Potential New Method to Improve Bioequivalence (BE) of Modified Release (MR) Drug Products by in vivo Dissolution Studies In Human GI tract

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Questions for Bioequivalence (BE) Standard for Generic Drug Products

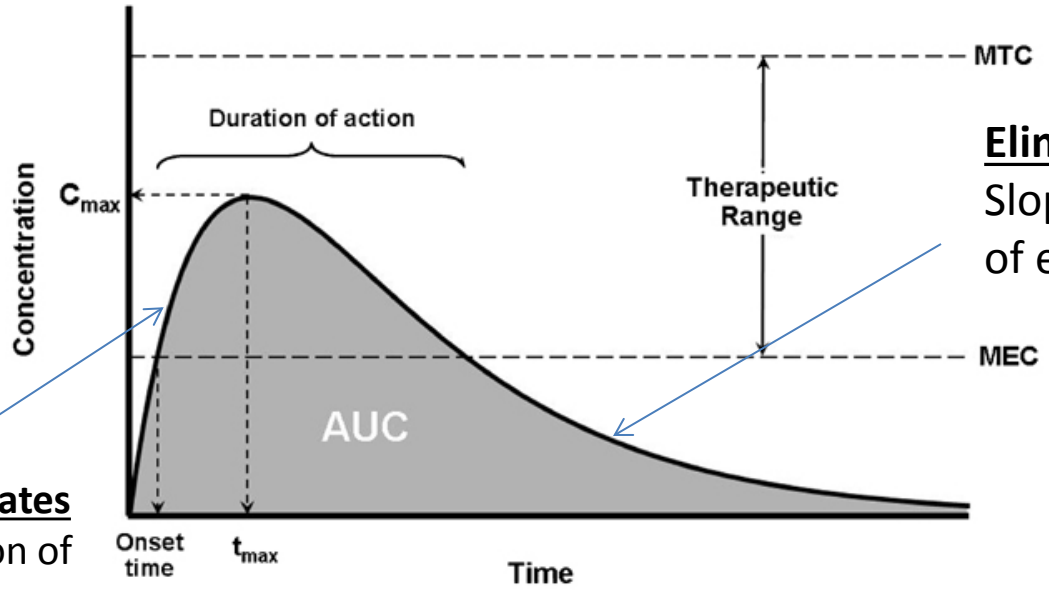
- Current standard for BE of immediate release (IR) drug products
  - AUC and Cmax comparison when release and dissolution is rapid (works fine)

- Current standard for BE of modified release (MR) and locally acting drug products
  - AUC and Cmax comparison when release and dissolution is slow (not working well)
  - Partial AUC --- improved
  - Need additional methods

- Composite Appearance Rate (CAR) and Plasma AUC/Cmax
  - CAR includes drug release, dissolution, absorption, precipitation, transit
  - CAR changes over time
    - Characterize MR and locally acting drug products
  - How to estimate --- individual deconvolution in comparison with oral solution
  - How to validate --- in vivo intubation to directly measure dissolution in GI tract
  - How to compare --- statistical comparison

Plasma AUC/Cmax in Current BE

Cmax
Highest concentration in systemic circulation



Elimination Dominates
Slope give indication of rate of elimination

Absorption Dominates
Slope give indication of rate of absorption

https://www.sciencebasedmedicine.org/generic-drugs-are-they-equivalent/

Area Under the Curve (AUC):
the systemic exposure of drug over time.

$$C = \frac{FDk_a}{V(k_a - k)}(e^{-kt} - e^{-k_a t})$$

ka to represent a complex release, dissolution, and absorption process?

These assumptions work for:
Oral solution --- OK
IR drug products --- OK for some BCS class compounds
MR and locally acting --- not OK

Composite Appearance Rate (CAR):

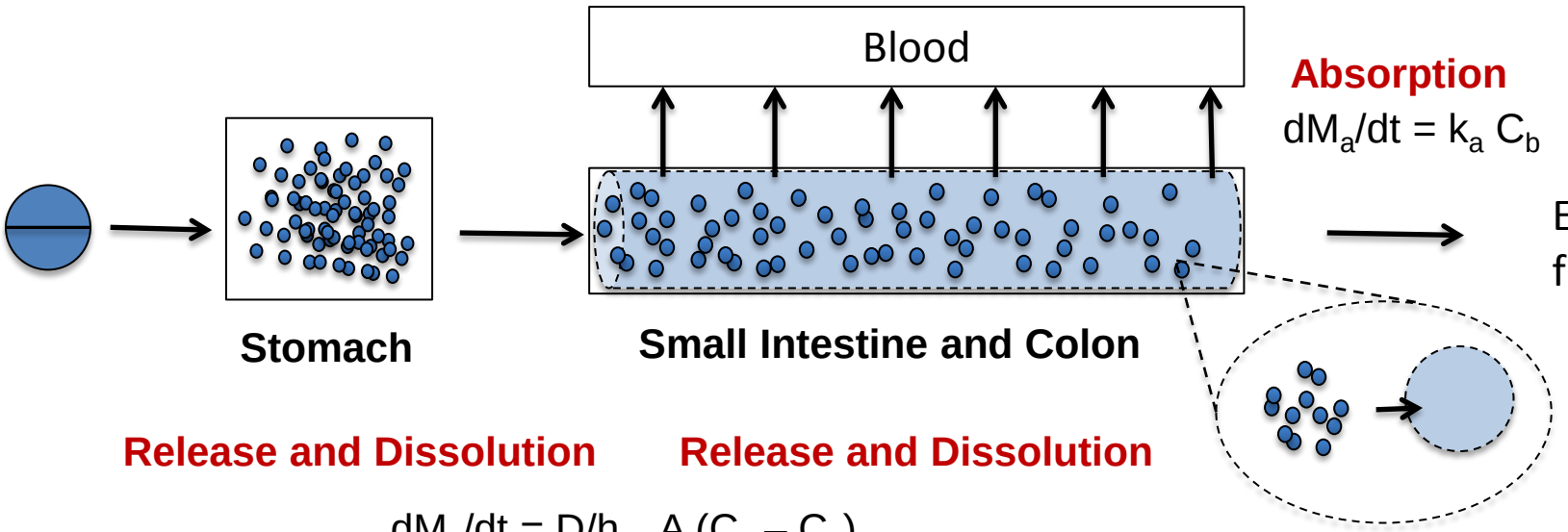
Drug Release, Dissolution, Precipitation, Absorption, and Transit in GI Tract

CAR is the net appearance of drug into systemic circulation
-useful for MR and locally acting drug products

How to estimate?
How to validate?
How to compare?

Composite Appearance Rate (CAR)

dM_p/dt

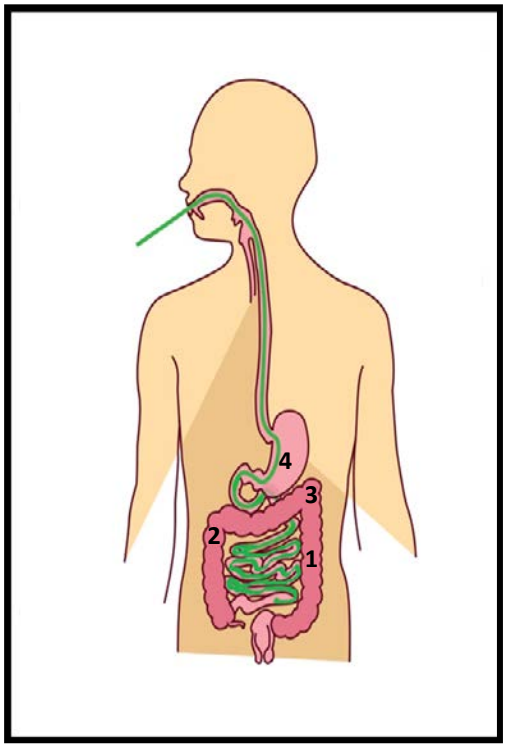


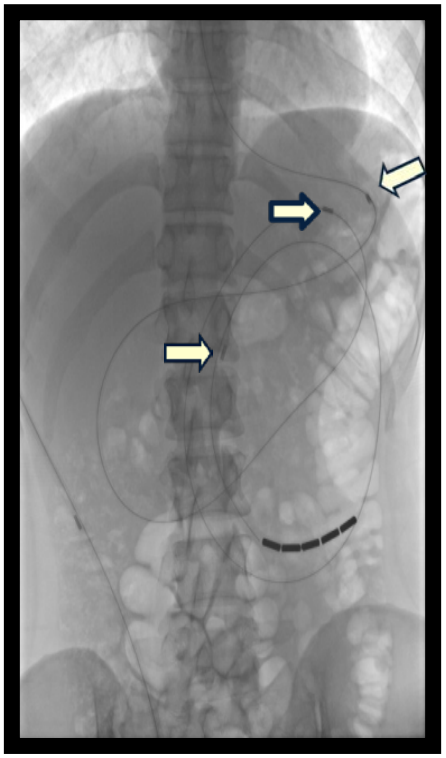
Modified from the slide of Greg Amidon

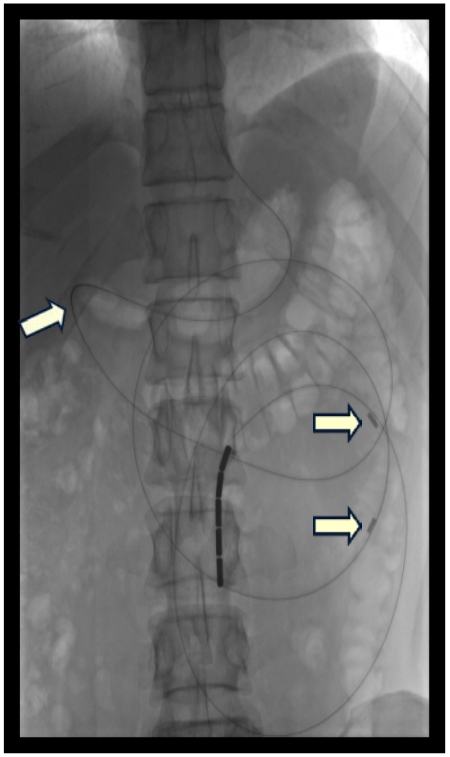
Need to Do:

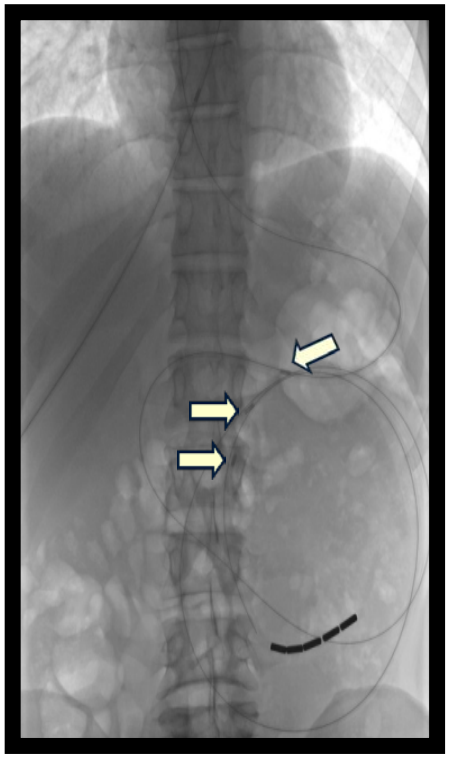
- *In vivo* drug dissolution in human GI tract
  - Modified release (MR) drug products in comparison with oral solution (need)
  - Locally acting drug products in comparison with solution (done)
  - IR drug products (on going)
- Deconvolution and validation of composite appearance rate (CAR) based on plasma profile of MR drug products in comparison with oral solution
- Statistical comparison of composite appearance rate (CAR) for BE study

Directly Measure Drug Dissolution of Locally Acting and IR Drug Products in Human GI tract









Port Locations:

1. Distal Jejunum/ Proximal Ileum
2. Proximal Jejunum
3. Duodenum
4. Stomach

Fluoroscopic photo of GI tube placement. Shown are 3 aspiration ports located in the stomach, proximal jejunum, and distal jejunum.

Proposed Future Studies

- Directly measure in vivo dissolution in human GI tract for Modified Release (MR) drug product in comparison with oral solution
  - MR drug product (e.g. Metoprolol, propose to do)
  - IR drug product (Ibuprofen, ongoing)
  - Locally acting drug product (Mesalamine, done)

- Estimate and validate Composite Appearance Rate (CAR) using deconvolution
  - In comparison with oral solution
  - Validate with in vivo dissolution data in human GI tract

- Statistical comparison of Composite Appearance Rate (CAR) for BE study

- Validate in vitro predictive dissolution device (iPD) –details in Dr. Amidon's presentation
- Develop software for bioperformance of oral drug products – details in Dr. Amidon's presentation
- Cross validate MRI study for transit of oral drug products- details in Dr. Amidon's presentation