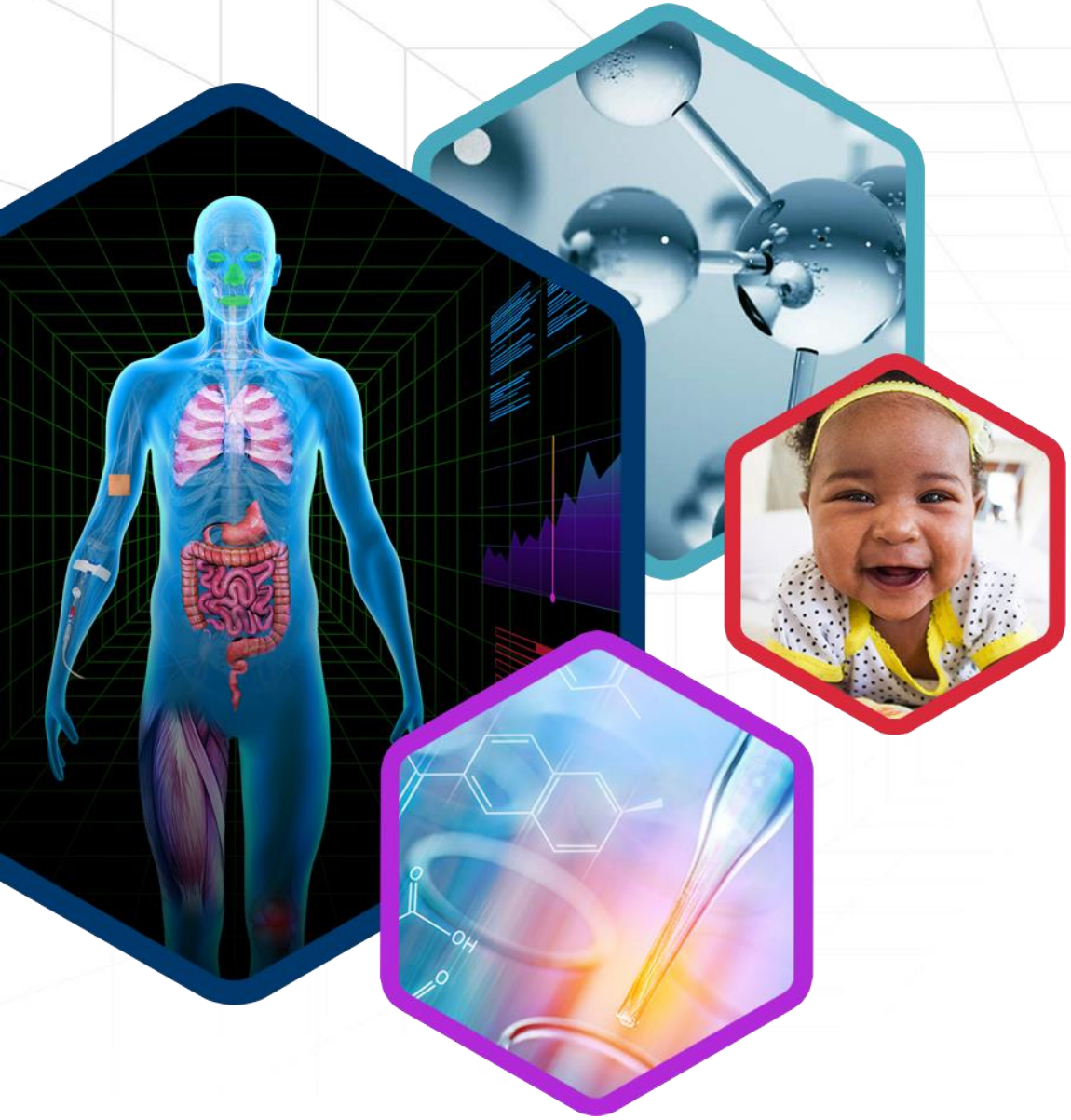

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Building Mechanistic IVIVC

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What is an *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 Vivo* Correlations (1997)

What is the purpose of an IVIVC?

- To reduce regulatory burden
- For dissolution method development:
  - Which *in vitro* method best correlates with a deconvoluted *in vivo* profile?
- For formulation design:
  - How do I develop my formulation to produce an *in vitro* dissolution rate that will achieve bioequivalence?
- To establish dissolution specifications

IVIVC Categories

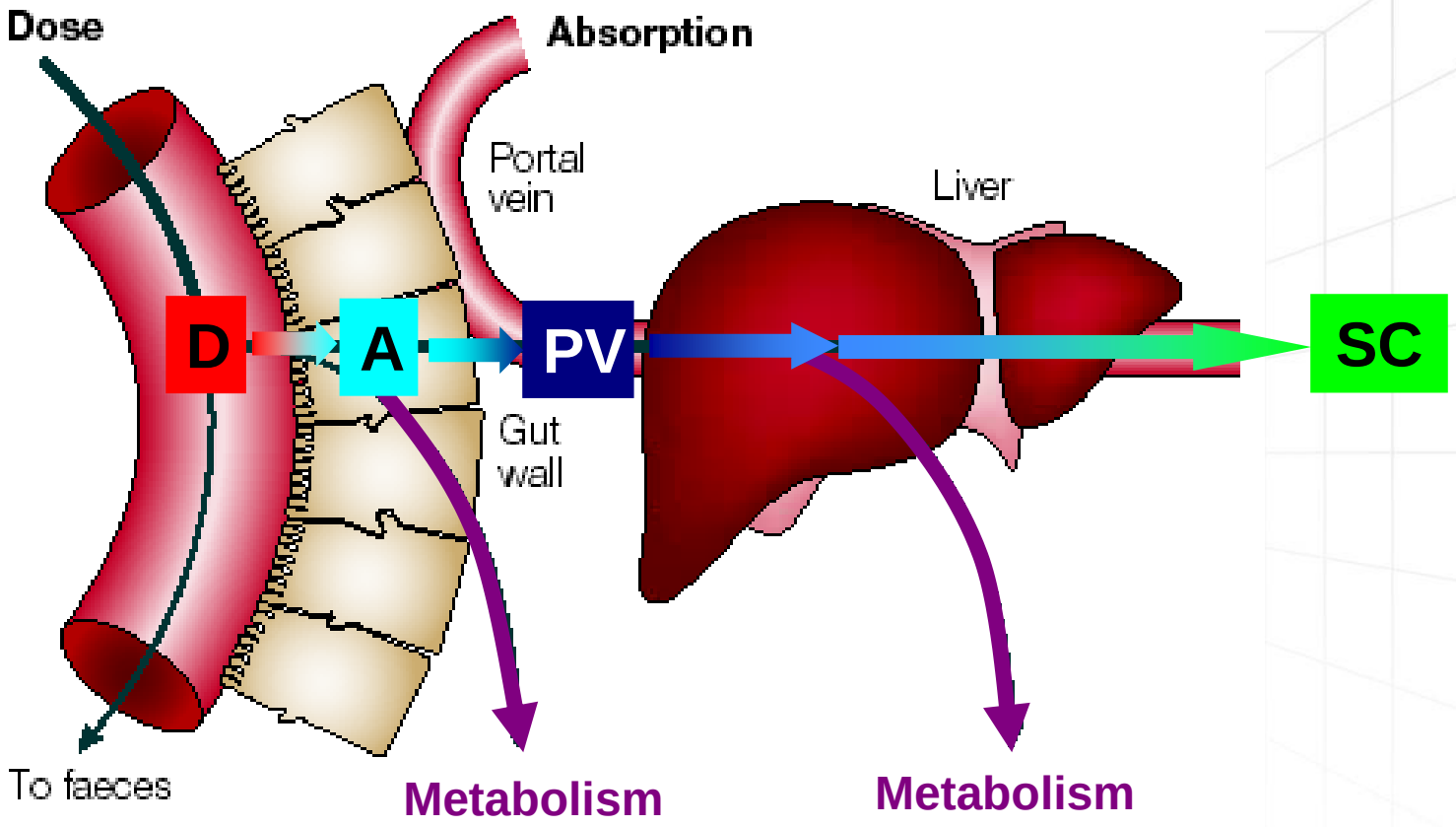
- Level A:
  - Point-to-point relationship between *in vitro* dissolution and *in vivo* input rate (can be linear or non-linear)
- Level B:
  - Correlation based on statistical moment analysis (*in vitro* dissolution time correlated with MRT)
- Level C:
  - Single point relationship between a dissolution parameter (e.g., $t_{50\%}$) and pharmacokinetic output (e.g., Cmax, AUC)

IVIVC – Level A

- Inputs:
  - *in vitro* dissolution data and *in vivo* Cp-time profiles for batches tested *in vivo*
  - *in vivo* Cp-time profiles for reference formulations
    - (IV, solution or IR doses – for building/calibrating PK model or UIR)

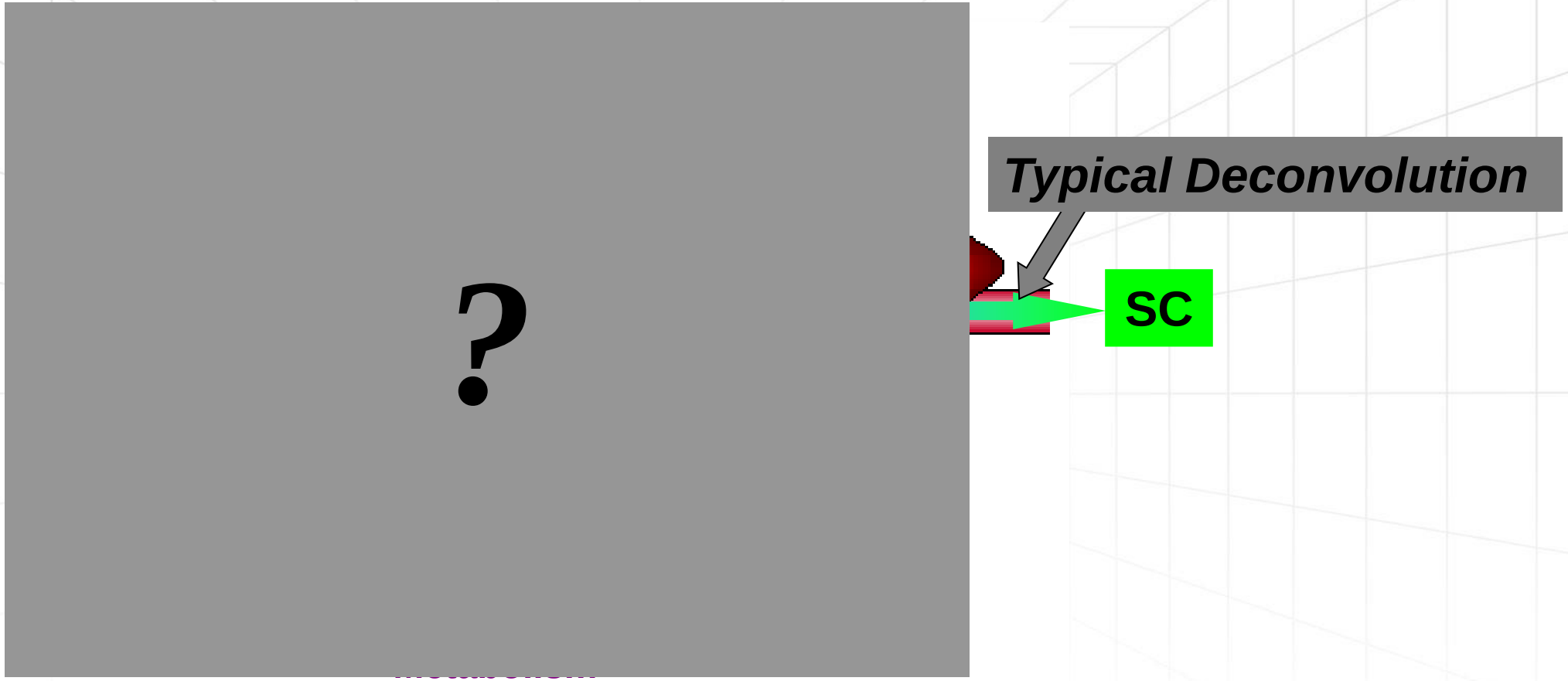
- Outputs:
  - Step 1 (“deconvolution”): *in vivo* input rate
  - Step 2 (“correlation”): point-to-point correlation between *in vitro* dissolution and *in vivo* input rate

Major Processes after Oral Administration



* Modified from van de Waterbeemd, H, and Gifford, E. ADMET In Silico Modelling: Towards Prediction Paradise? Nat. Rev. Drug Disc. 2003, 2:192-204

Deconvoluted In Vivo Profile



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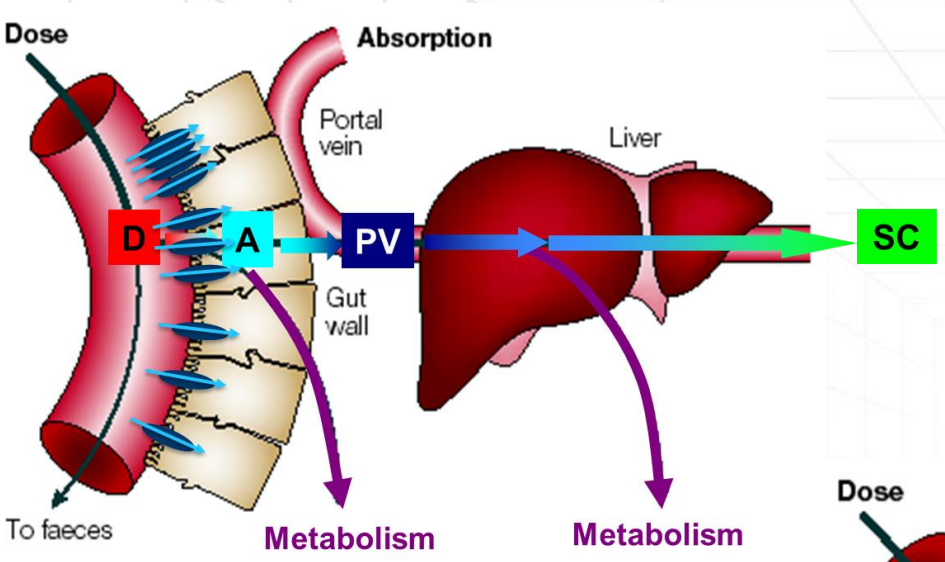
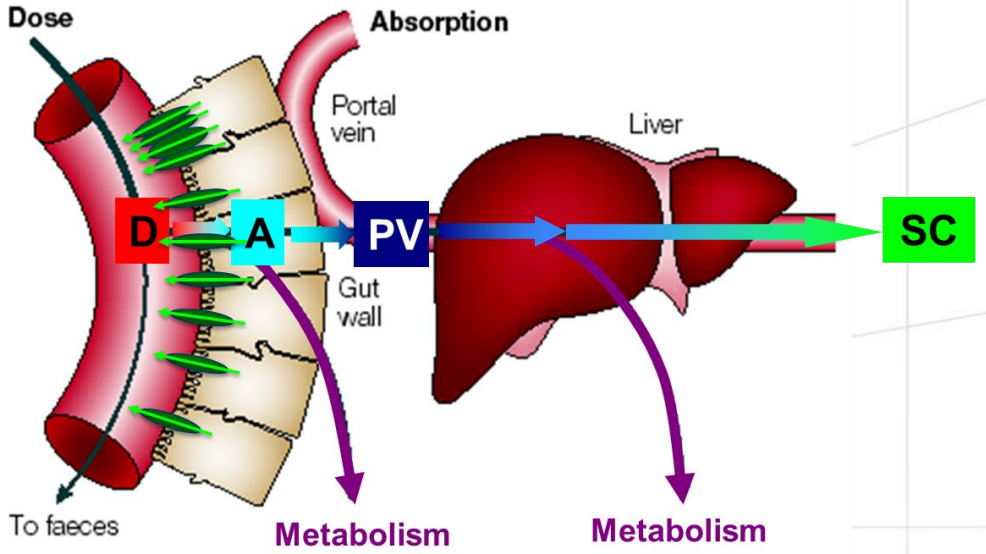
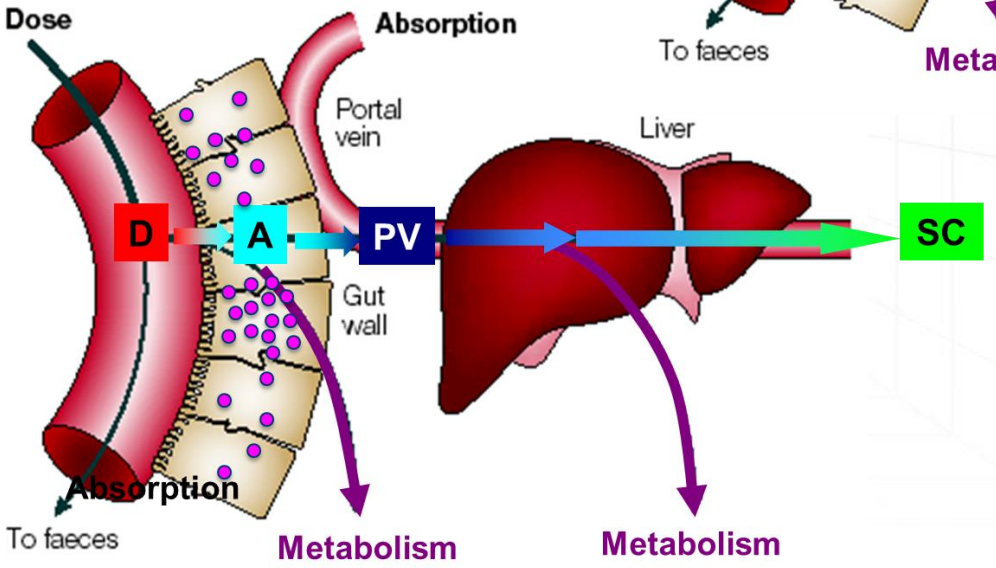
From Dissolution to Systemic Circulation





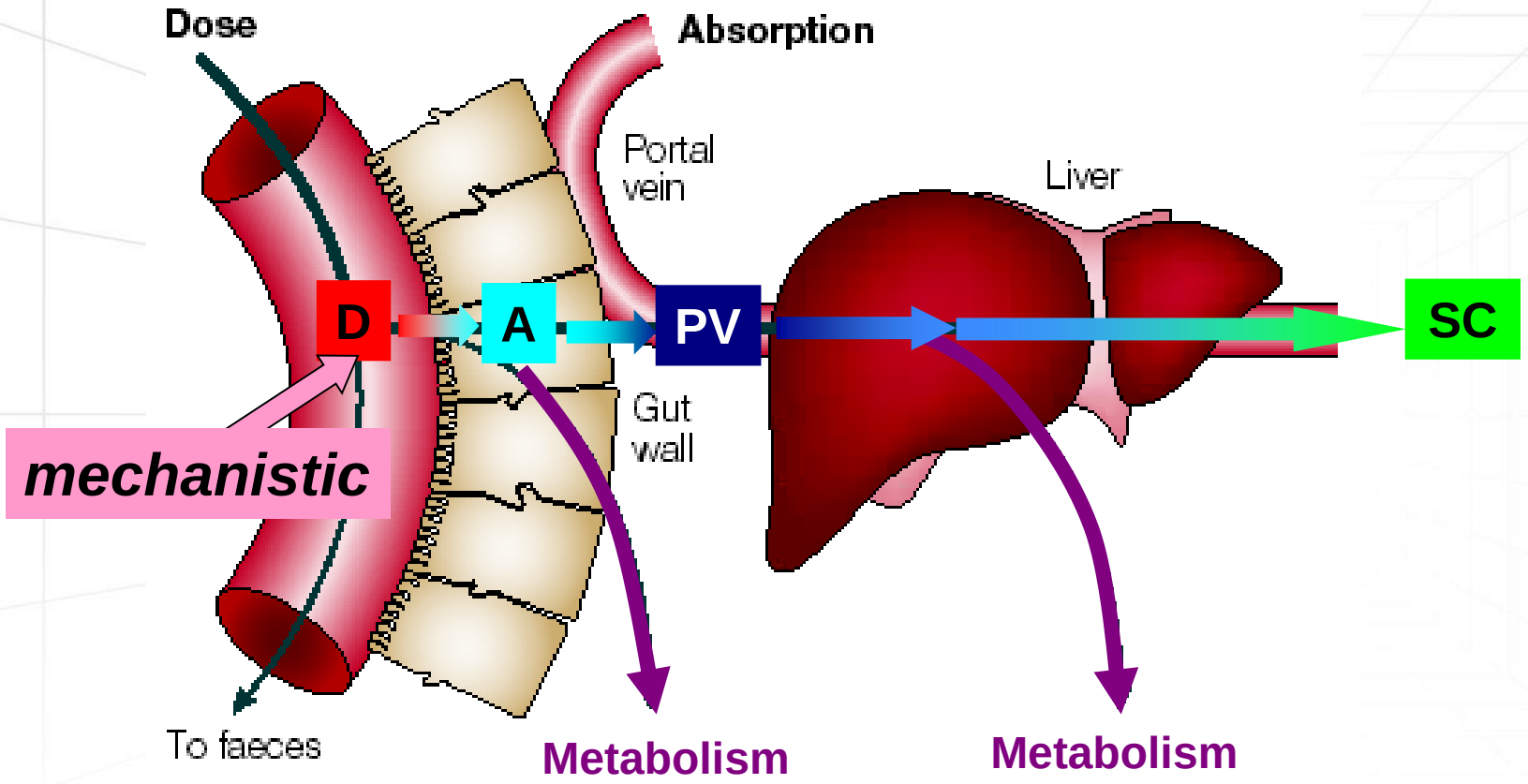


Additional processes impacting the rate and extent of compound in SC:

- Regional differences in absorption
- Regional differences in metabolism
- Saturation of first past extraction in gut and/or liver
- others

* Modified from van de Waterbeemd, H, and Gifford, E. ADMET In Silico Modelling: Towards Prediction Paradise? Nat. Rev. Drug Disc. 2003, 2:192-204

Mechanistic Deconvolution is Designed to Capture the Impact of those Additional Processes



- Requires model that incorporates all relevant mechanisms
- IV and/or immediate release PO data is used to calibrate the complete mechanistic absorption model/PK model

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Metformin IVIVC

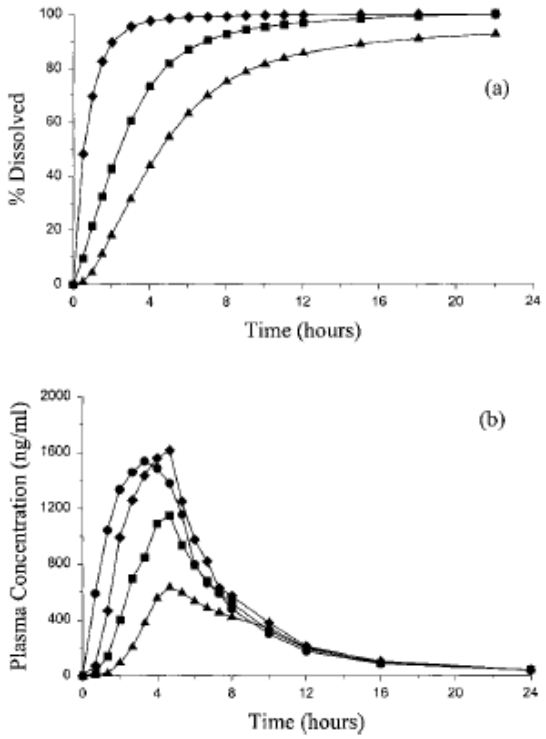


Figure 1. Mean *in vitro* dissolution data (panel a) and *in vivo* plasma concentration data (panel b) for metformin. *In vitro* data are mean of six-tablets for formulations A3 (◆), A7 (■), and A15 (▲), and *in vivo* data are mean from eight healthy volunteers for formulations IR (●), A3 (◆), A7 (■), and A15 (▲). Although *in vivo* data were collected up to 72 h after dose administration, data are shown for 24 h for clarity.

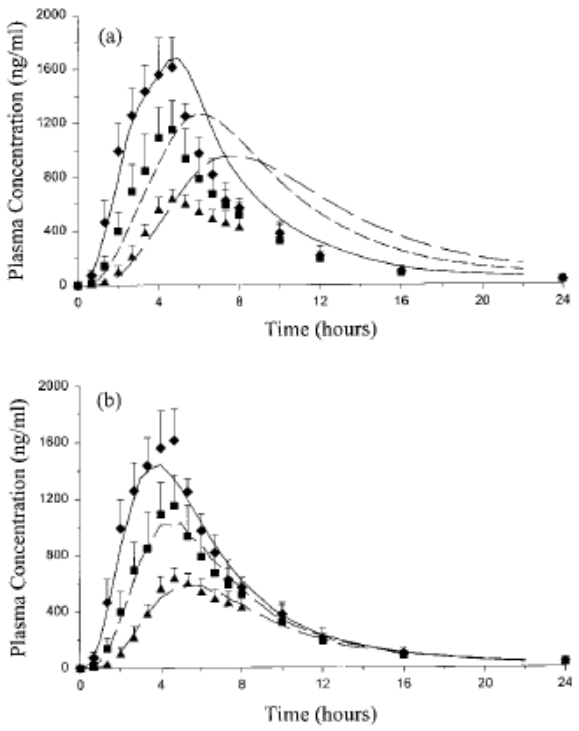


Figure 4. Mean observed (from n=8 healthy volunteers) and predicted plasma concentration values for metformin. Predictions were made using the basic and extended convolution models (shown in panels a and b, respectively) for up to 22 h only, based on availability of *in vitro* data. Symbols are observed means for formulations A3 (◆), A7 (■), and A15 (▲), and lines are the respective predictions. Error bars represent standard deviations of observed data.

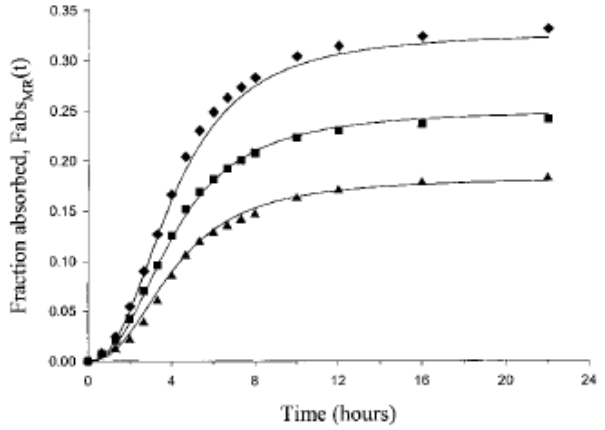
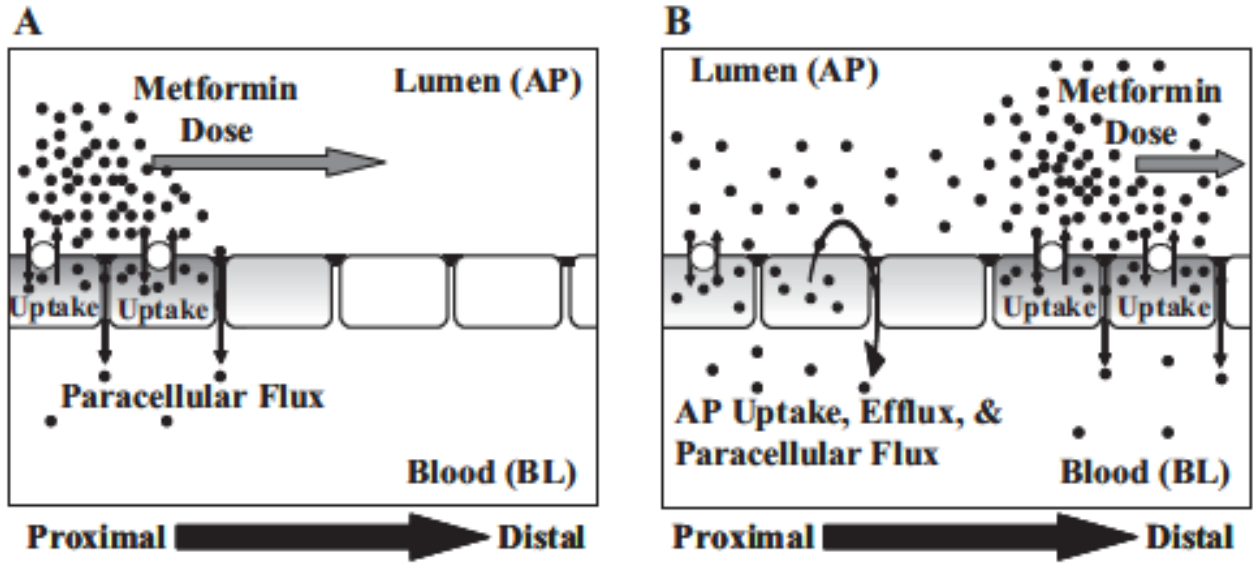


Figure 5. Observed and fitted values for $Fabs_{MR}$ (t). The observed data were obtained using eq. 1 for a period of 22 h after dose administration of formulations A3 (◆), A7 (■), and A15 (▲). Values are mean from eight healthy volunteers. Observed data were fitted to a Hill function, shown in eq. 2. For all these fitted curves, shown as lines, r^2 was >0.9.

- Different formulations exhibited differences in both rate and extent of drug getting into systemic circulation
- Generating successful IVIVC required scaling function for total fraction absorbed for each formulation

Balan – J Pharm Sci 2001, 90:1176-1185

Metformin Absorption



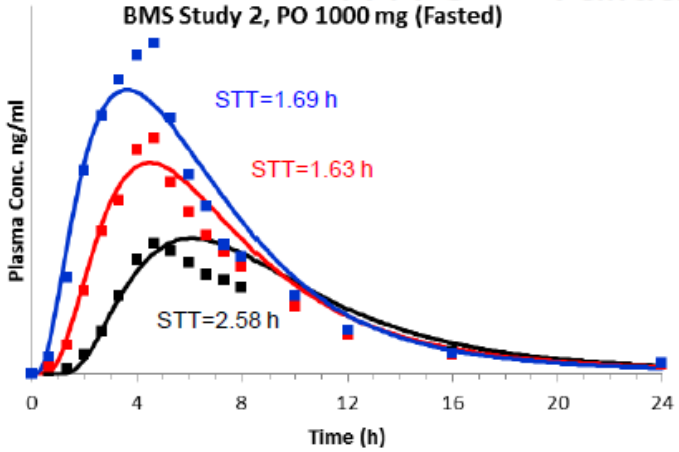
- Passive diffusion predominantly via paracellular pathway
- In human, paracellular pathway is most efficient in upper small intestine
- Proctor et al. proposed mechanism involving compound recycling through enterocytes to capture *in vivo* absorption

Proctor – DMD 2008, 36: 1650-1658

Metformin IVIVC

- Kakhi developed mechanistic absorption model for metformin
- Preliminary results showed improved predictability of the IVIVC

IVIVC – Validation Fasted State



Individual deconvolution, STT fitted to Ind ER profiles

Study	Formulation	Parameter	%PE
Fasted	Slow Int	AUC(0-t) ng h/ml	19.2
		Cmax ng/ml	4.5
	Medium Int	AUC(0-t) ng h/ml	12.4
		Cmax ng/ml	-10.3
	Avg Abs %PE Int	AUC(0-t) ng h/ml	15.8
		Cmax ng/ml	7.4
	Fast Ext	AUC(0-t) ng h/ml	5.7
		Cmax ng/ml	-14.0

Average deconvolution, STT fitted to Avg ER profiles

Study	Formulation	Parameter	%PE
Fasted	Slow Int	AUC(0-t) ng h/ml	3.9
		Cmax ng/ml	-23.0
	Medium Int	AUC(0-t) ng h/ml	-10.1
		Cmax ng/ml	-22.6
	Avg Abs %PE Int	AUC(0-t) ng h/ml	7.0
		Cmax ng/ml	22.8
	Fast Ext	AUC(0-t) ng h/ml	-9.1
		Cmax ng/ml	-16.9

Individual deconvolution, STT fitted to IR profile

Study	Formulation	Parameter	%PE
Fasted	Slow Int	AUC(0-t) ng h/ml	10.5
		Cmax ng/ml	7.0
	Medium Int	AUC(0-t) ng h/ml	16.0
		Cmax ng/ml	-7.9
	Avg Abs %PE Int	AUC(0-t) ng h/ml	13.2
		Cmax ng/ml	7.4
	Fast Ext	AUC(0-t) ng h/ml	1.7
		Cmax ng/ml	-19.6

16

IVIVC – Validation Comparison

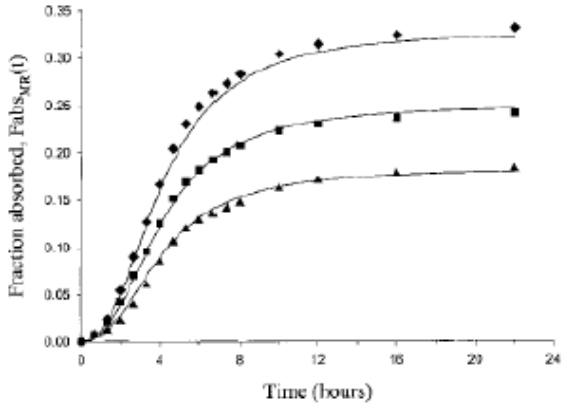
Study: Fasted State	Formulation	Parameter	%PE
Balan et al. Basic Convolution	Slow Int	AUC(0-22) ng h/ml	102.7
		Cmax ng/ml	50.4
	Medium Int	AUC(0-22) ng h/ml	56.1
		Cmax ng/ml	9.9
	Fast Int	AUC(0-22) ng h/ml	17.1
		Cmax ng/ml	3.9
Balan et al. Extended Convolution	Slow Int	AUC(0-22) ng h/ml	-1.6
		Cmax ng/ml	-7.3
	Medium Int	AUC(0-22) ng h/ml	1.4
		Cmax ng/ml	-10.8
	Fast Int	AUC(0-22) ng h/ml	-2.4
		Cmax ng/ml	-11.0
Phoenix WinNonlin Numerical Deconvolution	Slow Int	AUC(0-24) ng h/ml	46.8
		Cmax ng/ml	-22.9
	Medium Int	AUC(0-24) ng h/ml	26.9
		Cmax ng/ml	-41.5
	Fast Int	AUC(0-24) ng h/ml	-0.3
		Cmax ng/ml	-35.8

Kakhi – AAPS Annual Meeting 2015

Metformin IVIVC

IVIVC – Validation Comparison

- Mechanistic model predicted the changes in % of drug entering portal vein across the three formulations
- Similar trends were previously fitted using the extended convolution based approach



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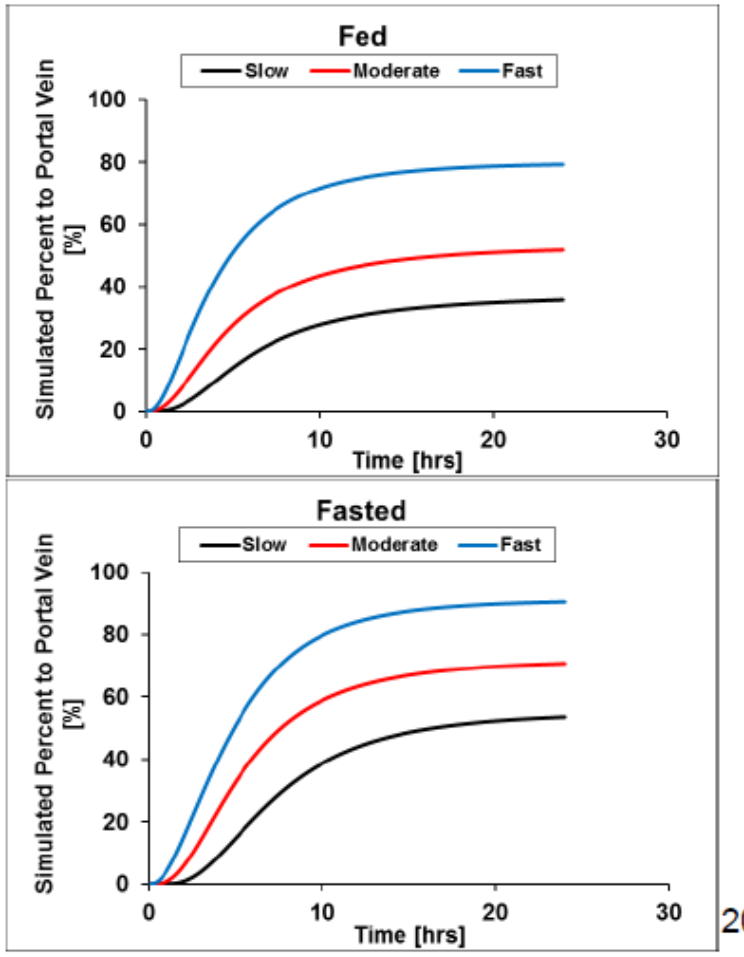
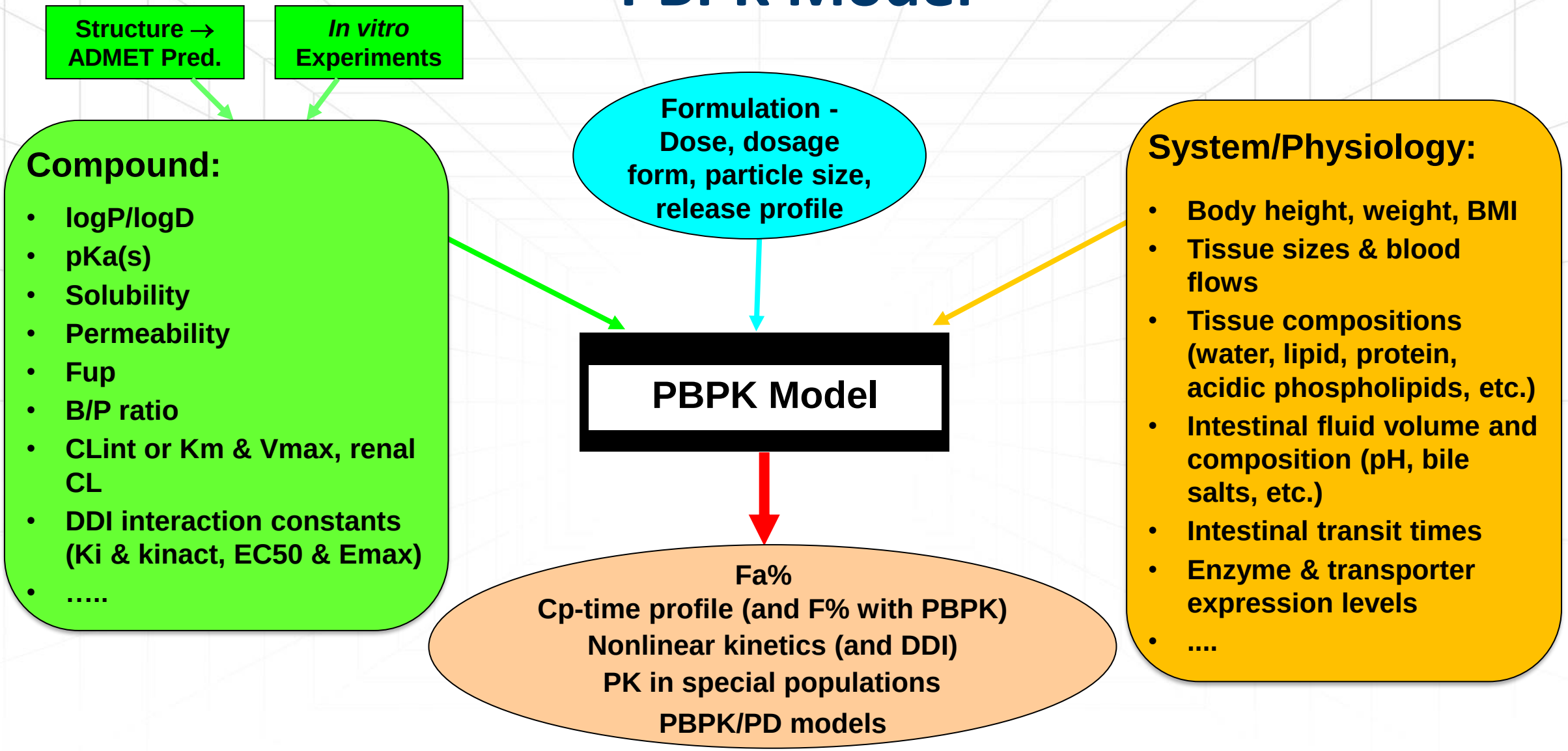


- The mechanistic model also predicted changes in the extent of drug entering portal vein for formulations with varying release rates

Building Mechanistic IVIVC

- Build mechanistic absorption/PK model for the API
  - Determine critical mechanisms impacting the drug absorption and pharmacokinetics
    - Include the mechanisms that lead to non-linear PK
  - Parameterize systemic disposition model
    - Ideally, using IV data
  - Parameterize absorption model
    - Using data from immediate release formulations
- Deconvolute *in vivo* release profiles
- Find relationship between *in vivo* and *in vitro* release profile and validate IVIVC

PBPK Model



Model Master File

- **Model Structure:**
  - Processes affecting drug absorption
    - Passive diffusion – paracellular and/or transcellular
    - Carrier-mediated transport and metabolism at the absorption site
    - Nonspecific binding at the administration site
    - Others
  - Processes affecting drug systemic disposition
    - Tissue distribution mechanisms
    - Elimination pathways
    - Others
  - Need to be provided by the sponsor (may be available in public sources)
- **Drug Inputs:**
  - Drug physicochemical properties
  - Drug pharmacokinetic properties (tissue distribution, Km and Vmax values for interaction with specific enzymes and transporters)
  - Need to be provided by the sponsor (may be available in public sources)

Model Master File

- **System Inputs:**
  - Independent of Drug/Formulation
  - Description of physiological parameters
  - Included with PBPK platform
    - Sponsor needs to specify the platform version used
    - Sponsor needs to specify any modifications from the default settings
- **Formulation Inputs – for IVIVC application:**
  - Type and composition of formulation
  - *in vitro* dissolution data
  - IVIVC equation
  - Need to be provided by the sponsor

Summary

- Mechanistic IVIVC expands the IVIVC utility to compounds undergoing complex mechanisms
- Successful mechanistic IVIVC requires building complete mechanistic absorption/PK model
  - More involved process (-)
  - Provides additional information on what impacts the exposure (+)
- Reporting/description of the model needs to include:
  - Model structure (Sponsor and/or public information)
  - Compound specific information (Sponsor and/or public information)
  - Formulation specific information (Sponsor)
  - System specific information (included with platform, but Sponsor needs to report exact platform version that was used and explain any modifications to default parameters)