in the Efficacy Working Party (EWP)	June/October 1996 February 1997
Transmission to the CPMP	March 1997
Transmission to interested parties	March 1997
Deadline for comments	September 1997
Re-submission to the EWP	December 1997
Approval by the CPMP	December 1997
Date for coming into operation	June 1998



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1615.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

…PBPK also extensively used by clinical pharmacology colleagues for drug interactions. Directly inform labeling of products.

Bristol-Myers Squibb

IVIVC Categories

- Level A *Most useful and is recommended*
  - Point to point comparison of the fraction of drug absorbed to the fraction of drug dissolved.
    - Correlation may or may not be linear and scale factors are permitted.
- Level B *Least useful for regulatory purposes*
  - Mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time.
    - Level B does not uniquely reflect the actual in vivo plasma curve.
- Level C *Useful for early stage formulation development*
  Multiple Level C can be as useful as a level A
  - Single point relationship between a dissolution parameter and a pharmacokinetic parameter.

Traditional IVIVC

Output

– Amount of drug reaching central compartment vs. time (systemic availability or F%)

– Does not tell us anything about how it got there:

- *Was it all absorbed and some lost to first pass extraction?*
- *Was only some of it absorbed with little or no first pass extraction?*
- *Was the in vivo release/dissolution anything like the in vitro experiment?*

Assumptions

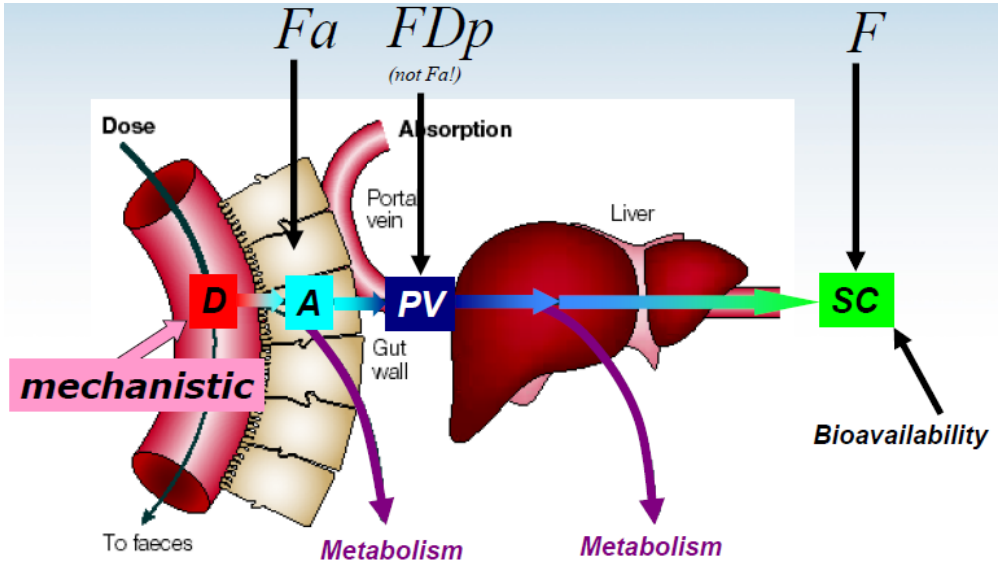
– Drug obeys compartmental model *(doesn't consider drug's true distribution)*

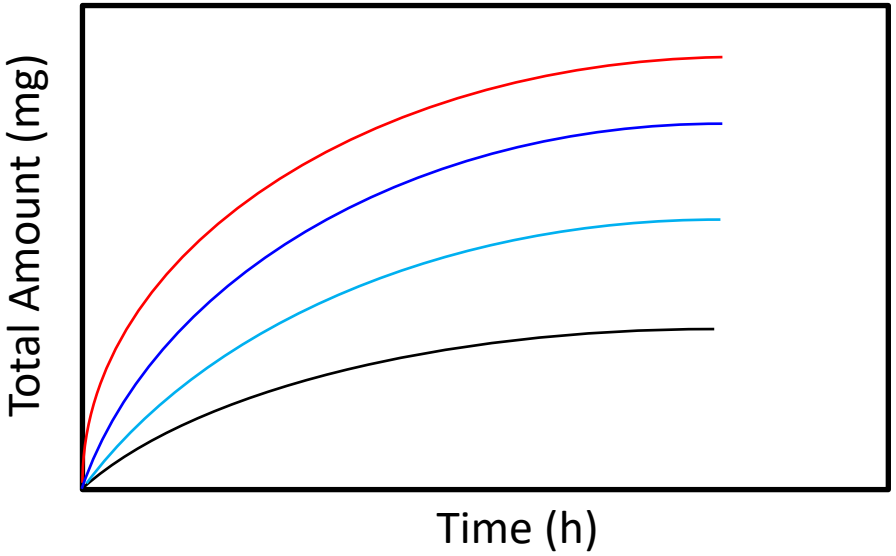
– First-order absorption *(limitation –not realistic)*

– No saturable (nonlinear) absorption or clearance *(limitation –what if drug is substrate for enzymes/transporters?)*

– Terminal oral plasma concentration-time points independent of absorption *(limitation –what about colonic absorption?)*

Mechanistic IVIVC





-- Dissolved in vivo (mechanistic deconvoluted)

-- Absorbed - Fa

-- Into portal vein

-- Systemic circulation - F (traditional deconvoluted)

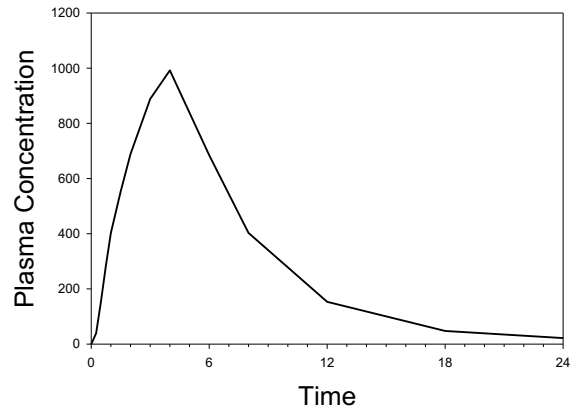
Outline

- Background
  - History
  - Applications
    - Formulation Development
    - Regulatory
  - Categories
- Development, Physiological, and In Vitro Considerations
- Case Studies
- Summary

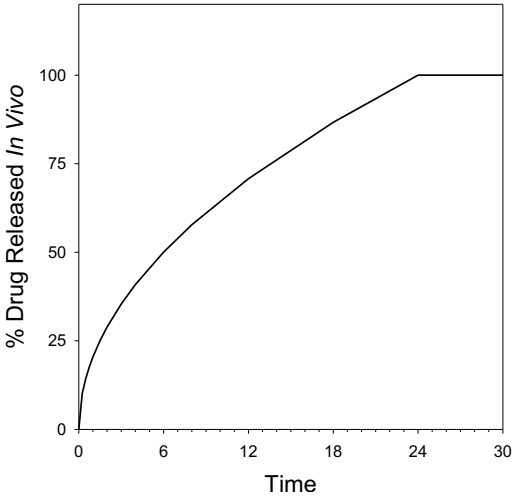
Developing a Correlation

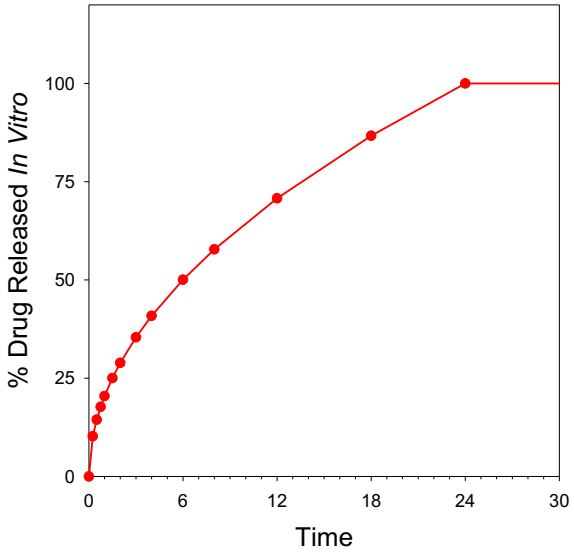
- Most Common Approach for Establishing Model
  - Develop formulations with different release rates, e.g., slow, medium, fast.
  - Obtain in vitro dissolution profiles and in vivo plasma profiles for these formulations.
  - Estimate the in vivo absorption (in vivo dissolution) time course using an appropriate deconvolution method.
  - Plot in vivo release against in vitro release to establish correlation.

Establishing an IVIVR

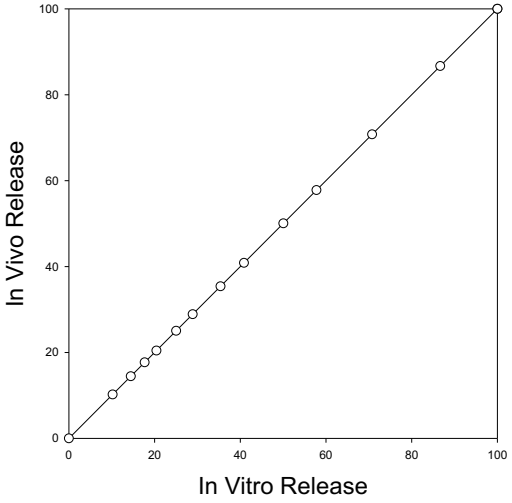


$$c(t) = \int_t^t c_\delta(t-u) \cdot r_{abs}(u) du$$



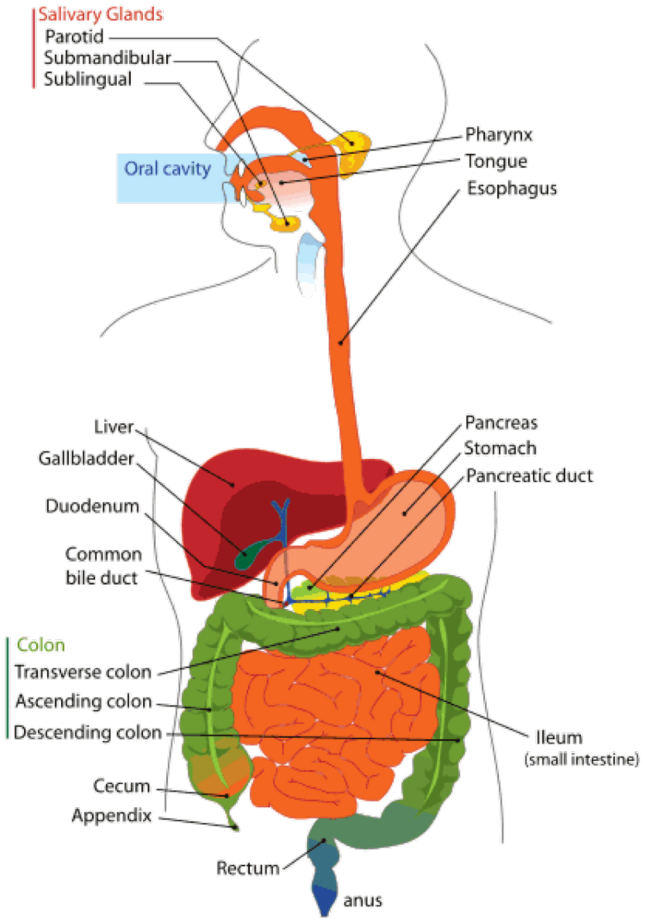


plot in vivo release against in vitro release



Bristol-Myers Squibb

Complexity of the GI Tract



- Stomach: enzymes, pH range 1.2 – 6.
- Intestines: enzymes, surfactants, lipids/carbohydrates/proteins, bacteria, pH range 4.5 – 7.5.
- Daily fluid exchange up to 13 L.

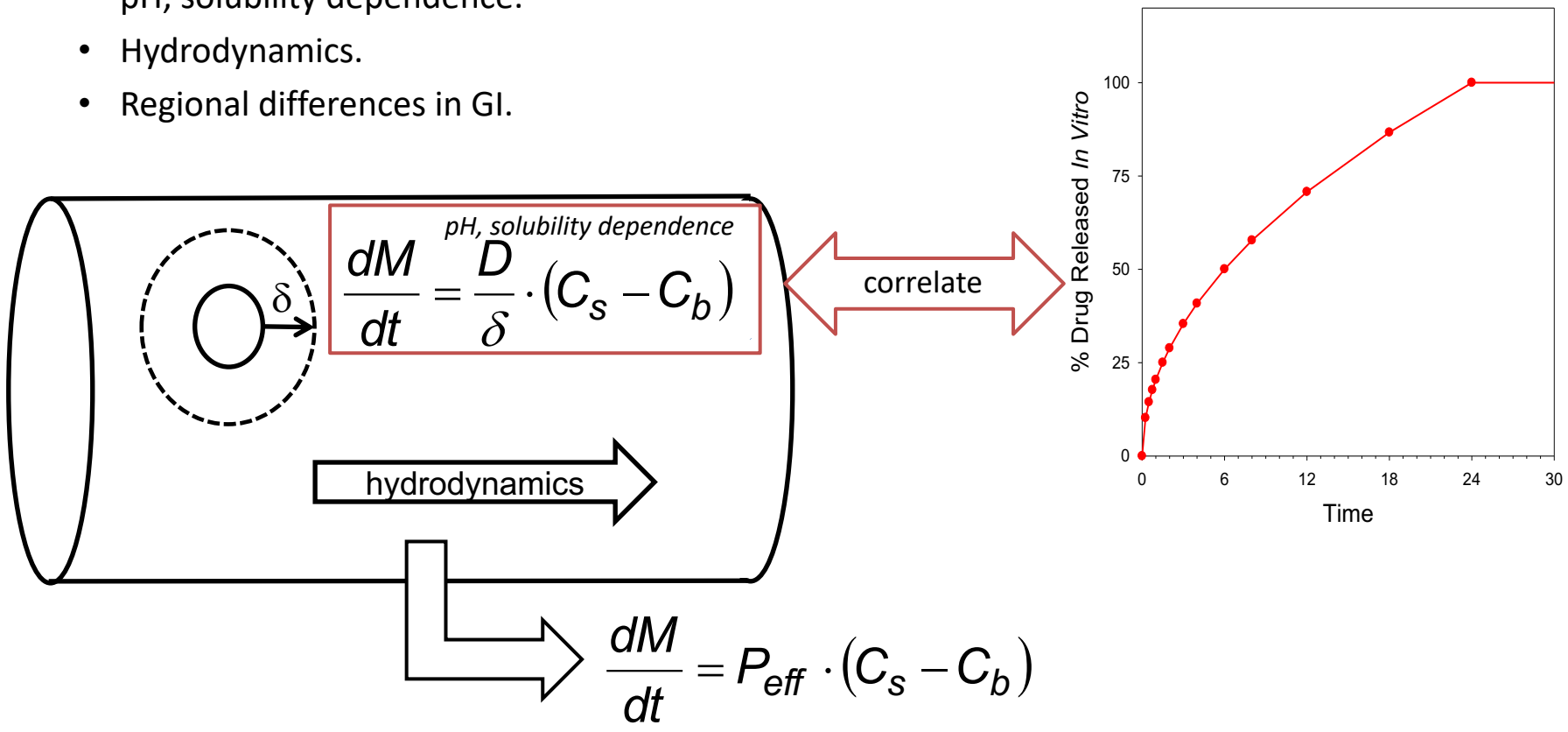
Dorland's Illustrated Medical Dictionary, 31st Edition (2007)

http://www.pediatricfeeding.org/gi_anatomy.html

Physiological Considerations

The rate limiting step to absorption is the dissolution

- The in vitro method should be designed such that the profile reflects the rate limiting mechanism for dissolution, e.g.
  - pH, solubility dependence.
  - Hydrodynamics.
  - Regional differences in GI.



Oh, et al, Pharmaceutical Research, Vol. 10, No. 2, 1993

IVIVC Development and BCS Considerations

Class	Solubility	Permeability	IVIVC?
I	High	High	Possible, if dissolution is rate limiting step
II	Low	High	Possible, if *in vitro* & *in vivo* dissolution are similar
III	High	Low	Limited, since absorption is rate limiting step
IV	Low	Low	Not expected (unless dissolution is identified as limiting step)

In Vivo Dissolution Behavior of BCS 2 Drugs

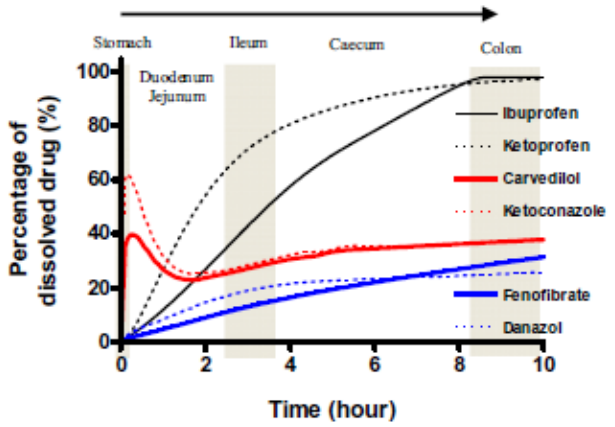
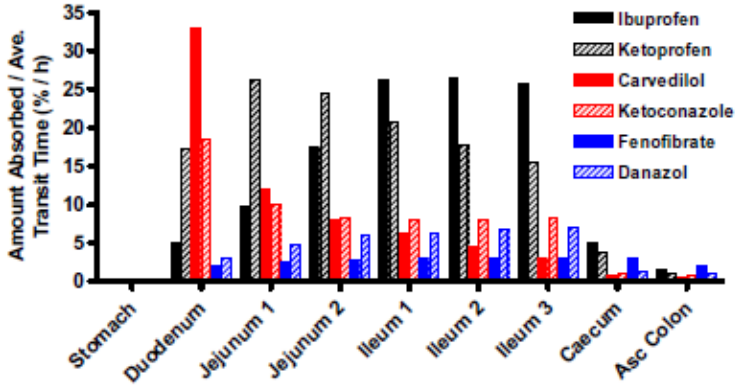


Fig. 2. Percentage of amount dissolved with an IR dosage. Black solid and dot lines represent BCS Class II weak acids, Red solid and dot lines represent BCS class weak bases and blue solid and dot lines represent BCS class neutrals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

BCS class 2 examples of time course of *in vivo* amount of drug dissolved and regional GI transit



BCS class 2 drug absorption in GI regions

Tsume, Y., Mudie, D. M., Langguth, P., Amidon, G. E., & Amidon, G. L. (2014). The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. *European Journal of Pharmaceutical Sciences*, *57*, 152-163.

Summary – Dissolution Method Perspective

During the early stages the dissolution conditions may be altered to attempt to develop a 1:1 correlation

- A few considerations:
  - Dissolution media
    - » Media composition(s) that more closely reflects in vivo environment
  - Hydrodynamics
    - » Apparatus, paddle speed, etc.
  - Length of test
    - » Formulations that release for extended periods of time may require longer dissolution tests.

Outline

- Background
  - History
  - Applications
    - Formulation Development
    - Regulatory
  - Categories
- Development, Physiological, and In Vitro Considerations
- Case Studies
- Summary

Modified Release Tablet (Adult and Pediatric)

Formulation Attribute	Biopharmaceutics assessment (In silico, in vitro, in vivo)	Outcome/Significance
Release rate IVIVC/R	▪ In vivo matrix tablet release has positive deviation from in vitro ▪ In vitro release from hydrophilic matrix has shear sensitivity	▪ Prototype compositions with more diffusion controlled release for clinical assessment ▪ Refine in vitro to understand shear sensitivity
Dosage form (tablet/multi-particulates)	▪ Multi-particulate technology has release lag time and more disperse GI transit time ▪ Multi-particulate must release faster for equivalent exposure	▪ Adaptive clinical trial to verify release target for new dosage form/mechanism ▪ Can new release kinetics achieve same exposure profile?
Dose levels	▪ Demonstrated XR release rate and manufacture is drug load specific (+ dose size limitations)	▪ Set critical design element for prototype formulations ▪ Use PBPK and allometry to ID target for development ▪ GastroPlus aligned for exposure predictions

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Compartmental Absorption Modeling and Site of Absorption Studies to Determine Feasibility of an Extended-Release Formulation of an HIV-1 Attachment Inhibitor Phosphate Ester Prodrug

JONATHAN BROWN,[1] CALY CHIEN,[2] PETER TIMMINS,[1] ANDREW DENNIS,[1] WALTER DOLL,[3] ERIK SANDEFER,[3] RICHARD PAGE,[3] RICHARD E. NETTLES,[2] LI ZHU,[2] DENNIS GRASELA[2]

[1]Drug Product Science and Technology, Bristol-Myers Squibb, Moreton, Merseyside CH46 1QW, UK

[2]Discovery Medicine and Clinical Pharmacology, Bristol-Myers Squibb, Pennington, New Jersey, 08534

[3]Scintipharma Inc., Lexington, Kentucky, 40503

Drugs that show region-specific absorption pose challenges to the establishment of IVIVR… limitations of in vitro dissolution method to mimic the changing in vivo environment

Table 1. Model Parameters

	Parameter	Value (Exploratory Modeling)	Value (Optimized Modeling)
Physical–chemical	Dose	486.7 mg[a]	486.7 mg[a]
	Log D	1.7 at pH 6.5	1.7 at pH 6.5
	Solubility	250 mg/mL	250 mg/mL
Physiology			
	Permeability	1.34×10^{-4} cm/s	1.34×10^{-4} cm/s
	Ascending colon compartment transit time	13.5 h	2.1–24.0 h[b]
Absorption scale factors			
	Stomach	0.0	0.0
	Duodenum	25.46	5.901–265.6[b]
	Jejunum 1	26.87	6.294–283.3[b]
	Jejunum 2	30.17	7.046–317.2[b]
	Ileum 1	34.36	8.001–360.2[b]
	Ileum 2	39.73	9.348–420.8[b]
	Ileum 3	47.27	11.11–500.0[b]
	Cecum	0.302	0.082–0.950[b]
	Ascending colon	0.424	0.049–0.450[b]
Pharmacokinetic			
	Oral clearance (CL/F)	0.29 L/(h kg)	0.22—0.54 L/(h kg)[b]
	Apparent volume of distribution (V/F)	0.50 L/kg	0.15—0.57 L/kg
	K_{12}	0.01 L/h	0.02—0.13 L/h
	K_{21}	0.06 L/h	0.13—0.70 L/h

[a]Dose of BMS-626529 equivalent to 600 mg BMS-663068.
[b]Range of values (minimum–maximum) employed in optimized models ($n = 8$) of individual subjects.

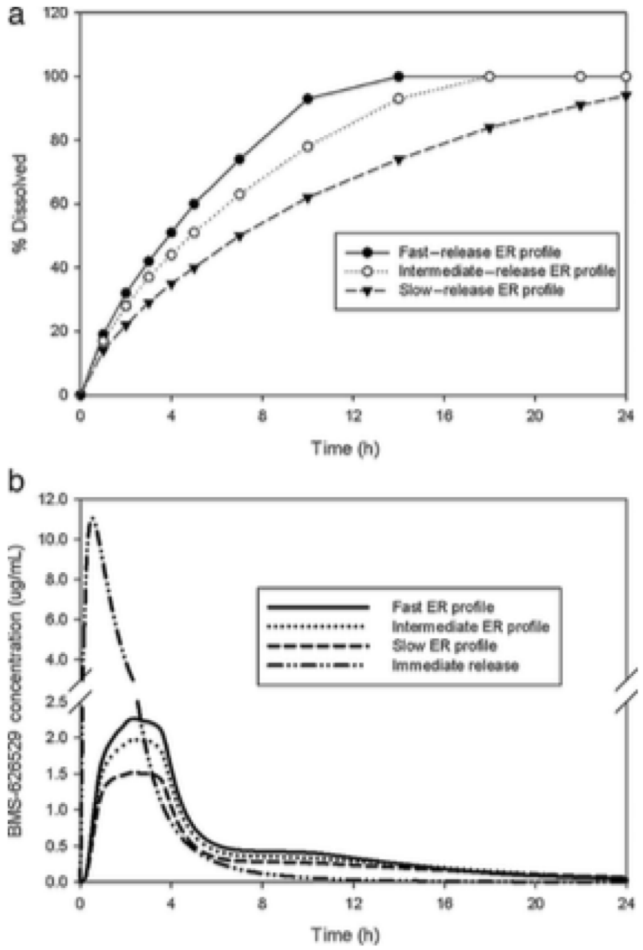


Figure 4. (a) Experimental drug release profiles used in refined compartmental modeling of extended release. (b) Simulated plasma concentration–time profiles of BMS-626529 from refined compartmental modeling delivered as 600 mg BMS-663068 in extended-release and immediate-release formulations.

In vitro method as well as potential p-glycoprotein and cytochrome P450 interactions suggested as sources of error

Table 4. Model-Predicted (Pred.) Versus Observed (Obs.) Parameters Following Delivery of 600 mg BMS-663068 as Fast-, Intermediate-, and Slow-Releasing Extended-Release Tablets

		Extended-Release Tablet Formulation		
Pharmacokinetic Parameter		Fast	Intermediate	Slow
C_{max} (μg/mL)[a]	Pred. (n = 8)	2.20 (28)	1.92 (28)	1.48 (28)
	Obs. (n = 15)	5.21 (29)	4.41 (31)	1.81 (56)
$AUC_{(0-7)}$ (μg h/mL)[a]	Pred. (n = 8)	12.68 (24)	11.33 (23)	9.12 (22)
	Obs. (n = 15)	21.41 (34)	18.96 (29)	9.42 (50)
C_{12} (μg/mL)[a]	Pred. (n = 8)	0.31 (40)	0.27 (42)	0.21 (42)
	Obs. (n = 15)	0.13 (54)	0.16 (84)	0.09 (69)

[a]Geometric mean (CV%)

Modified dissolution methodology and non-linear dose-absorption kinetics in ACAT modelling has enabled percent error in prediction of Cmax and AUC to be reduced for three prototype formulations

Formulation	PK Parameter	Prediction Error (%)	
		pH 6.8/ 100rpm Linear kinetics	pH 4.5/150 rpm Non-linear kinetics
Fast release	Cmax	-58	5
	AUC	-41	1
Intermed release	Cmax	-56	- 18
	AUC	-40	- 15
Slow release	Cmax	-18	18
	AUC	-3	8

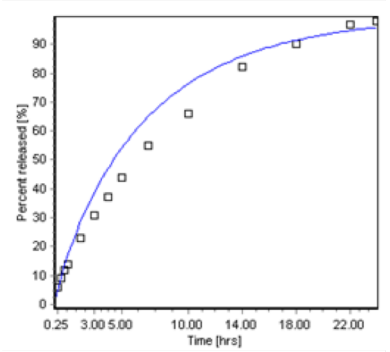
JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 102, NO. 6, JUNE 2013

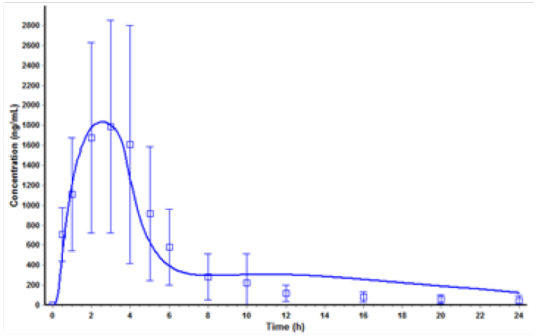
Bristol-Myers Squibb

IVIVC/R MR Dosage Form Design – Mechanistic Deconvolution

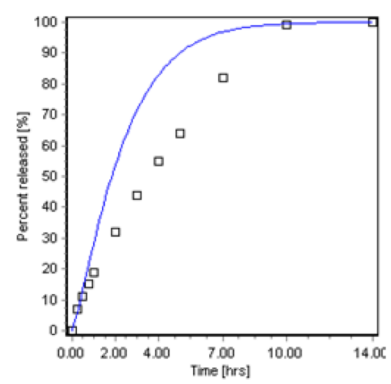
Release rate:

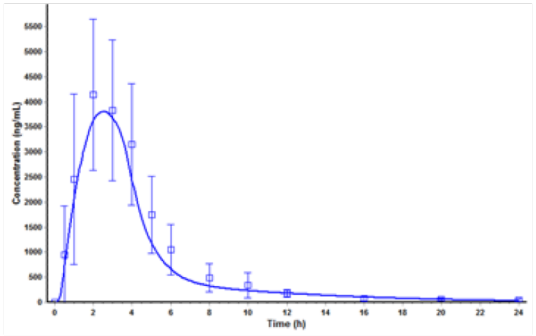
Slow



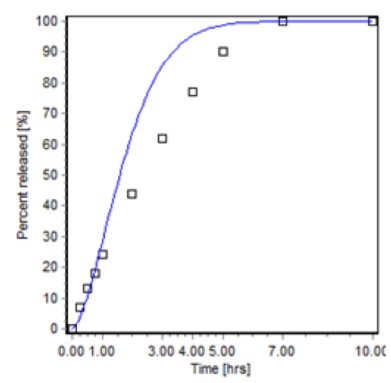


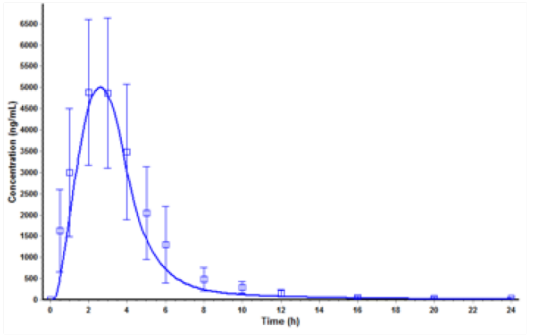
Medium





Fast





Deconvolute MR tablet formulations
Simulated *in vivo* release – IVIVC/R

- All in vivo profiles track in vitro data for early time points (<~2-3hrs) and exhibit positive deviation for ~2-10hrs.
- Impact of hydrodynamics and in vivo motility.
- Diffusion and erosion for matrix tablet in vivo… minimal erosion in vitro

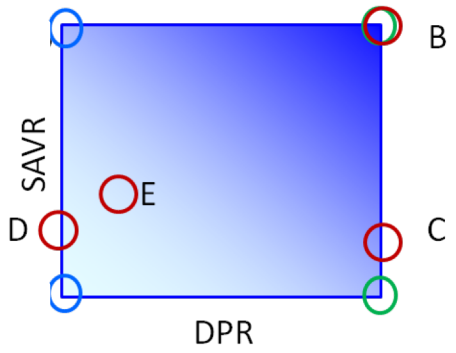
AAPS J. 2019 Jan 23;21(2):19. doi: 10.1208/s12248-019-0292-3

Bristol-Myers Squibb

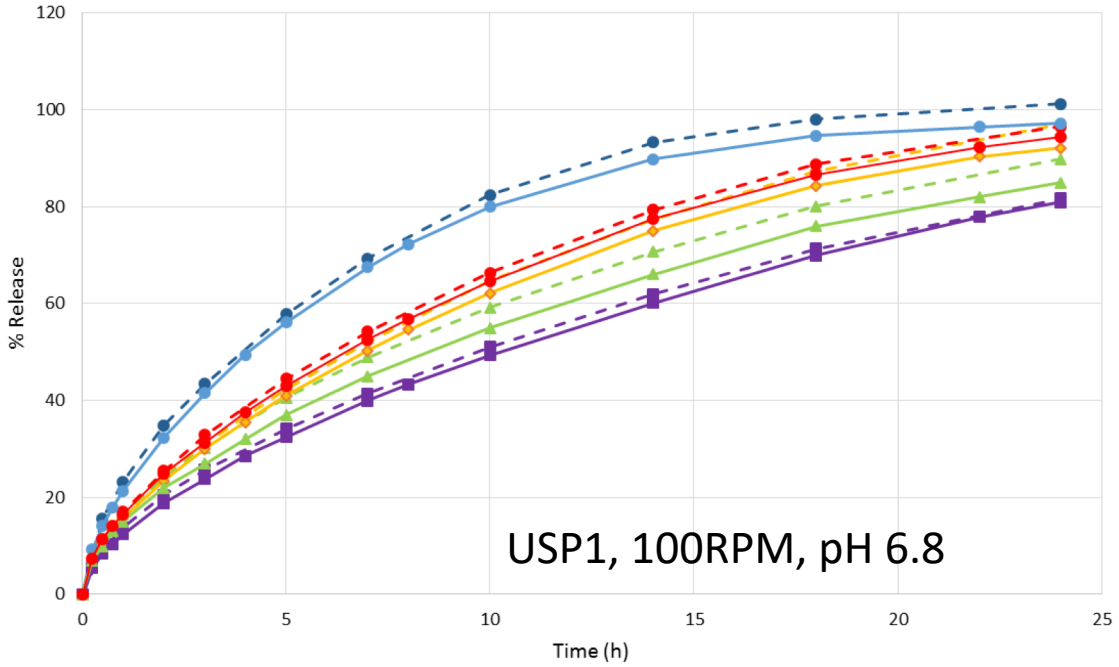
QbD Design Space: Dissolution Space Defined by PBPK

Altered hydrophilic matrix tablet dimensions

- Requires new composition
- PBPK simulated formulation space to design exploratory clinical studies and identify IVIVC/R



Treatment	Description
A	Reference
B	fast
C	med
D	slow

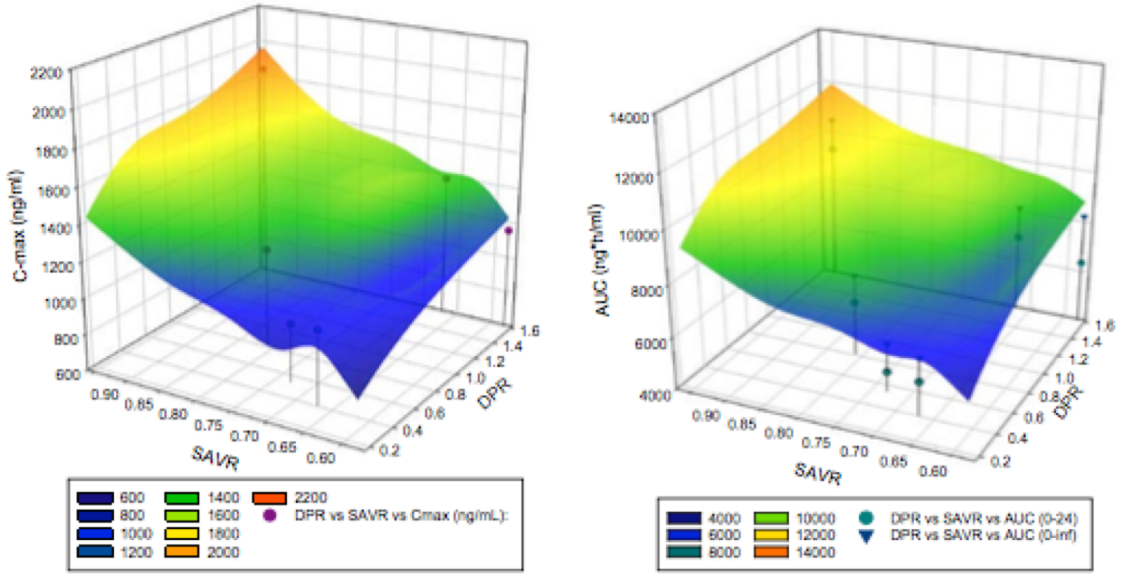


Dashed lines: Trial batches
Solid lines: Development batches

Bristol-Myers Squibb

Clinical IVIVC Verification (QbD Design Space)

Figure 8 - Surface Plots of BMS-663068 PBPK predicted and observed clinical data for C_{max} (left) and AUC (right) as a function of drug-to-polymer ratio (DPR) and surface-area to volume ratio (SAVR).



Response surface	G+ predictions in advance of clinical study (AUC predicted surface represents AUC (0-t))
Points	Observed exposure from clinical study (AUC shows 0-t and 0-inf for comparison)

in vivo – in silico

Treatment Release rate	Observed/Simulated	C_{max} rel%	$AUC_{(0-t)}$ rel%	$AUC_{(0-inf)}$ rel%
Original MR tablet	Observed (target 100%)	87%	103%	102%
Fast	Observed	133%	125%	118%
	Simulated	138%	124%	118%
Medium	Observed	REF	REF	REF
	Simulated	REF	REF	REF
Slow	Observed	76%	80%	90%
	Simulated	80%	82%	84%

Achieved IVIVC level A Criteria from Mechanistic PBPK model

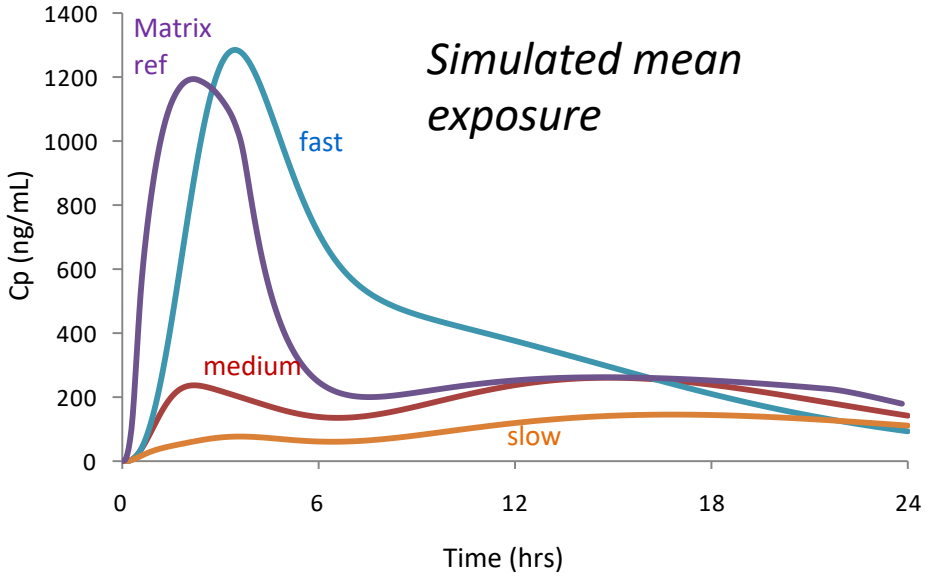
AAPS J. 2019 Jan 23;21(2):19. doi: 10.1208/s12248-019-0292-3

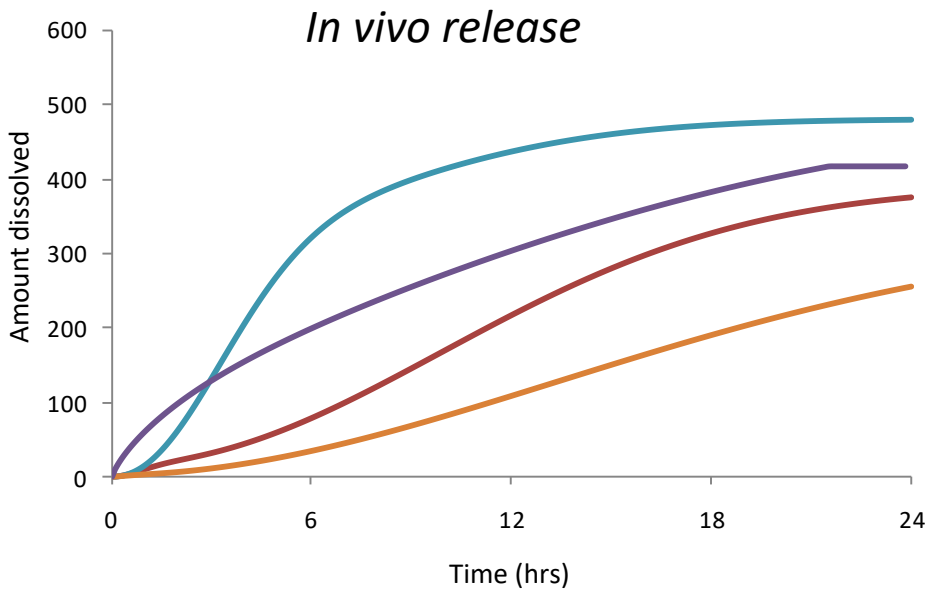
Bristol-Myers Squibb

Extend Simulations to Design Multi-Particulate Formulation

PBPK simulated *in vivo* release

Input *in vitro* release data (USP I method, pH 6.8)

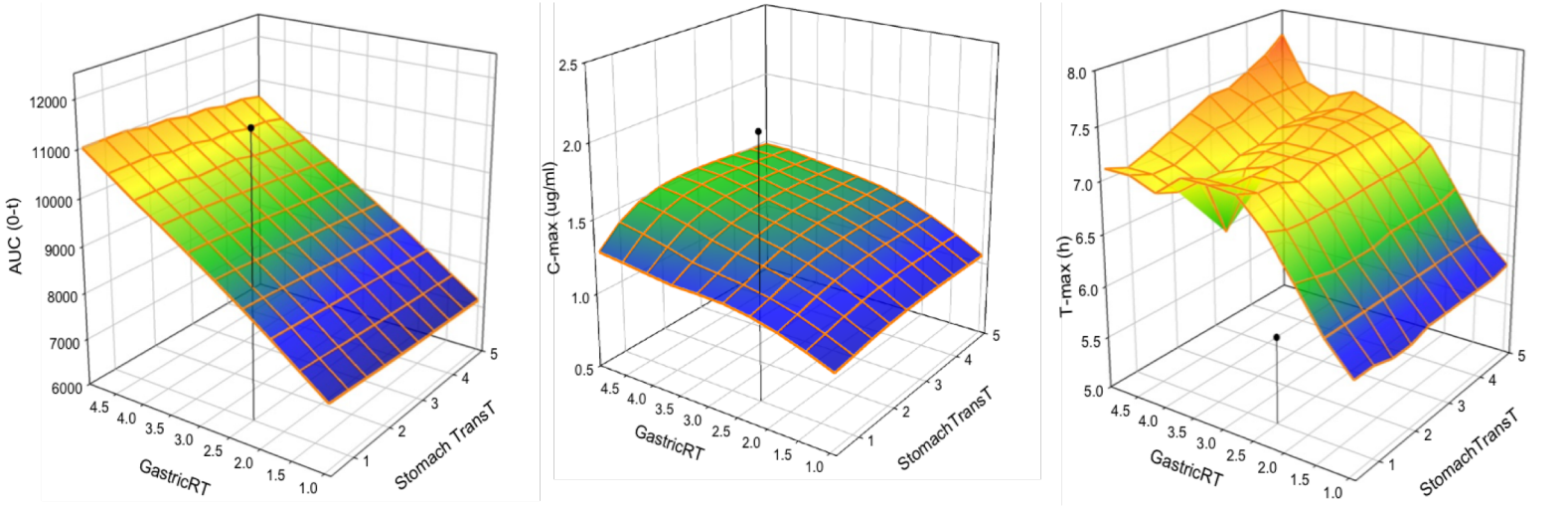




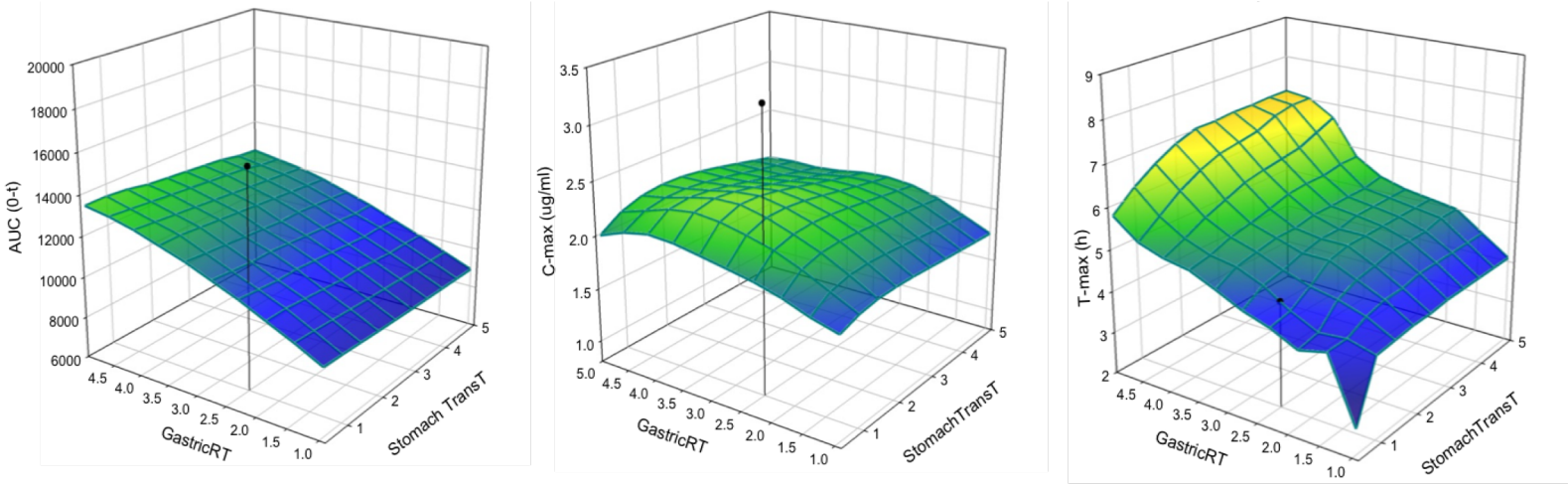
- Slowest profile provides exposure well below target range
- Clear impact of lag time … all are well below matrix tablet for t<3 hrs
- Target unique in vitro release rates relative to existing matrix tablet

Multi-Particulate MR Simulations

Slow Release Simulations



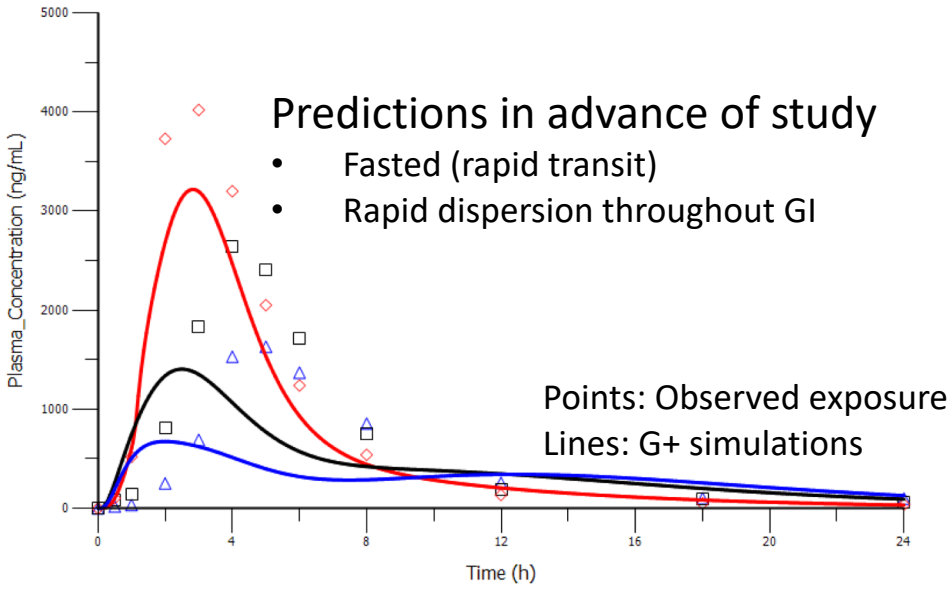
Medium Release Simulations

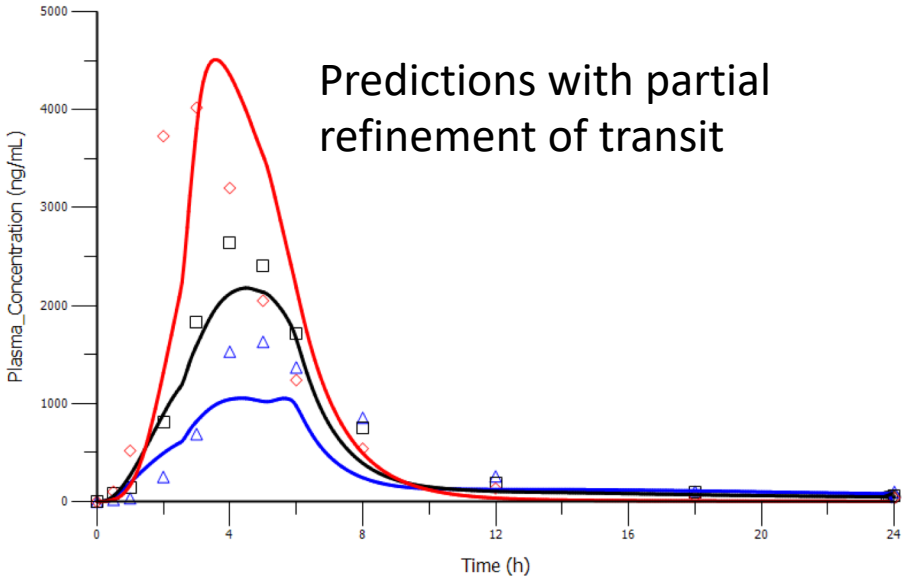


- Surfaces = Predicted exposure from current GastroPlus model settings
- Points: Z-axis = Clinical results for AUC, C-max and T-max (left to right)
- Points: X/Y-axis = Optimization of gastric retention time and stomach transit across all treatments (F,M,S).

Bristol-Myers Squibb

Simulated and Observed Multi-Particulate Plasma Concentrations





Treatment	Description (pore former/coating wt%)
H	Slow MPF
I	Med MPF
J	Fast MPF

1. Extended MPF transit times clearly improve model simulation results
2. More refinements for the model to address dosage form behavior
3. Concurrent in vitro dissolution analysis and development to explore alternate methodologies

Prior IVIVC useful to guide QbD development, but doesn't directly span to new formulation technology (matrix vs coated particulates)

Bristol-Myers Squibb

Range of Observed GI Transit Times for Dosage Forms

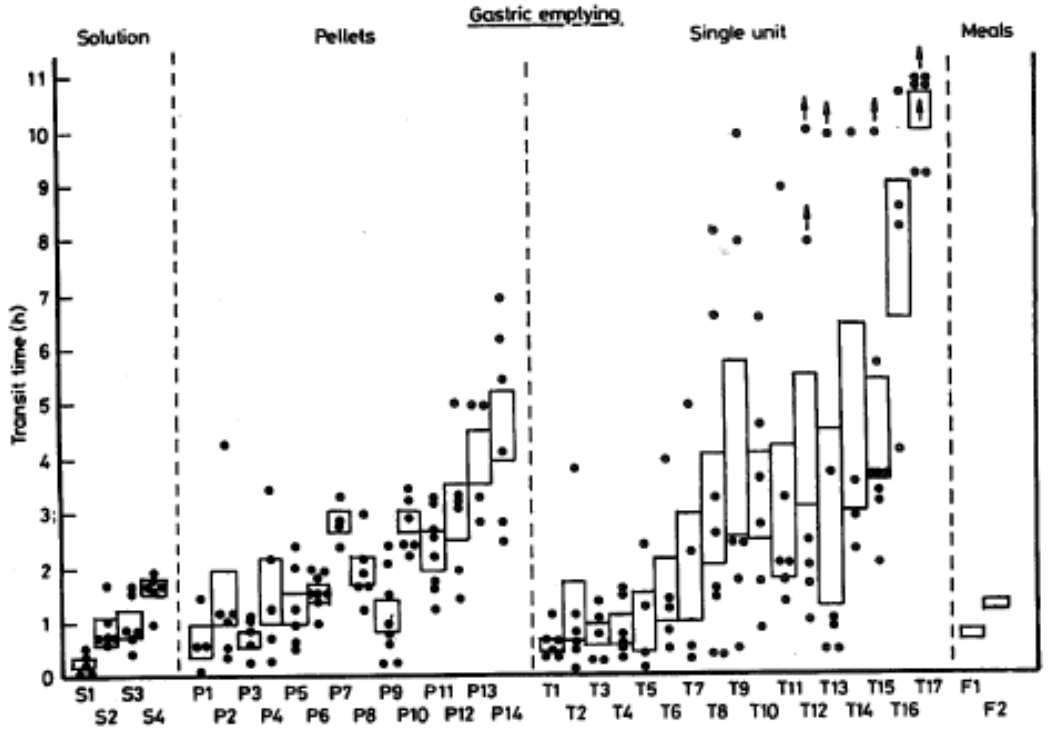


Fig. 1 *Gastric emptying of pharmaceutical dosage forms. Individual data points as filled circles.* Mean±SEM.

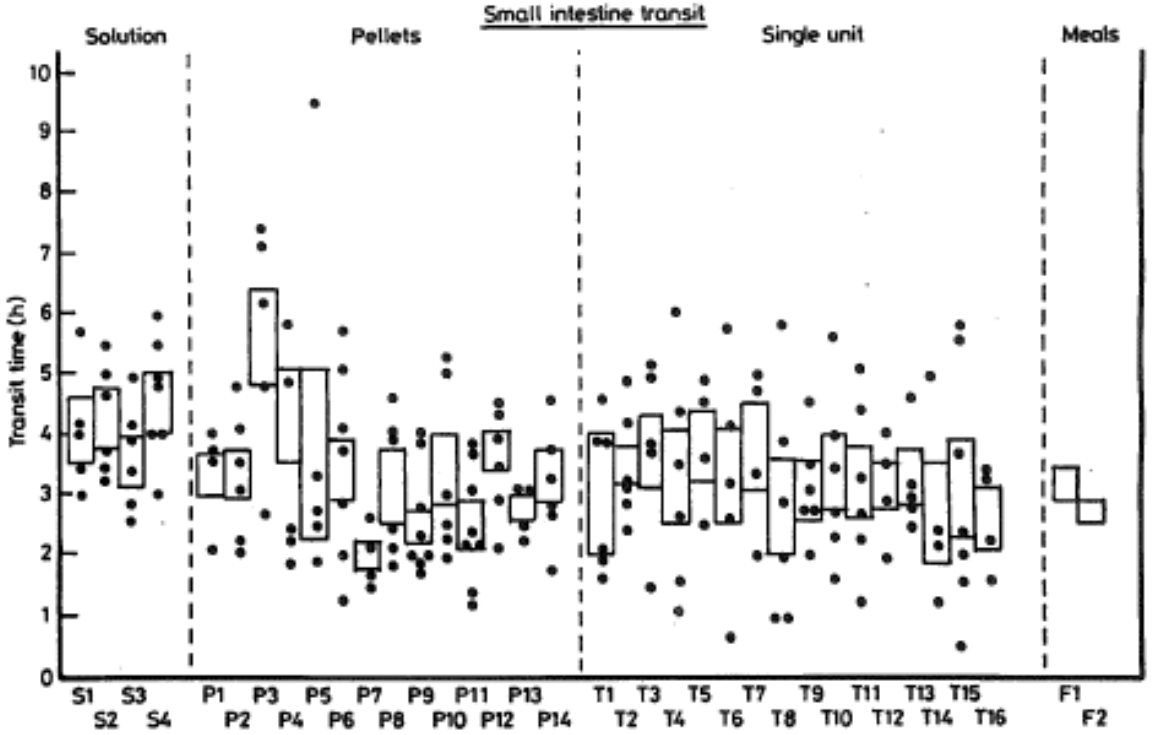


Fig. 2 *Small intestinal transit of pharmaceutical dosage forms.* Mean±SEM.

SS DAVIS, JG HARDY, JW FARA Gut,1986,27,886–892

Reference MR Matrix and Multi-Particulate IVIVC (2015)

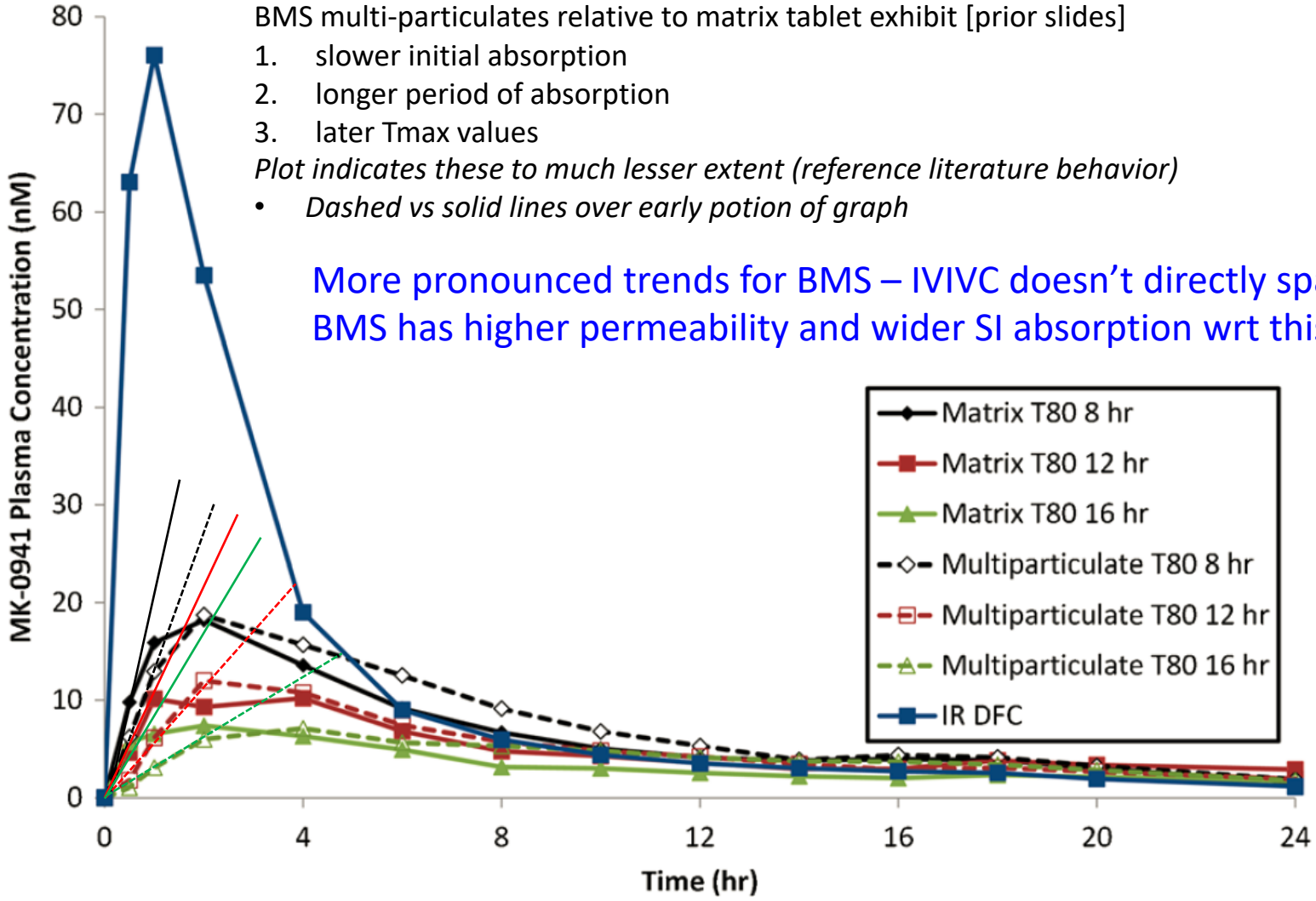
BMS multi-particulates relative to matrix tablet exhibit [prior slides]

1. slower initial absorption
2. longer period of absorption
3. later Tmax values

Plot indicates these to much lesser extent (reference literature behavior)

- *Dashed vs solid lines over early potion of graph*

More pronounced trends for BMS – IVIVC doesn't directly span formulation technology. BMS has higher permeability and wider SI absorption wrt this BCS 3 compound.



Kesisoglou, F., Xia, B., & Agrawal, N. G. (2015). Comparison of Deconvolution-Based and Absorption Modeling IVIVC for Extended Release Formulations of a BCS III Drug Development Candidate. *The AAPS journal*, 1-9.

Takeaway: Applying PBPK and Traditional IVIVC in QbD

- Mechanistic modeling is strong compliment to traditional IVIVC models and expands the possible application to many compounds that exhibit complex PK
  - PBPK models integrate and extend multidisciplinary knowledge. Full ADME knowledge extends possible applications/successes.
- IVIVC achievable for both *MR and IR* with more mechanistic possibilities across all in vivo release rates
- PK absorption modeling is a critical interface for clinical and product development
  - Correlation of biorelevant dissolution and clinical outcomes
- Expanding the regulatory use of PBPK modeling will establish greater precedent and guidance for mechanistic IVIVCs relative to traditional methods

Acknowledgements

Thank you for your attention

Moderators and Conference Organizing Committee

Bristol-Myers Squibb:

Jonathan Brown

Claire Jackson

Ishani Savant

John Crison

Qi Wang

Neil Mathias

Ming Zheng

Peter Timmins

Sailesh Varia

Bristol-Myers Squibb