Regulatory Product Research:
Oral Systemic Drug Products

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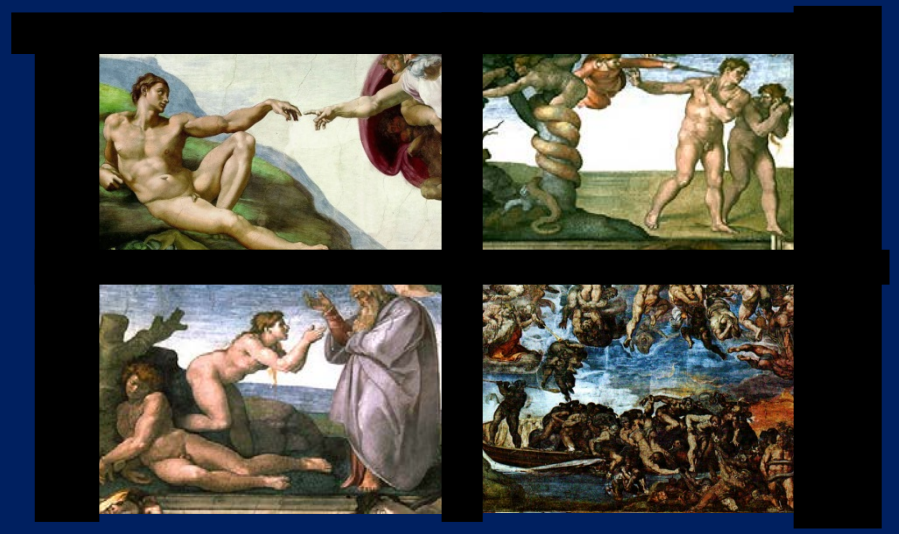
BE Science Needs

- Cmax and AUC Predictors
- BE is Different Products **Same** Drug (API)
- ‘DME’ of ‘ADME’-PK is the Same
- Mechanistic Analysis at Absorption Site (The ‘A’ of ADME)
- Extending BCS, oral (IR & MR) and other routes

BCS



Extending The Science of ‘Biowaivers’

Immediate Release (IR)

- BCS Class I: Slower Dissolution?
- BCS Class III : Quantative same, Qualitative Similar
- BCSa Class II & IV: SubClasses A,B, C

Modified Release (MR)

- Dynamic and changing luminal environment
- Transport (& transporters) and metabolism along the GIT

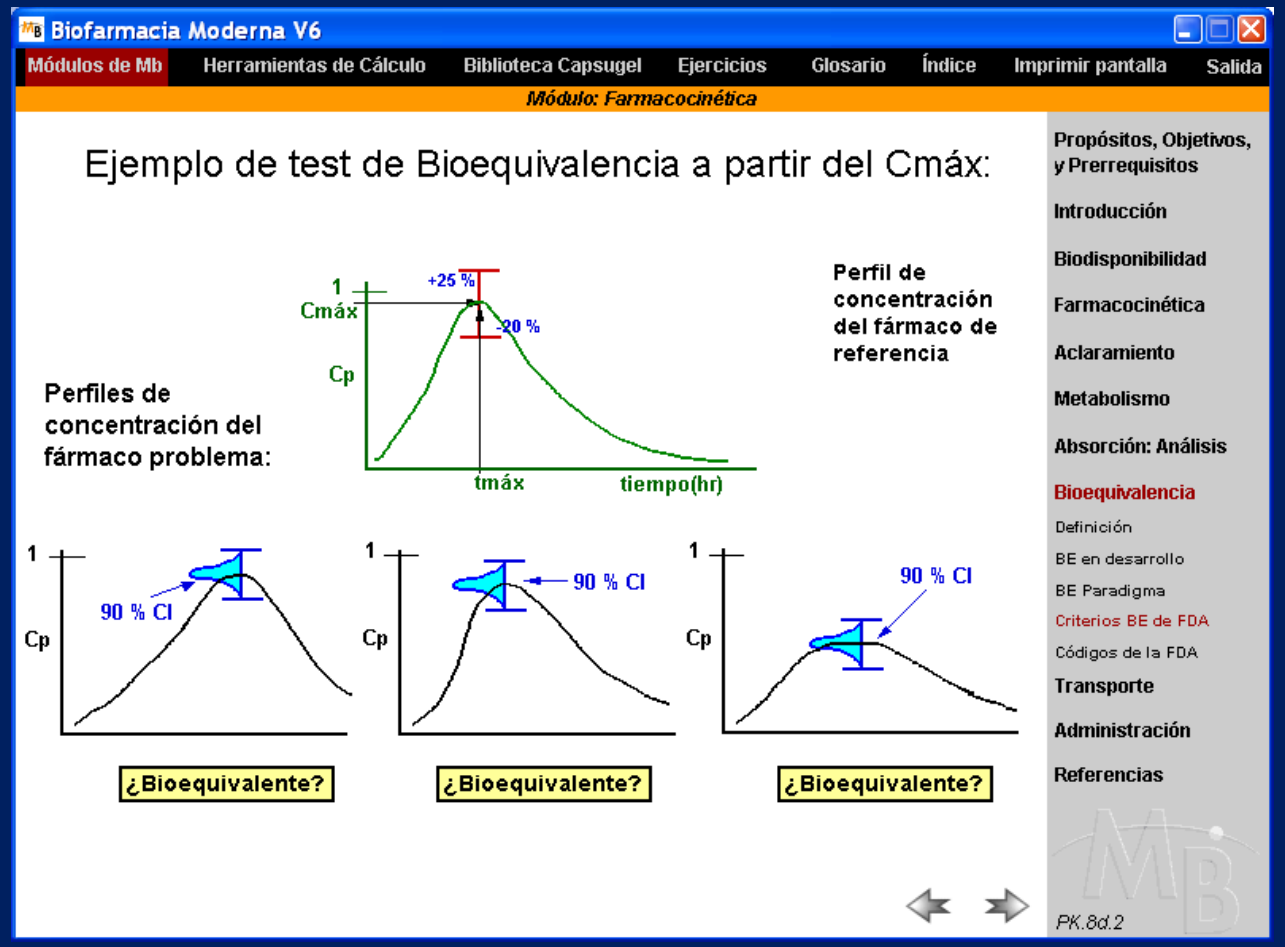
Key Science for Oral is *in vivo* Dissolution

- *In Vivo* Predictive *in Vitro* methods (iPD)
- Media and Method
- Not a QC Method
- Needed for Product Development & Regulatory Decisions
  - Product Changes (SUPAC)
  - Dose scaling (biowaivers)
  - QbD
  - PAT

Setting & Evolving Regualtory Standards in the 21st Century

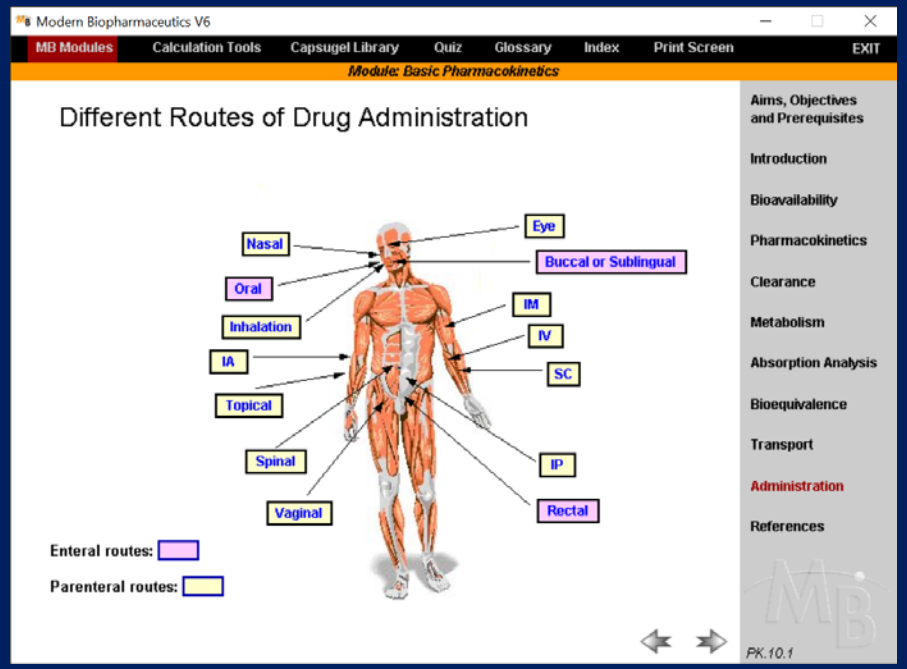
- Innovative New Delivery Technologies
- Modernizing Manufacturing and Production Methods
  - QbD & PAT Initiatives
  - What do we target short of expensive human studies
- Drug Product Focused Research
  - Both Brand (innovator) and Generic
- Pharmaceutical Product Regulatory Research Institute (P2R2)

BE Gold Standard: Systemically Active Drugs

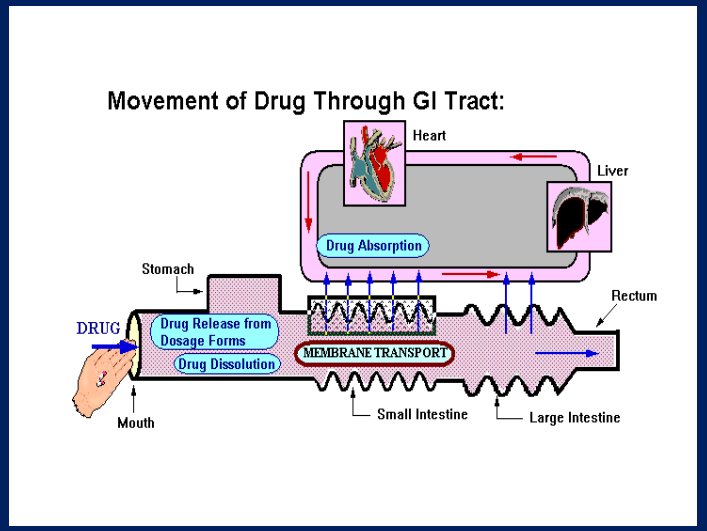


- Cmax and AUC
- BE is Relative BA
- Same Drug (API)
- DME of ADME is the Same
- BE is science of ‘A’

The Science of Relative BA (BE) is the Absorption at the Site of Application



$$M_{abs}(t) = \int_0^t \iint_A (P_{eff} \cdot C) dA dt$$



Evaluation of BE as Relative BA adds Complexity (Cmax & AUC)

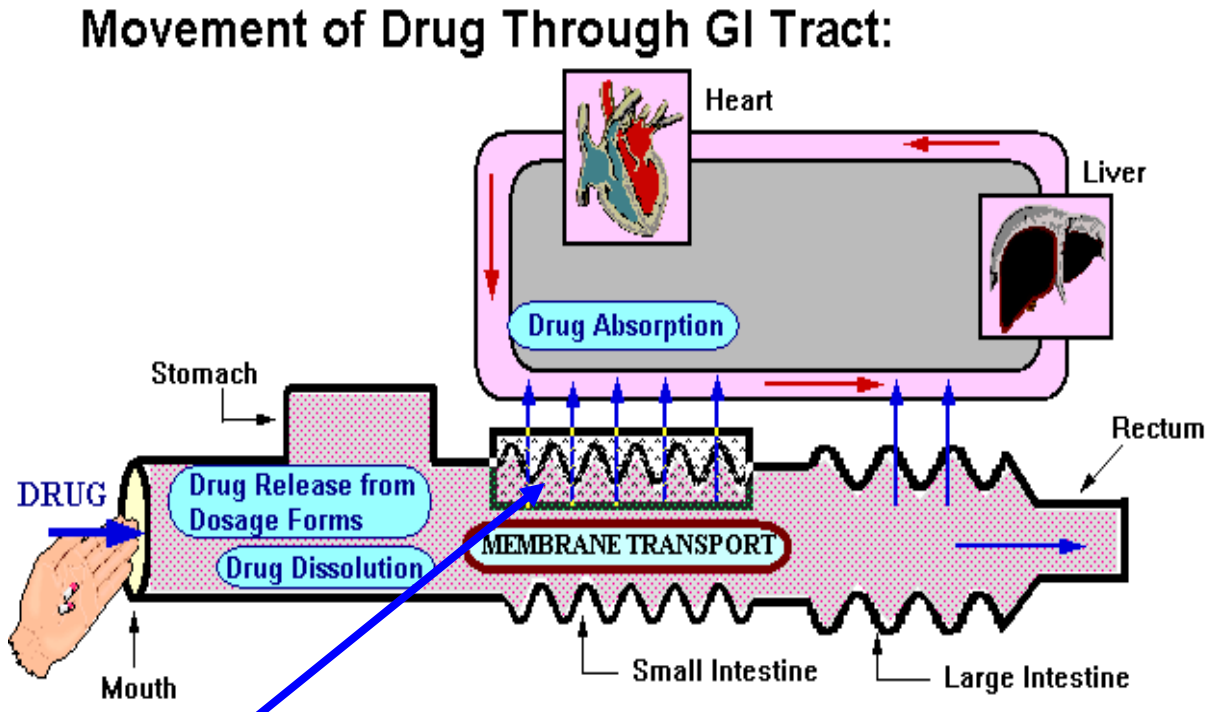
- Is First-Pass Metabolism linear?
- Vd kinetics vs. elimination kinetics?
- Is Clearance linear?
- Affect the ‘DME’ not the ‘A’.

BE Science is at the Absorption Site

- Product differences (Same Drug)
- Product altering Site (Permeability, Peff)
- Product changes with Time at Site, (C at absorbing surface)
  - Evaporation of solvent (vehicle)
  - API solid state changes

$$\mathrm{M}_{abs}(\mathrm{t}) = \int_0^t \iint_A (P_{eff} \cdot C) dA dt$$

Oral Products



$$\text{Flux} = j = P_{eff} \cdot C$$

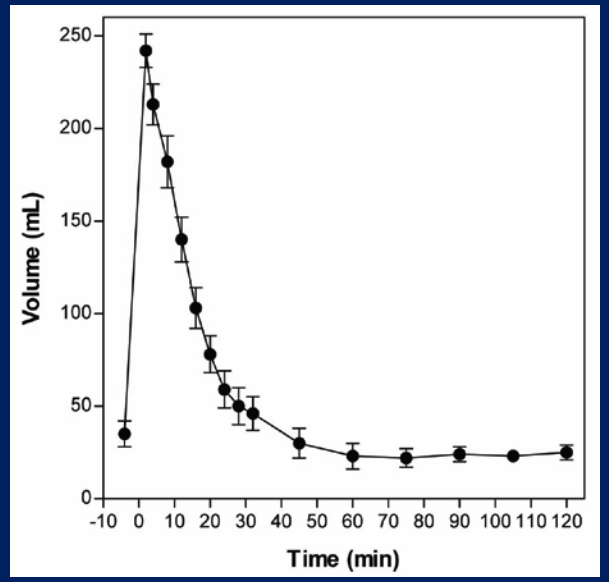
Measure Gastrointestinal Variables During Drug Absorption

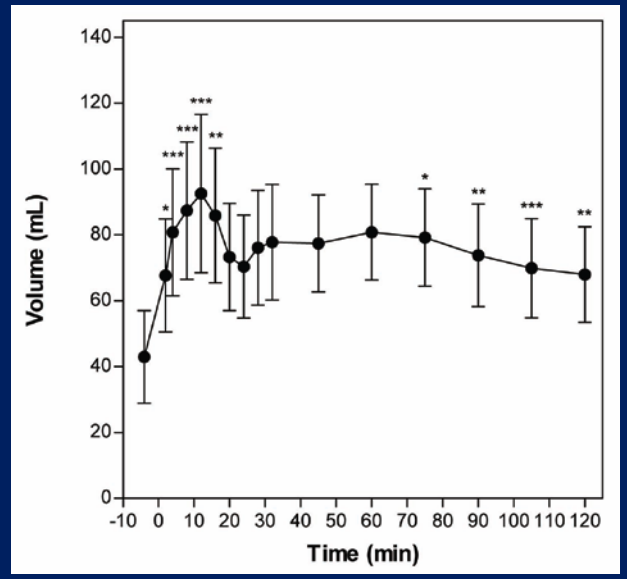
- Gastric Emptying & duodenal appearance
- Intestinal transit & segmental absorption
- Gastrointestinal motility: fasted and fed
- GI Variables: pH, buffer capacity, viscosity luminal solubilization
- Physical-chemical product changes: Solid state, pKa(*in vivo*)

Oral IR and MR

- Oral IR Absorption from Upper Small Intestine
  - Solubilization, buffering, Volume under BE conditions
- Oral MR: Entire GI Tract
  - Changing luminal environment
  - Transit and release in GIT
  - Absorption ‘wndows’
  - Fasted vs. Fed dosing and transit
  - Dosage form factors: Size, Disintegrating vs. Non-Disintegrating
    - Shear rate and hydrodynamic variables

Mean GI Fluid Volume*





Stomach

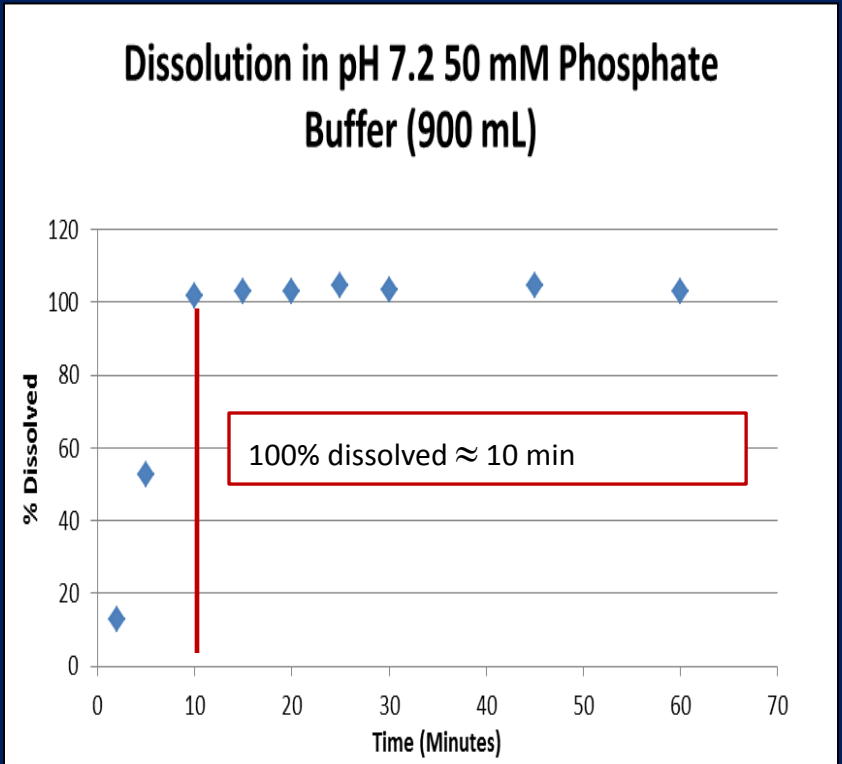
Small Intestine

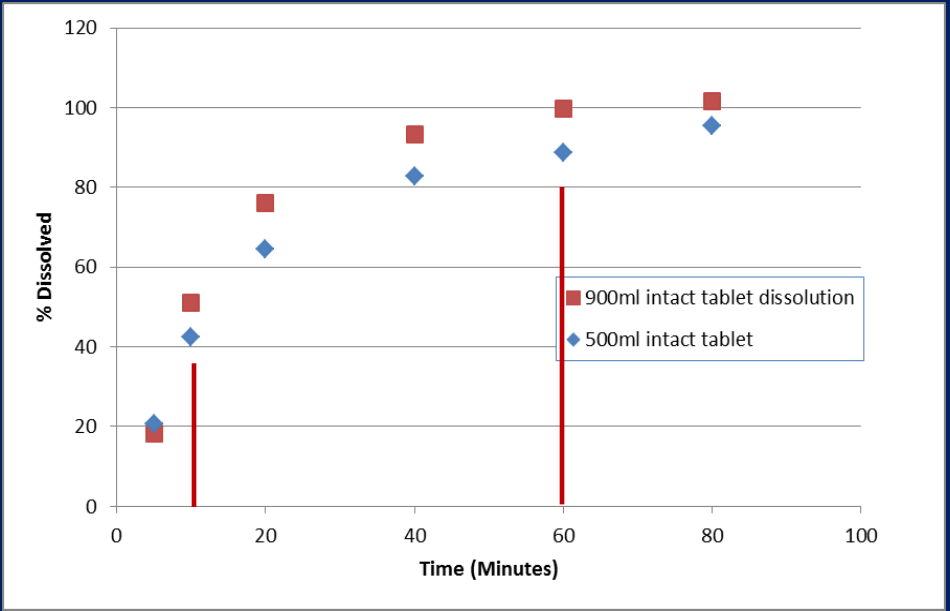
* Marciani L, et.al., Mole. Pharmaceutics,

Dissolution of Clinical Dosage form

(800 mg Dr. Reddy's Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO_3 buffer (15% CO_2 & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C





Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

BCS Subclass: Absorption Profile

API

- A= Acid
- B=Base
- C=Neutral

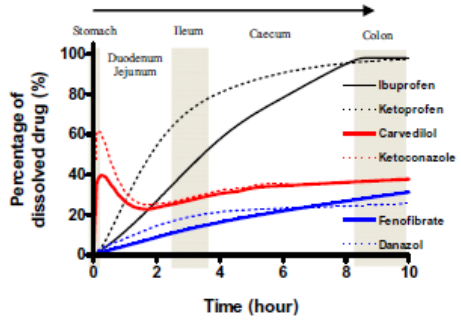


Fig. 2. Percentage of amount dissolved with an IR dosage. Black solid and dot lines represent BCS Class II weak acids, Red solid and dot lines represent BCS class weak bases and blue solid and dot lines represent BCS class neutrals. (For interpretation of the references to color in this figure legend,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

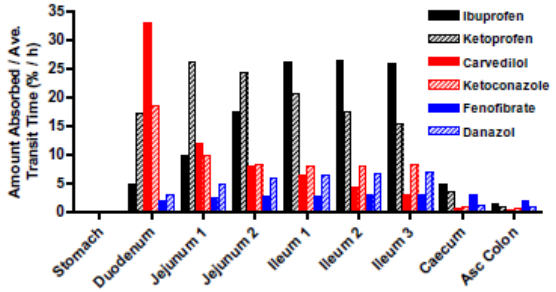


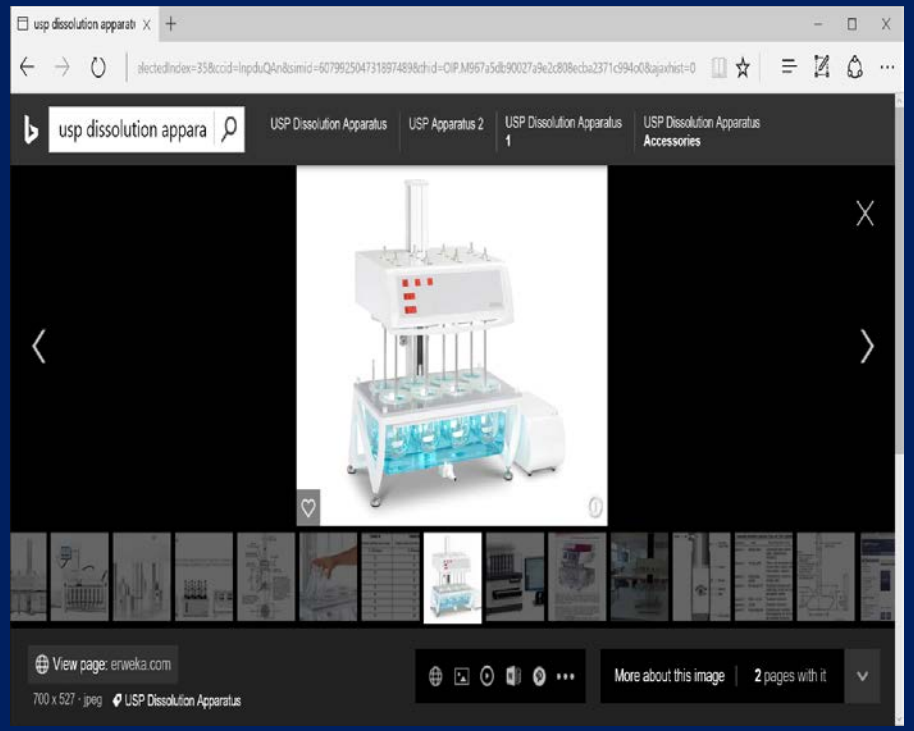
Fig. 3. The absorption rates of BCS Class II drugs in each GI segment. Percentages of amount absorbed after oral administration of an IR dosage are divided by the average transit time and are plotted as a function of each GI segment. Black bars represent BCS Class II weak acids, Red bars represent BCS class weak bases and blue bars 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 SubClasses * Dissolution (iPD)

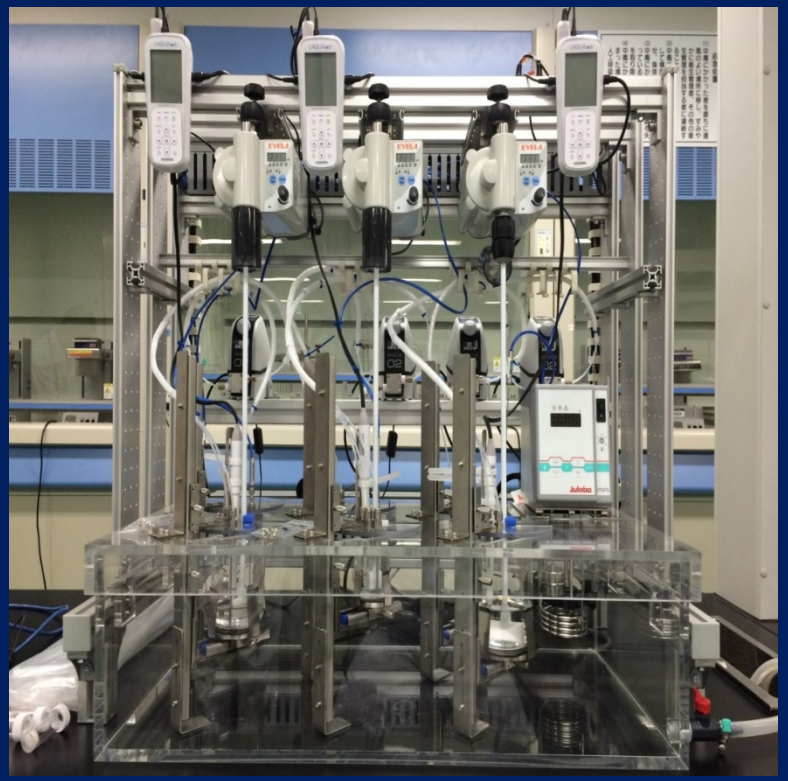
BCS Class	0.1 N HCl	pH 6.5	Permeability	Media*
I	High	High	High	PIB**
IIa	Low	High	High	15 and 30 min in PGB** then PIB**
IIb***	High	Low	High	15 or 30 min in PGB** , then PIB**
IIc	Low	Low	High	Dissolution 15 and 30 min in PGB** , Then PIB** + surfactant to match in vivo solubilization
III	High	High	Low	Same as I
IVa	Low	High	Low	Same as IIa
IVb**	High	Low	Low	Same as IIb**
IVc	Low	Low	Low	Same as IIc

Transition to *in vivo* relevant Dissolution

USP



iPD



Gordon's real BCS

solubility

hi → lo

permeability

lo → hi

formulation ← Purgatory

bioavaila-bility limbo →