Linking *In Vitro* Dissolution to *In Vivo* Performance of Extended-Release Drug Products

Source: https://sofrigam.com

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MCERSI & FDA Workshop
The Evolution of Biopharmaceutics:
Risk Assessment and Clinical Relevance

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Outline

- Linking *in vitro* and *in vivo* data
  - ER: *In vitro* behaviors vs. *in vivo* performance
  - IVIVC/R development: Strategy and Key considerations
- Case studies
  - Test methods, *IVIVC* and applications
  - API, formulation and *In Vitro-In Vivo* linkage
- Summary

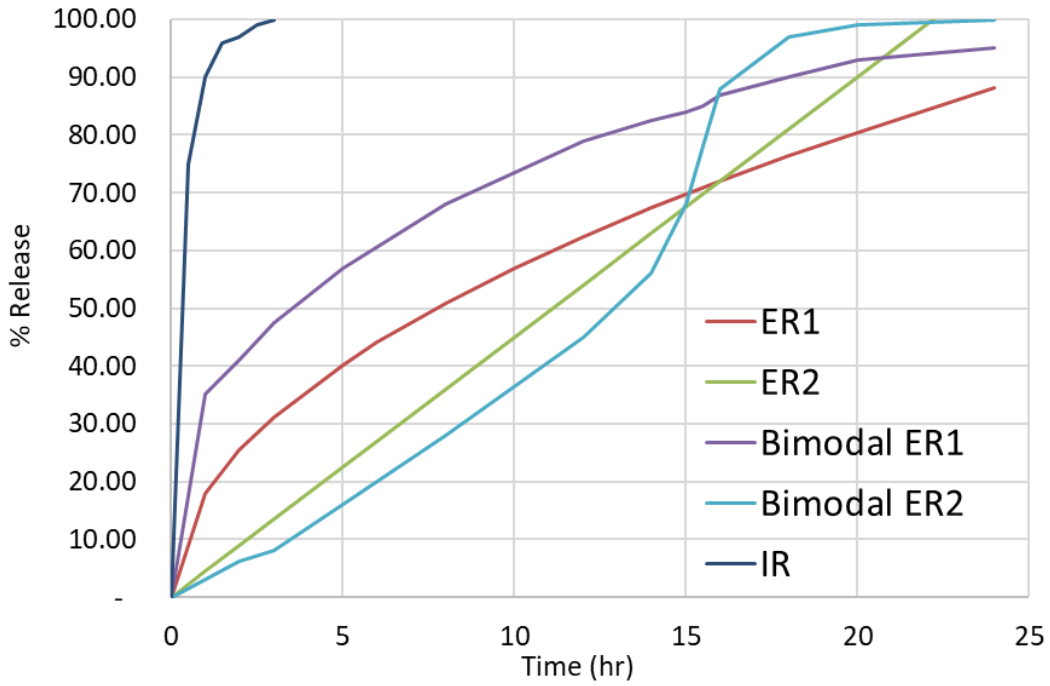
Linking *In Vitro* Dissolution to *In Vivo* Performance

- Benefits of a quantitative or semi-quantitative *in vitro-in vivo* relationship (IVIVC/R)
  - Use *in vitro* test to assess or predict *in vivo* performance
    - Bridge a critical gap between *in vitro* drug release and clinical performance
  - Serve as an important tool for product and process understanding
    - Guide product and process development
    - Set meaningful specifications to assure safety/efficacy
  - Justify waiver of *in vivo* BE studies to support product development and post-approval changes
  - Provide a significantly increased assurance of product quality throughout the lifecycle of a drug product
    - Minimize risks to patients by ensuring *in vivo* performance

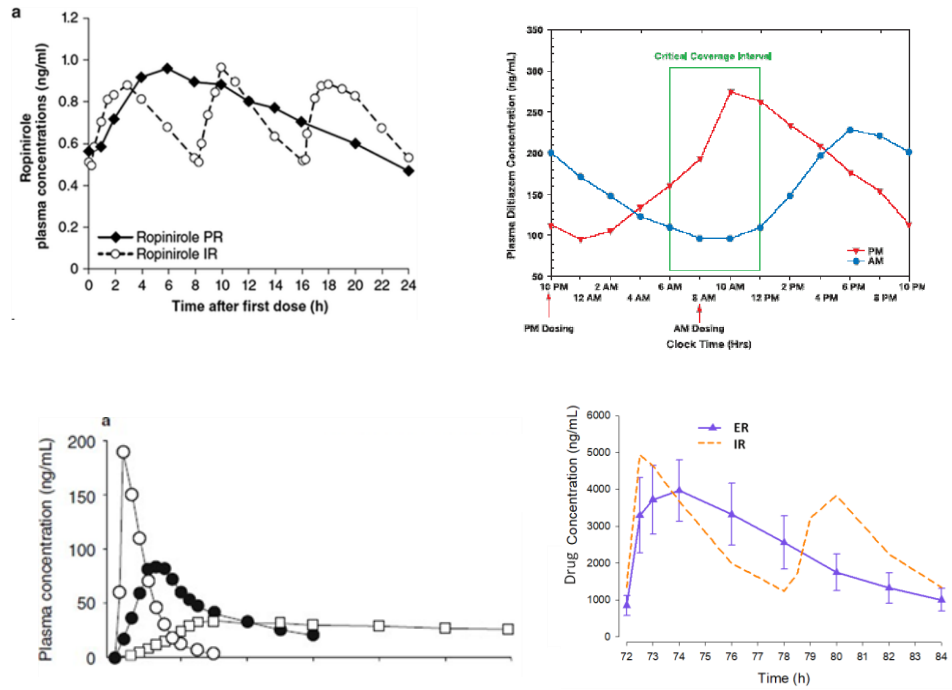
Extended-Release Products: *In Vitro - In Vivo* Linkage

- Alter drug release rate/pattern to achieve desired *in vivo* PK
  - **By design**, absorption is limited by drug release
  - Increased chance for *in vitro - in vivo linkage* → *IVIVC/R* → More important & valuable for ER products

Examples of ER Profiles



Examples of PK



J. Clin. Pharmacol 43(1): 1149 (2003);

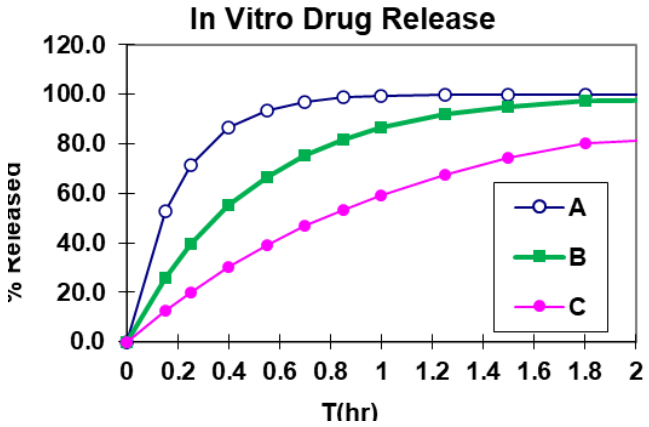
ER Product Development:

In Vitro Behaviors vs. *In Vivo* Performance

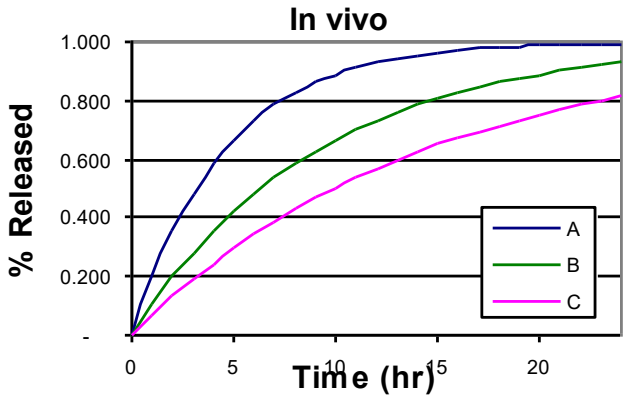
Linking *In Vitro* to *In Vivo* Data

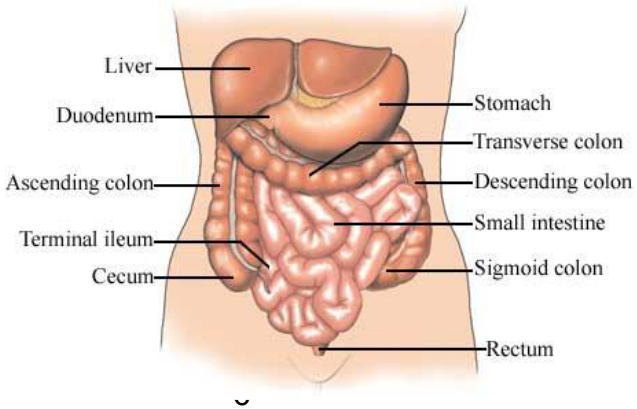
- ER product development
  - Design begins with a target PK and *in vitro* testing

In vitro test (e.g., drug release)

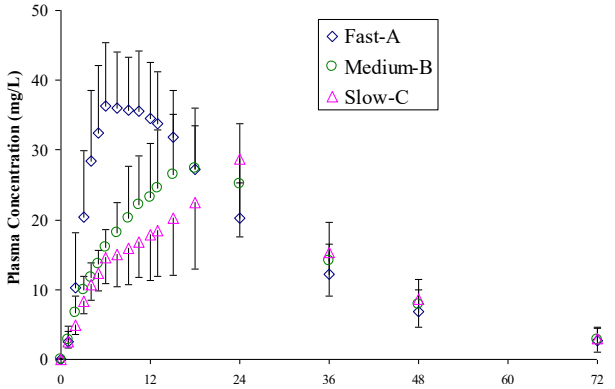


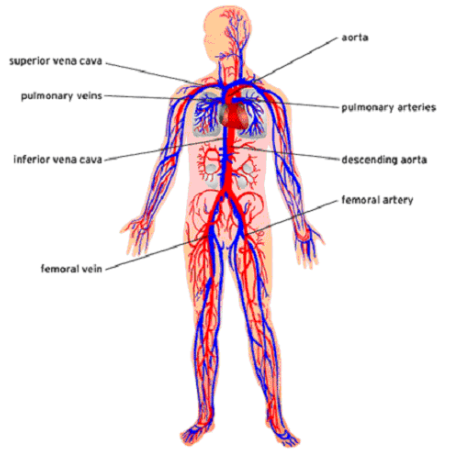
In vivo drug release/absorption In the GI tract





In vivo response (e.g., PK profiles)

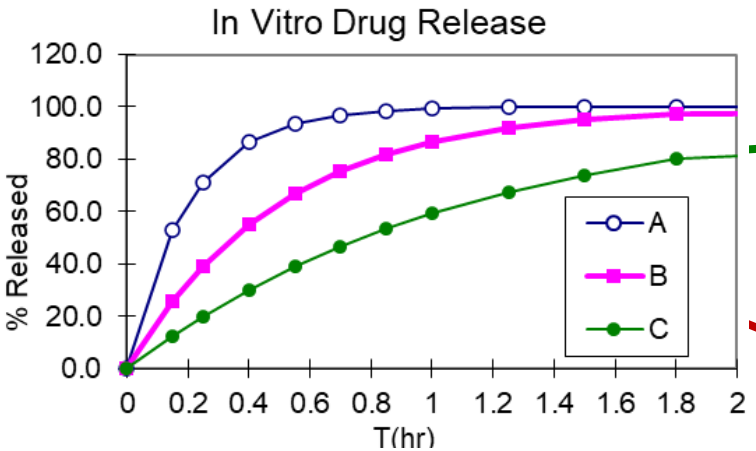




Linking *In Vitro* to *In Vivo* Performance

- *In vitro* and *in vivo* relationship in ER product development
  - *Quantitative (IVIVC)*
  - *Semiquantitative (IVIVR, e.g., rank order, mapping)*
  - *None*

***In vitro* test**

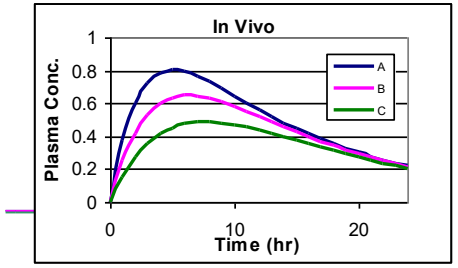


IVIVR

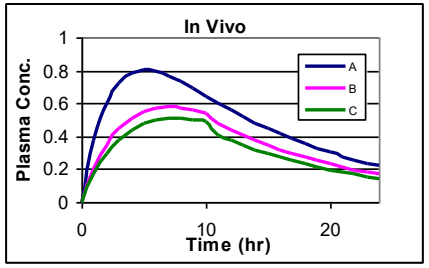
No IVIVR

In vivo PK

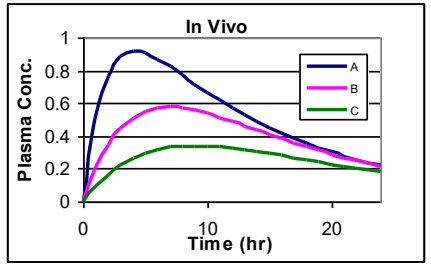
(I) Predictive



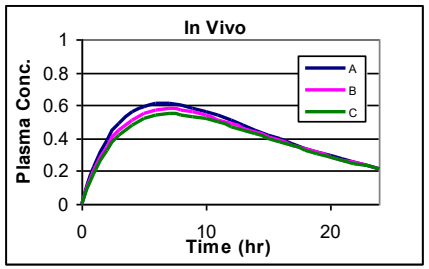
(II) Rank order

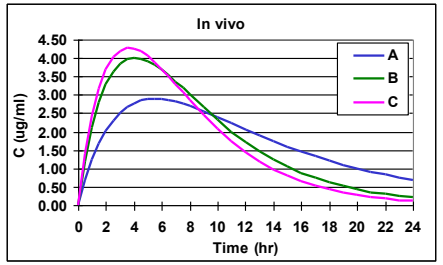


(III) Under-discriminative



(IV) Over-discriminating





Linking *In Vitro* to *In Vivo* Performance

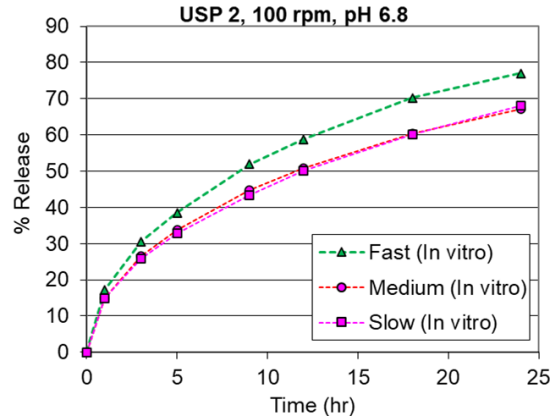
- *IVIVR* Examples in ER product development

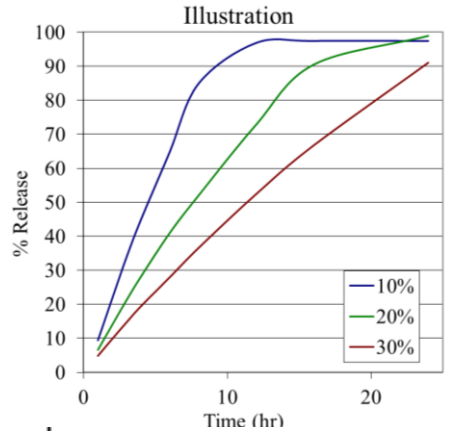
In vitro test: *Under-discriminating*

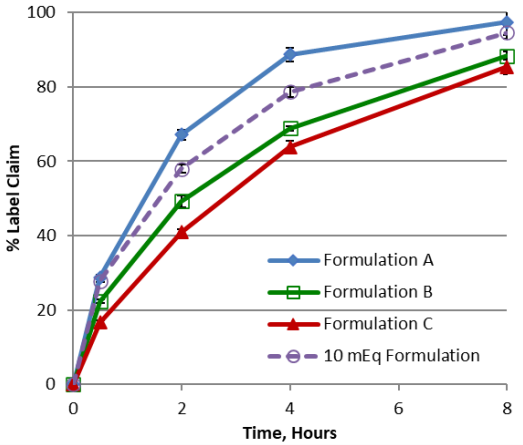
Over-discriminating

Rank-order, Over-discriminating & Under-discriminating

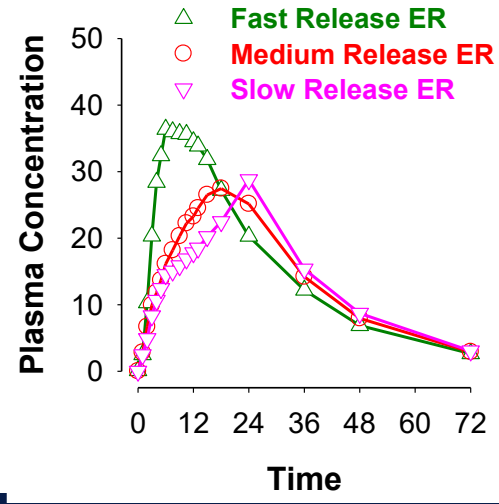
In Vitro

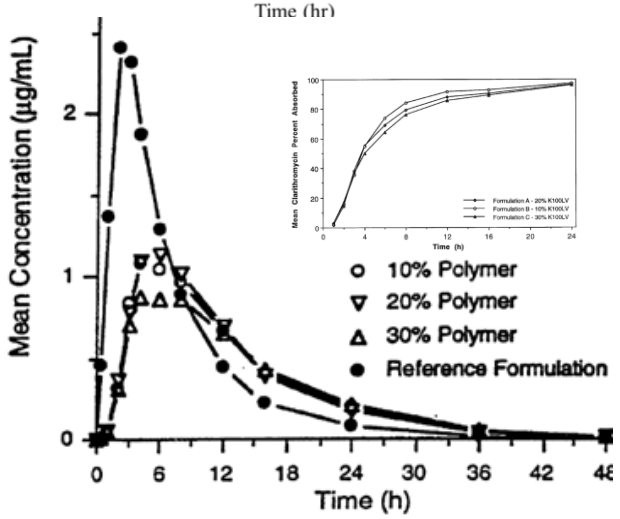


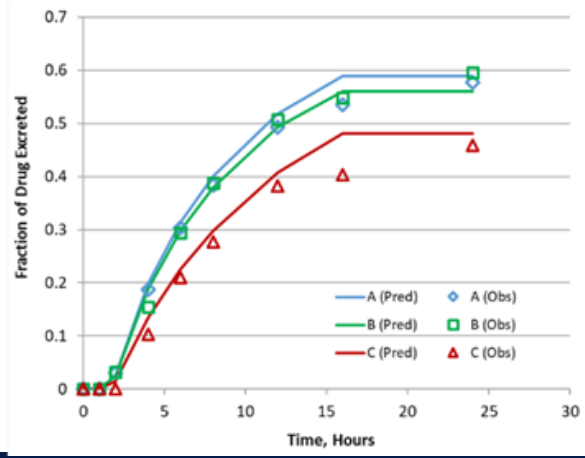




In Vivo





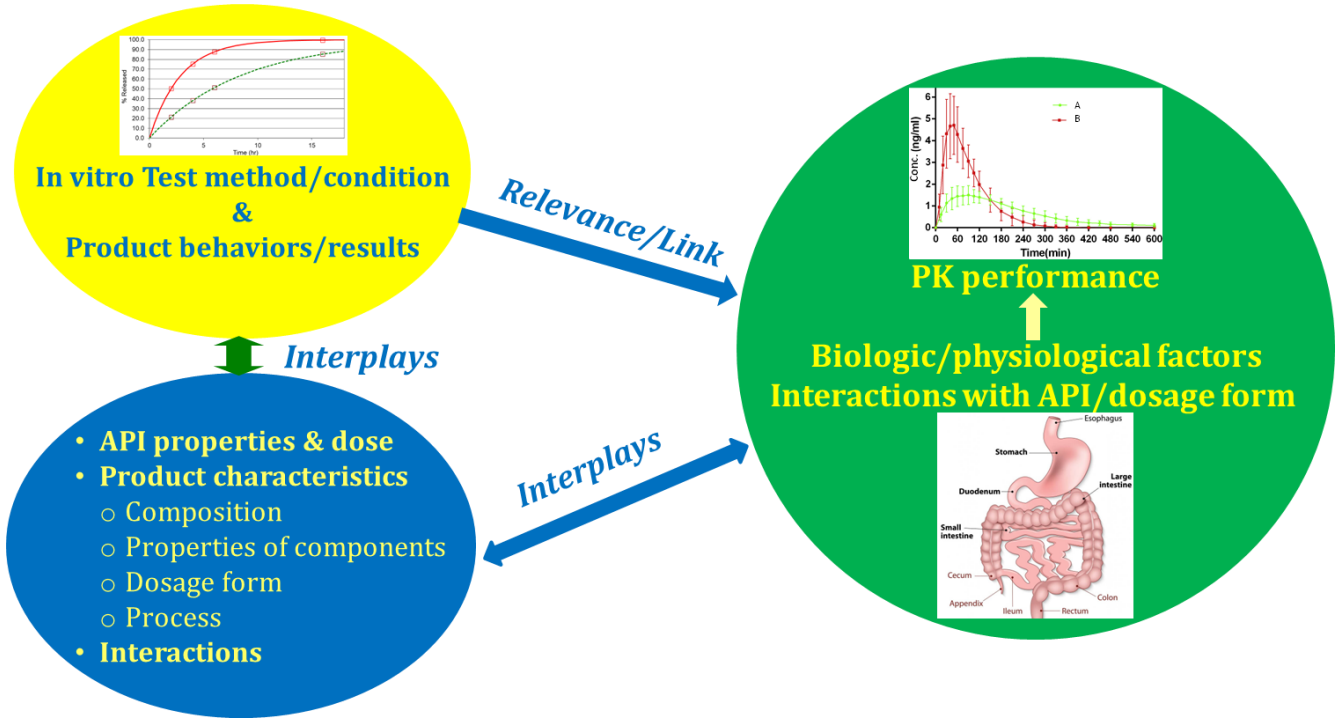


Linking *In Vitro* to *In Vivo* Performance

- *In vitro-in vivo* linkage
  - *In vivo* data: **Invariant**
  - *In vitro* data: **Adjustable**
- **Strategy** for bridging or reducing the gap with *in vivo* data
  - **Adjustment of *in vitro* test conditions to align with *in vivo* apparent absorption**
    - Rate, differentiation, kinetics

Key to Linking *In Vitro* and *In Vivo* Data

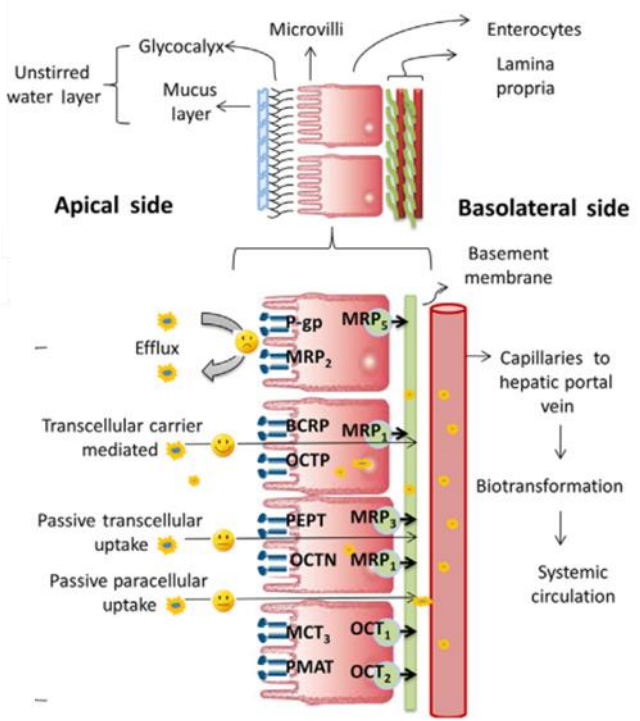
- Understanding the influence of
  - ***API, formulation, test method/condition, absorption mechanisms and environment, as well as their interplay,*** on *in vitro* and *in vivo* behaviors/performance of a dosage form

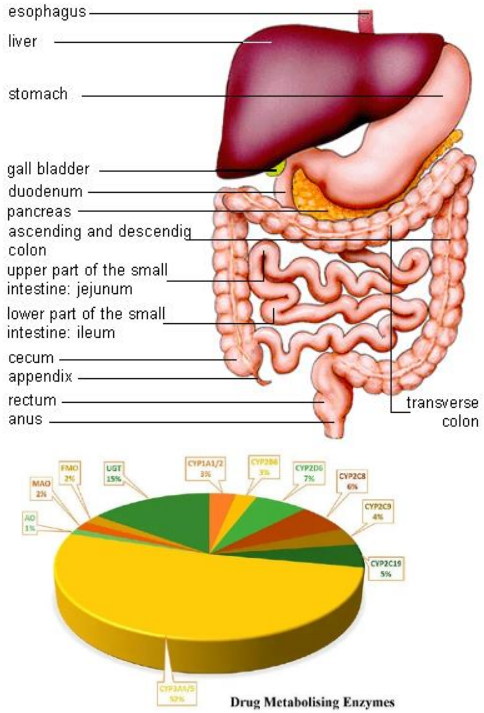


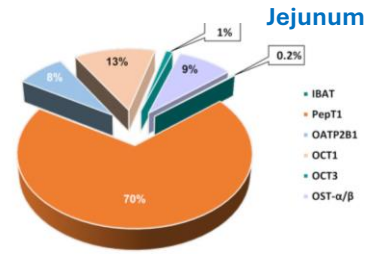
- **Integrated considerations**
  - **API**: Biopharmaceutical characteristics (physicochemical, apparent absorption, pH and regional dependence, dose, etc.)
  - **Product**: Dosage form and formulation design, release control mechanism, impact of *in vitro* and *in vivo* environments
  - ***In vitro* release test**: Impact of test conditions on API and formulation
  - ***In vivo* PK**: Absorption behavior attributable to API, formulation, GI factors & interactions

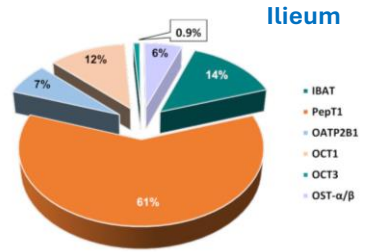
Assessing *In Vitro* and *In Vivo* Discrepancies

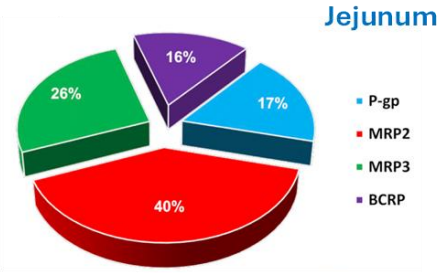
- Understanding ***in vivo*** data and its influencing factors
  - ***In vivo* data** = ***f*** *(drug properties, formulation, biological/physiological variables, release location and interactions)*
  - Study design, variability and power, adequate *in vivo* differentiation (or lack of)
  - Data analysis, modeling, constraints and limitations

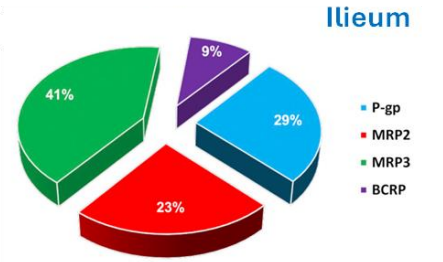








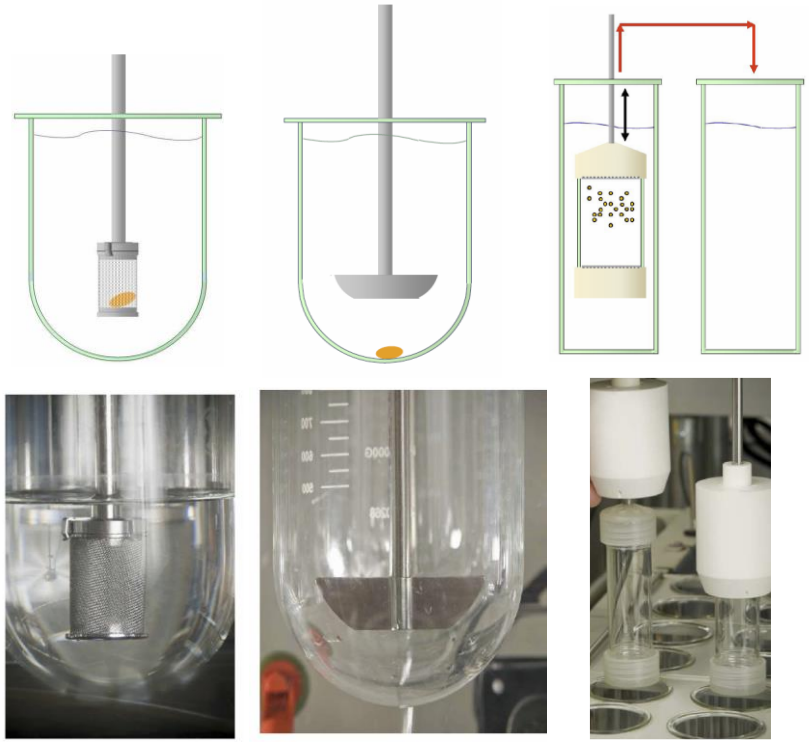




Source: Acta PharmaceuticaSinicaB;7(3):260 (2017); Curr Opinion in Pharmacol 13:847 (2013); Drug Metab Disp 47:854 (2019) ; Clin Pharmacokinet 55:673 (2016); J. Med. Chem. 64(5):2339 (2021)

Assessing *In Vitro* and *In Vivo* Discrepancies

- Understanding ***in vitro*** test and data
  - ***In vitro* data** = ***f*** (drug properties, formulation/process, test method, conditions, interactions and method artifact)
  - A static and well-controlled environment
  - Low hydrodynamics and shear stress conditions **for ER drug release**
  - Possible differences from ***in vivo* drug release**
    - Impact of the test environment and possible interactions (API/polymer – media, mixing, etc.) on API, dosage form and release
    - Release rate, kinetics and/or mechanisms

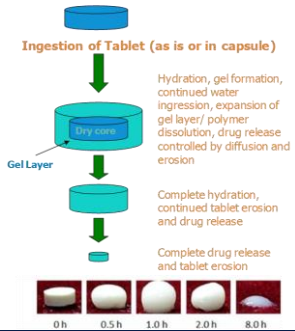


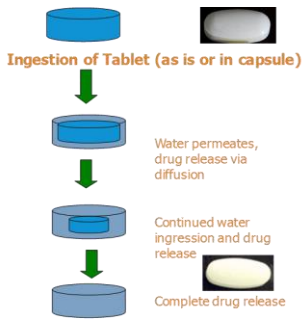
ER Products: Focus on Drug Control Release Principles and Factors

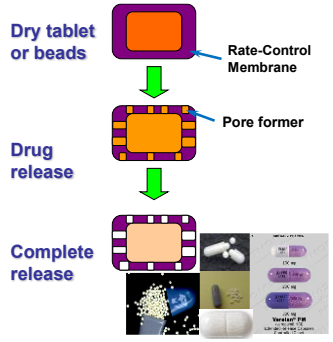
- Key: Understanding of common ER technologies and release controls
  - Impact of API properties, **formulation design** and release mechanism on *in vitro* and *in vivo* results

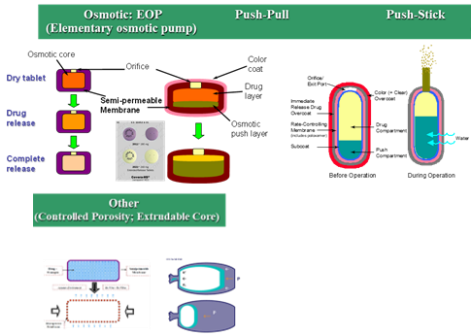
API (Dose/solubility)	**Common ER systems and dominant release mechanism**			
	Hydrophilic matrix	**Hydrophobic matrix**	**Reservoir**	**Osmotic pump *(authentic, pseudo)***
High*	**Polymer dissolution/erosion**	**NA**	**NA**	**Osmotic pressure**
Low	API Diffusion	API Diffusion	API Diffusion	Osmotic pressure
In vitro* vs. *in vivo	Slower rate	Slower – Similar rate		Similar rate
Sensitivity to medium & mixing	High	High	High	(a) Low (b) Low - Medium (Pseudo system)
Sensitivity to shear stress	Low - Medium (Formulation design – dependent)			

** Relevant to today's NCEs*









Assessing *In Vitro* and *In Vivo* Discrepancies

- **Approach for adjusting *in vitro* tests**

(A) Focus on **environmental aspects** of release testing

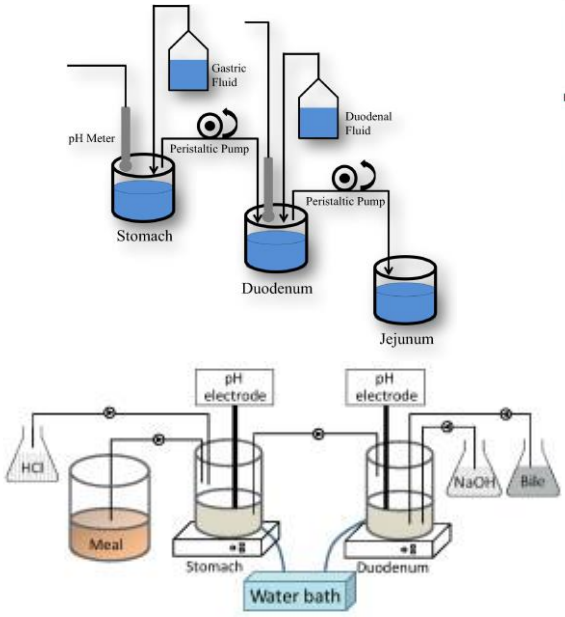
  - Attempt to mimic selected *in vivo* parameters/conditions *in vitro* using testing systems more complex than USP apparatus

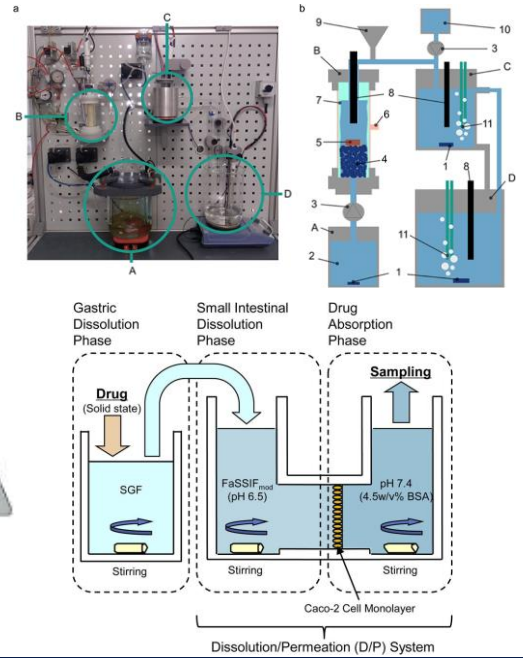
(B) Evaluate and address **likely causes of discrepancies** between *in vitro* and *in vivo* release**,** based on specific API and formulation characteristics, for guiding adjustment of *in vitro* test conditions

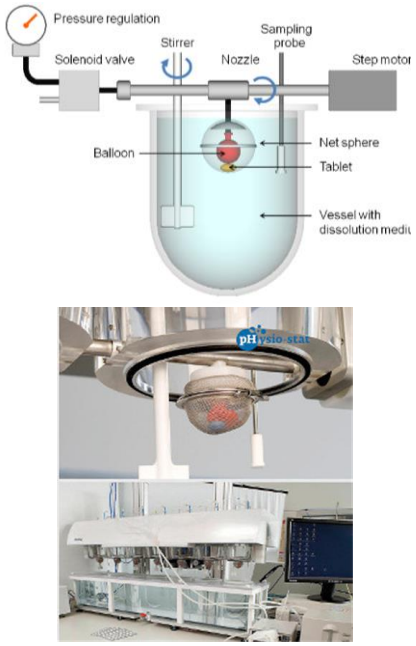
  - **ER:** Focus on release control mechanisms, rate and differentiation in relation to API, formulation and *in vitro* testing
  - Priority: USP apparatus suitable for QC testing of commercial products

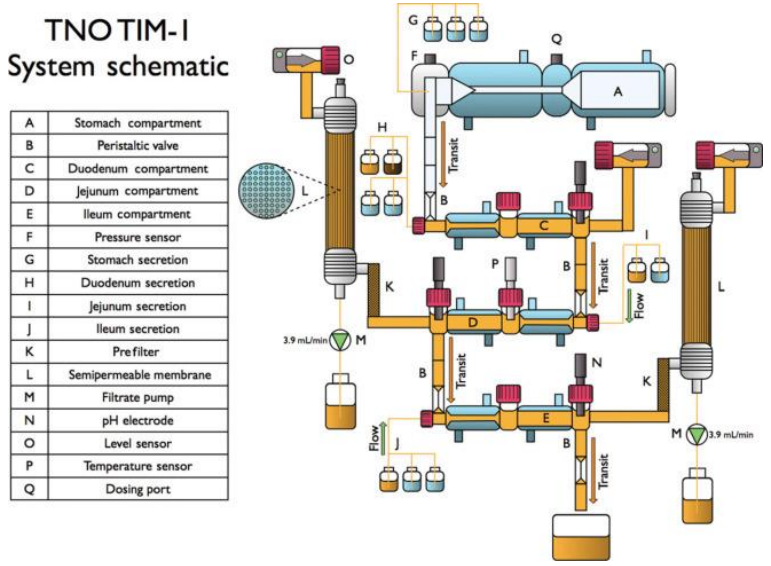
Assessing *In Vitro* and *In Vivo* Discrepancies

- **Examples of A:** Complex *in vitro* setups for IR and MR products
  - Incorporating dynamic component
  - Simulating one or more specific GI conditions (**test media**, hydrodynamics, mechanical stress, motility, transit, secretion, food, permeation, …)
    - Multi-vessels, Physiolution (stress), PhysioCell, Multi-compartments (TNO), etc.
- **Status:** (1) No one-size-fits-all system; (2) Utilized in R&D; (3) Not suitable for QC testing





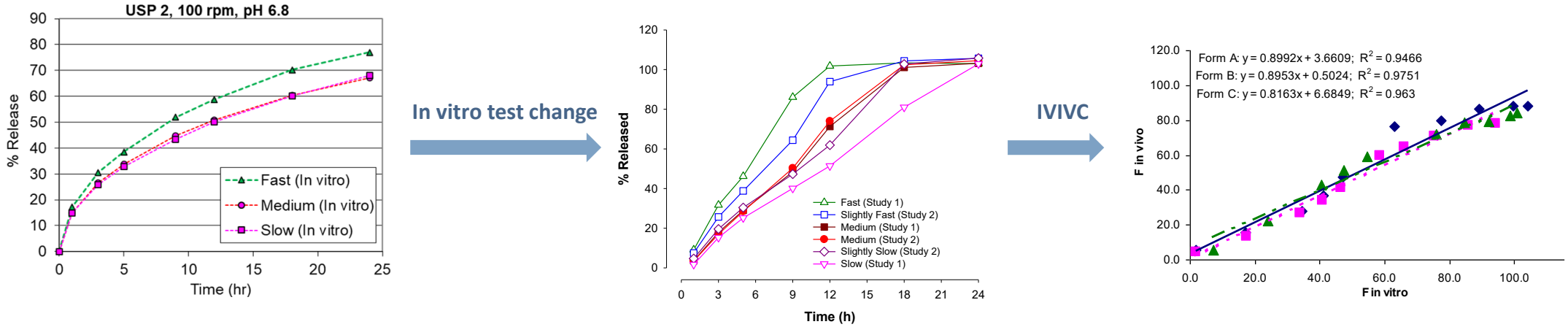




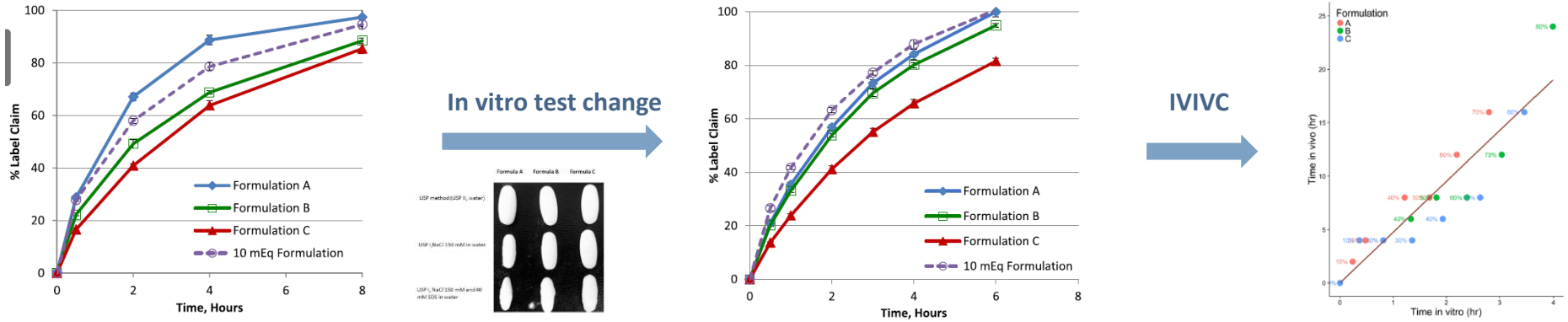
In Vitro Dissolution Absorption System (IDAS); AAPS PharmSciTech, 16(4): 922 (2015); Eur. J. Pharm. Sci. 57:264 (2014); 76:203 (2015) ; Eur. J. Pharms Biopharm. 101:103 (2016)

Assessing *In Vitro* and *In Vivo* Discrepancies

- **Examples of B:** Focusing on the assessed product-specific causes of *in vitro* and *in vivo* data discrepancies
  - ***In vitro* adjustment**: Release mechanism/gel strength → Release rate, kinetics and differentiation



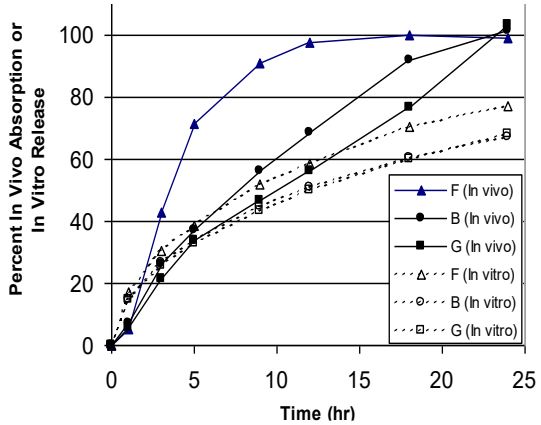
  - ***In vitro* adjustment**: Tablet strength → Release differentiation (diffusion mechanism unchanged)

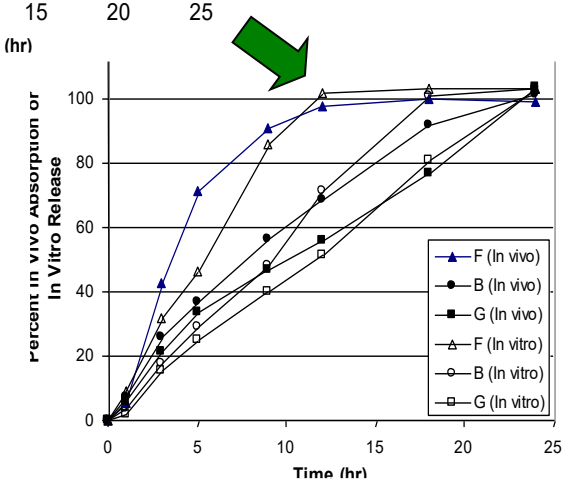


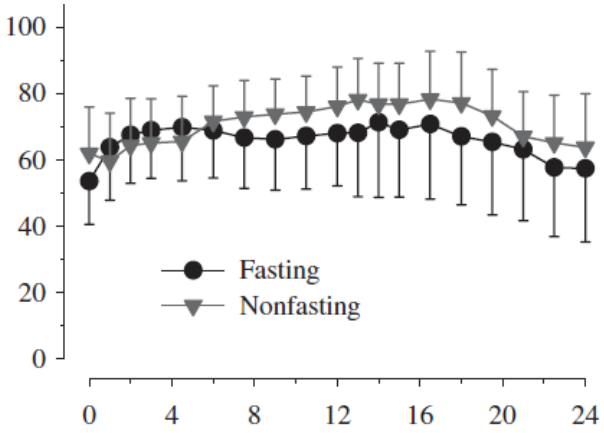
Case Studies

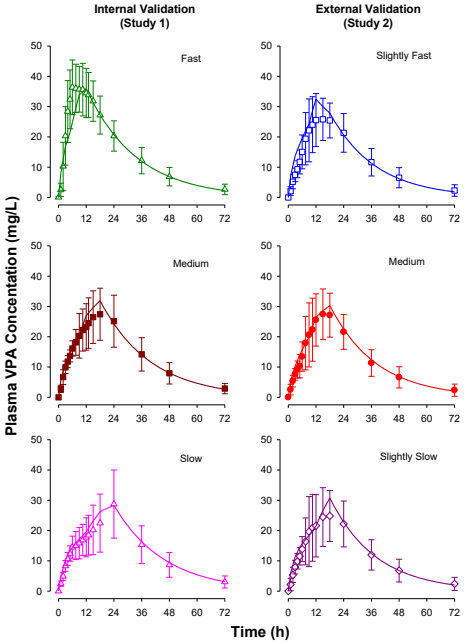
Case Study: Test Methods, *IVIVC* and Applications

- ER tablets; NTI drug
  - ~ 20 hrs *in vivo* absorption
- *In vitro* vs. *in vivo* data
  - **Initial method (A)**
    - Slower release
    - Under-discriminating
    - Different kinetics
    - IVIVC is formulation-dependent
  - **New method (B)**
    - Developed based on formulation characterization and *in vitro* test modifications
    - Level A *IVIVC* validated internally and externally
    - **Suitable for QC testing**



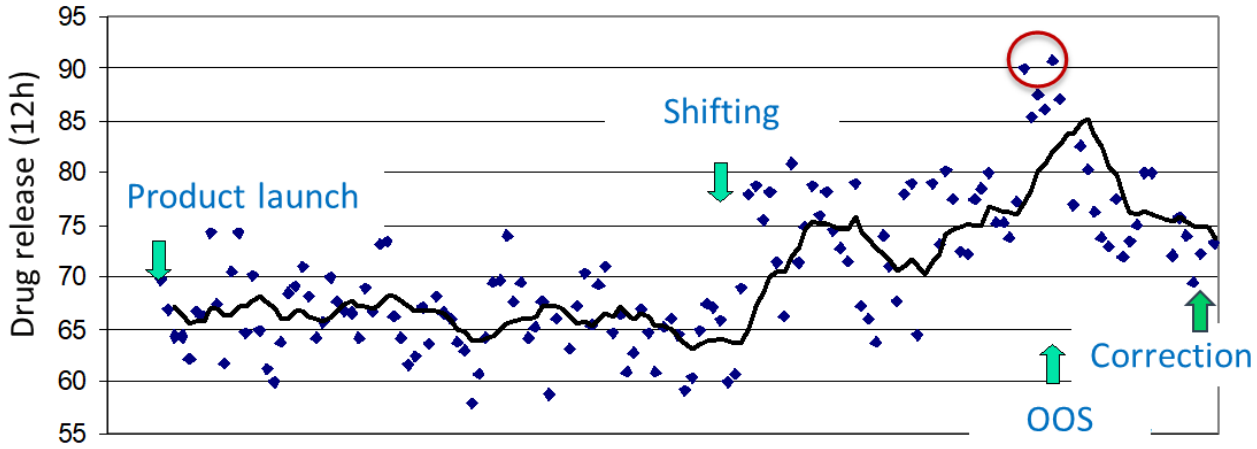




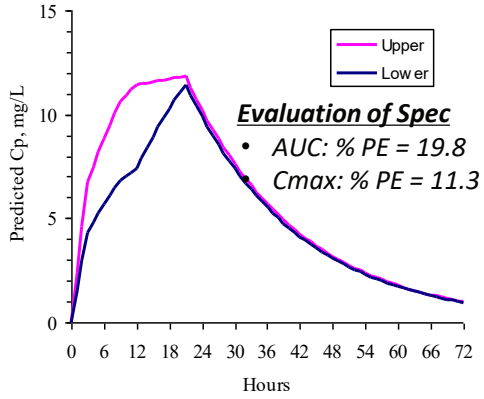


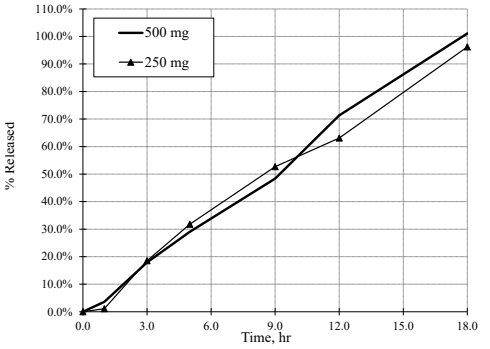
Case Study: Test Methods, *IVIVC* and Applications

- Applications of *IVIVC*
  1) Supported **wide dissolution limits** (> ± 10%)
  2) Supported biowaivers of **site change**
  3) Supported **new formulation** development of a new strength
  4) Ensured **commercial product quality and performance**
     - Following product launch & > 100 successful commercial batches
       - Dissolution drifting → OOS despite wide dissolution spec limits



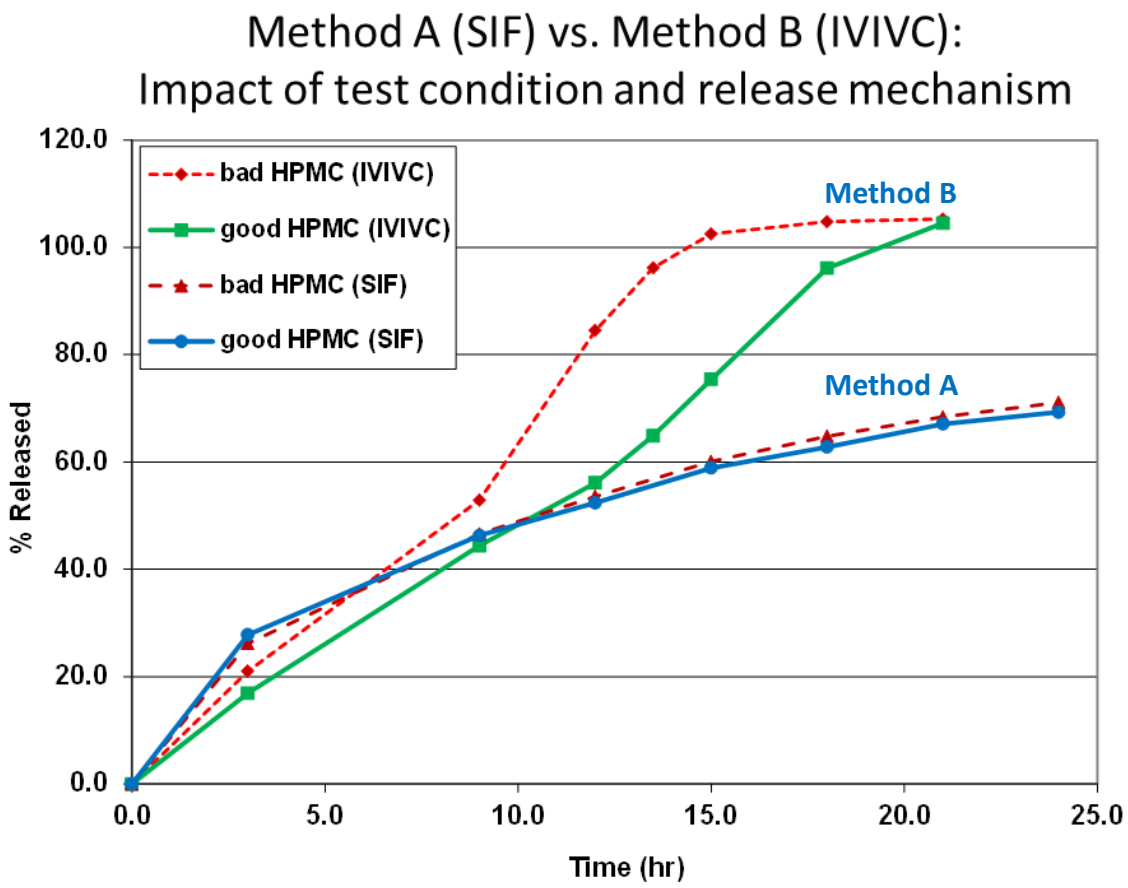
Production Lot





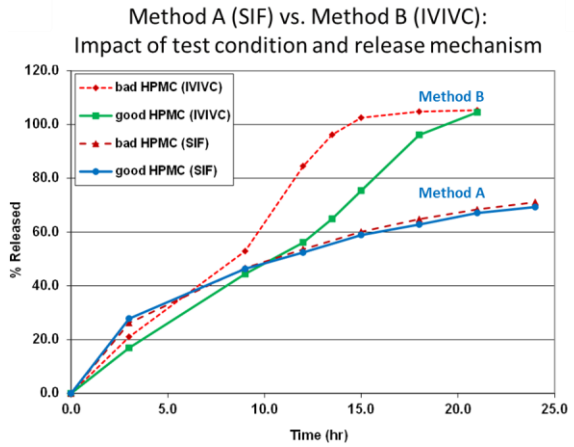
Case Study: Test Methods, *IVIVC* and Applications

- Root-cause investigations
  - Altered critical polymer properties identified
- Problem mitigation
  - Additional polymer controls implemented
- **Noteworthy**
  - Dissolution changes would not have been detected by **Method A**
- **Method B**
  - "Minimize risks to patients by ensuring *in vivo* performance" of commercial batches

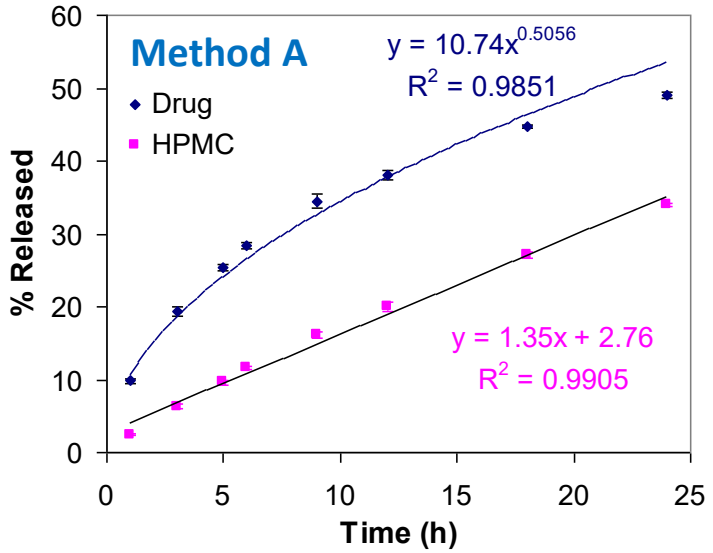


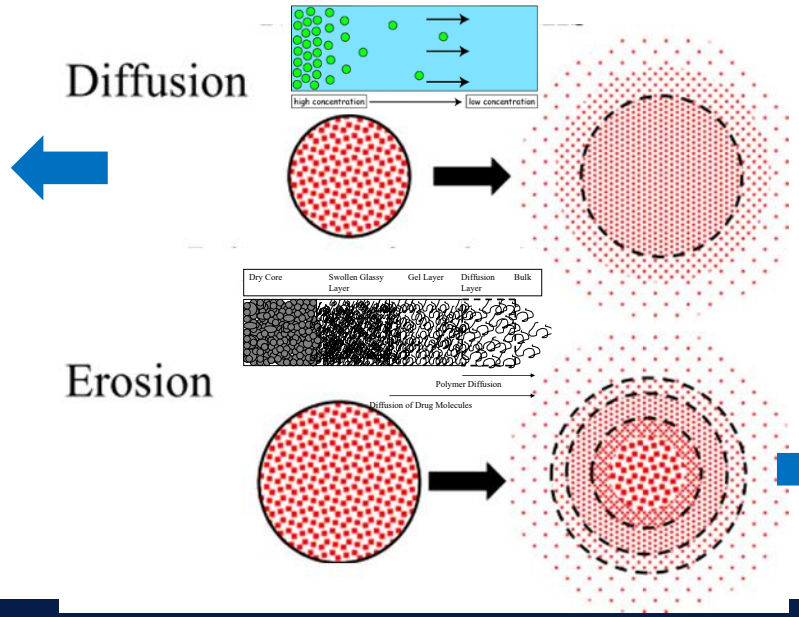
Case Study: Test Methods, *IVIVC* and Applications

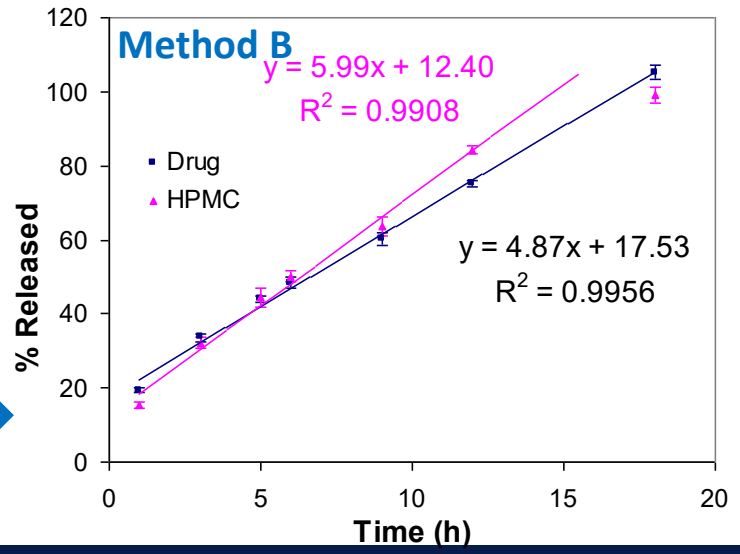
- Understanding differences between two test methods
  - Method A
    - **Diffusion controlled**: Driven by concentration gradient (solubility)
    - Less sensitive to polymer changes
  - Method B (IVIVC)
    - **Erosion controlled**: More sensitive to polymer changes



Comparing drug release with polymer release



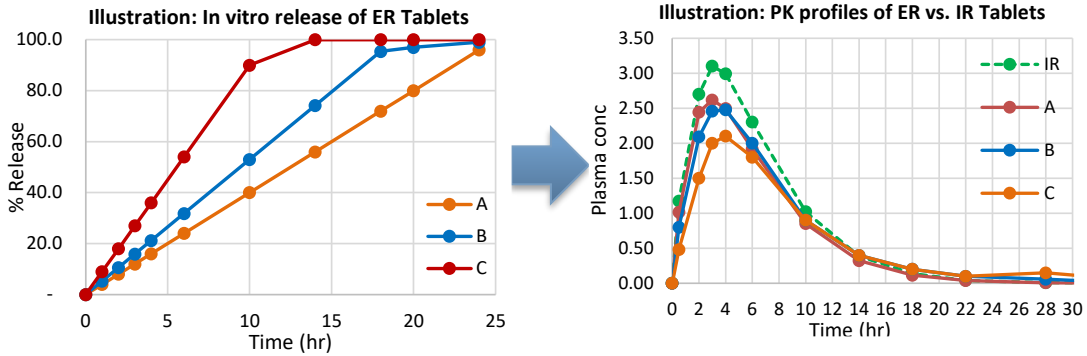




Case Study: API, Formulation and *In Vitro-In Vivo* Linkage

- ER tablets of sodium salt of a poorly soluble weak acid
  - **S = 0.15 µg/ml,** pH-dependent; High permeability, Substrate of Pgp and CYPs
  - ER design target: ~ 12 hrs *in vivo* absorption
- ER product development
  - ER formulations A – C
    - Truncated absorption at 4-5 hrs
    - **F_{rel} < 30%** vs IR → Absorption window within the small intestines
  - Evaluation of **absorption truncation**
    - Disproportionation of the sodium salt (very weak acid) → very low solubility → **Poor colonic absorption**

Illustrative data



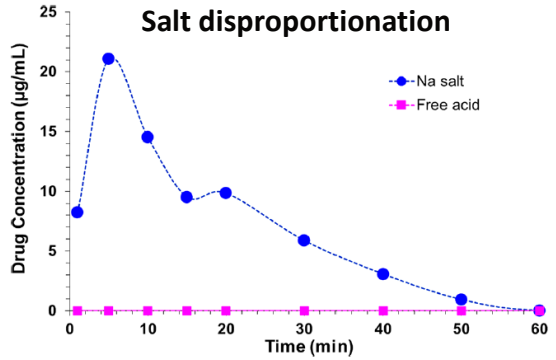


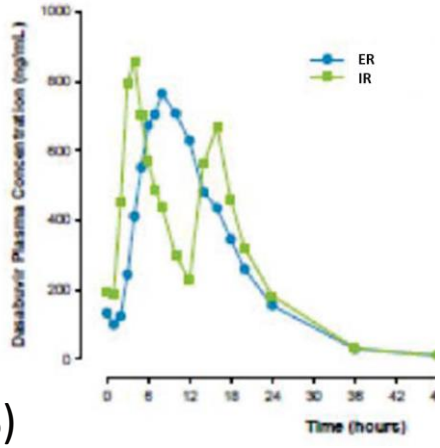
Figure 4. Dasabuvir free acid anhydrate and monosodium Form I powder dissolution in water at 37 °C.

Source: Mol. Pharmaceutics 19:2367 (2022);

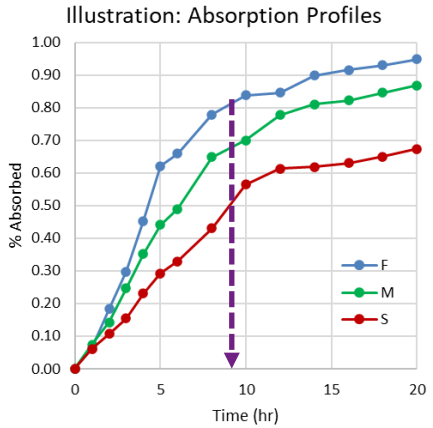
Case Study: API, Formulation and *In Vitro-In Vivo* Linkage

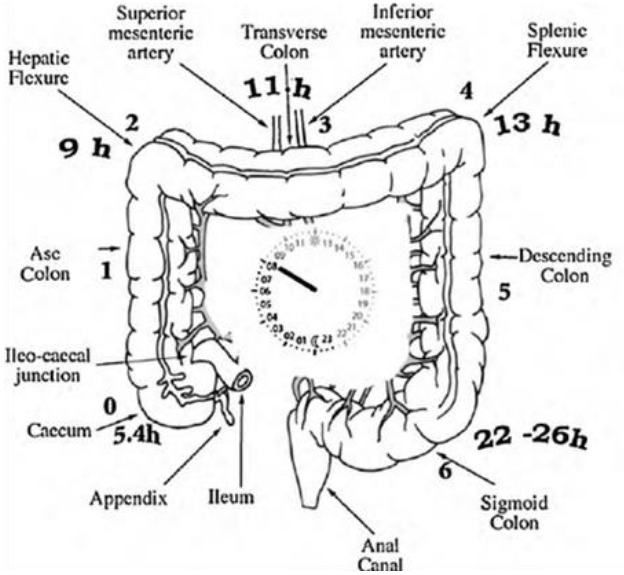
- ER product development (Cont'd)
  - New ER formulations
    - Incorporate inhibition of salt disproportionation in ER formulation to **maintain supersaturation** in the large intestines
    - *In vivo* absorption: Extended from **4 hrs to > 12 hrs** (F_{rel} ~ 90% vs. 30%)
    - **Biphasic absorption @ ~ 9 hrs** (~ transit through ascending colon)
  - *IVIVC* development
    - Adjust *in vitro* test condition to align with *in vivo* absorption

PK (ER vs. IR)



Deconvolution



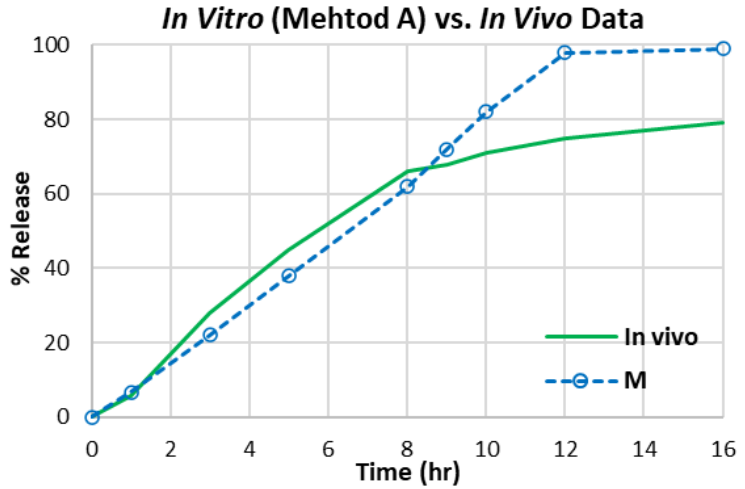


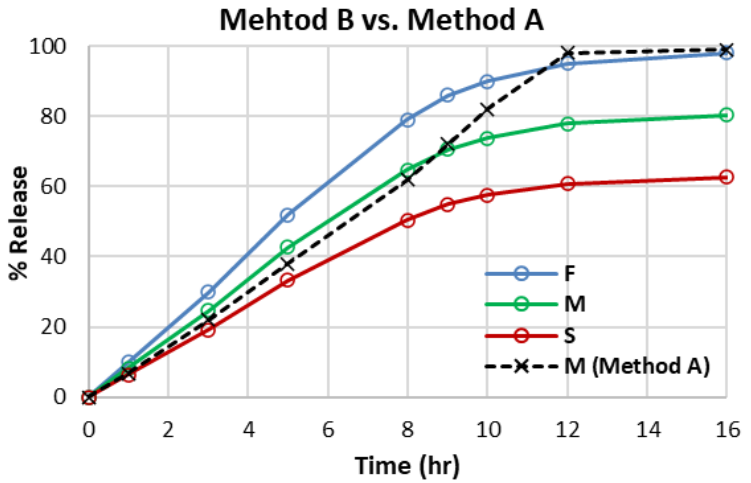
FDA Data base: NDA 208624Orig1s000; C. Wilson, Int. J. Pharm. 395: 17 (2010)

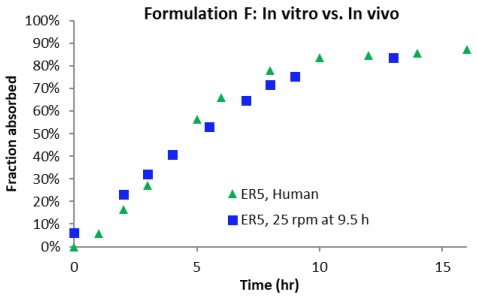
Case Study: API, Formulation and *In Vitro-In Vivo* Linkage

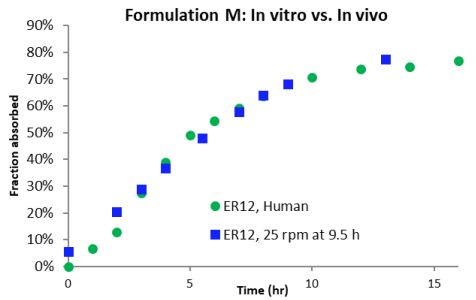
- *IVIVC* development (Cont'd)
  - Challenge
    - How to generate ***in vitro*** **biphasic** profiles of dissolution that reflect *in vivo* absorption profiles ?
  - **Test method A**
    - USP 2, 100 rpm, optimized test medium
    - Release rate ~ *In vivo* rate **except after 9 hrs**
  - **Test method B**
    - USP 2, **100 rpm until 9.5 h**, change to **25 rpm**
    - Release profile mimicking *in vivo* profiles
  - **Alternative**
    - Method A + PBBM modeling

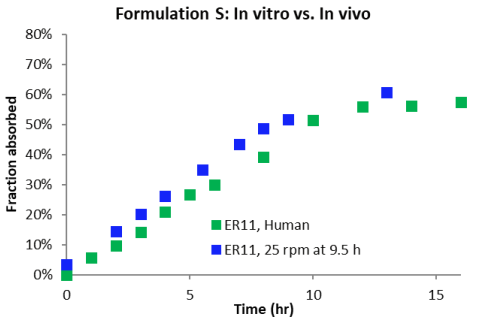
Illustrative data











US patent: US6,010,718; US6,551,616; C. Wilson, Int. J. Pharm. 395: 17 (2010)

Summary

- Linking *in vitro* drug release to *in vivo* absorption performance
  - Highly desirable → Ability of an *in vitro* test to **assess or predict** *in vivo* performance (*IVIVC/R*)
  - High-risk ER products: More critical, valuable & feasible
- Developing predictive *in vitro* tests for ER dosage forms
  - Understanding API properties, ER principles, formulation design and *in vitro* test methods in relation to *in vivo* apparent absorption, **on a case-by-case basis**
  - Applicable for QC testing of commercial batches