OBJECTIVES

Modeling for controlled oral drug delivery

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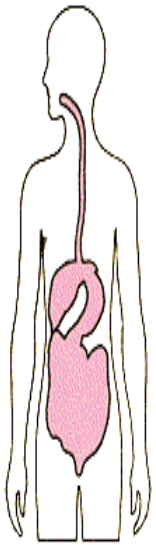
1. Develop a complete pharmacokinetic model for predicting orally administered drug release profile
   - Drug Release Model + Compartmental Absorption and Transit (CAT) model.

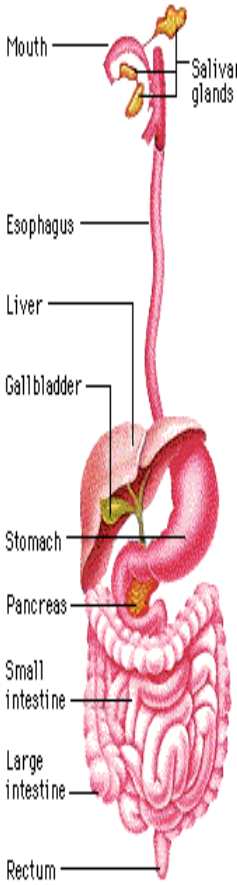
2. Personalized Tablet
   - Suggest optimal geometry of drug tablet
   - Exploit Personal Pharmacokinetic characteristics (e.g. peak plasma concentration; area under the curve (AUC); bioavailability needed to obtain desired plasma concentration profiles within therapeutically required range).

3. Design polymer carrier & excipients for the drug using molecular modeling.

4. Identify and incorporate appropriate pharmacodynamics model into the design framework

MAIN ORAL DRUG DELIVERY STEPS





Drug dissolution and degradation

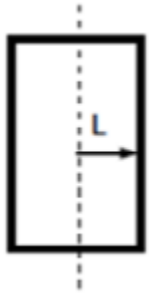
Gastric emptying

Intestinal transit, intestinal permeation and transport

Intestinal metabolism and hepatic metabolism

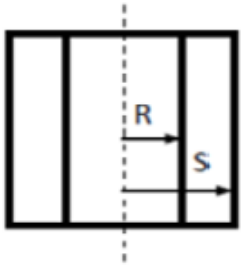
Marshall, S., 2006. Clinical Pharmacokinetics 45, 177-197.

DISSOLUTION MODEL



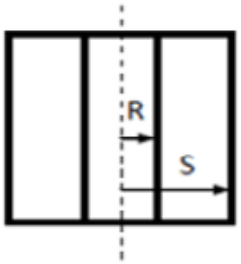
- Polymer comes into contact with water (bodily fluid)

Solid drug tablet



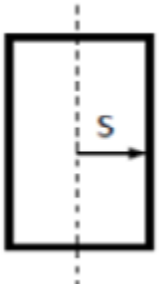
Polymer Swelling

- Two distinct fronts
- Swelling interface at R
- Polymer-water interface at S
- Drug diffusion out of gel layer



- R decreases because of drug release
- S decreases because of polymer dissolution

Polymer dissolution

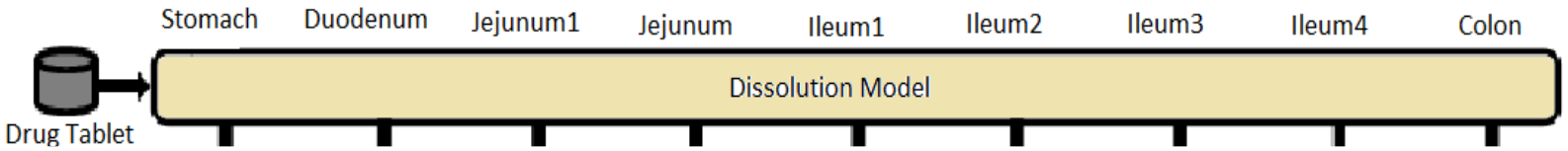


Complete drug dissolution

2L = Thickness of the tablet
2R = Thickness of the tablet at any time “t”
2S = Thickness of the swollen tablet

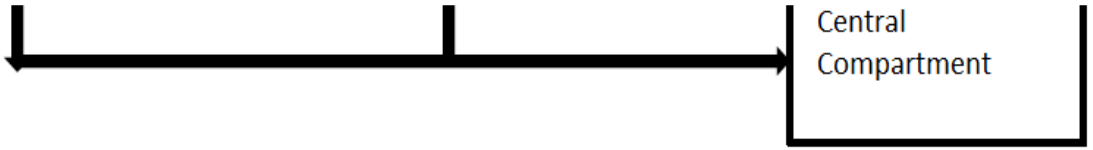
Narasimhan, B., Peppas, N.A., 1997, Journal of Pharmaceutical Sciences 86, 297-304.

PHARMACOKINETIC MODEL *(proposed)*



1. Geometry of drug tablet

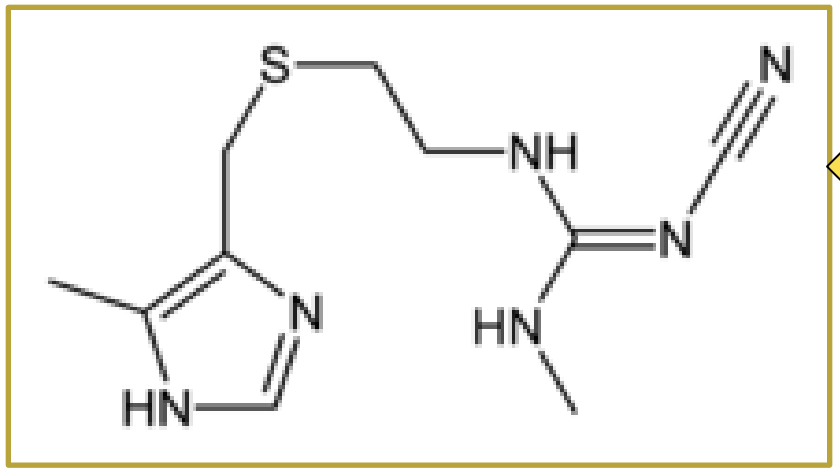
2. Pharmacokinetic characteristics:
   - Peak Plasma Concentration
   - Area under the curve (AUC)
   - Bioavailability needed to obtain desired plasma concentration profiles within therapeutically required range).
   - First pass metabolism (liver)

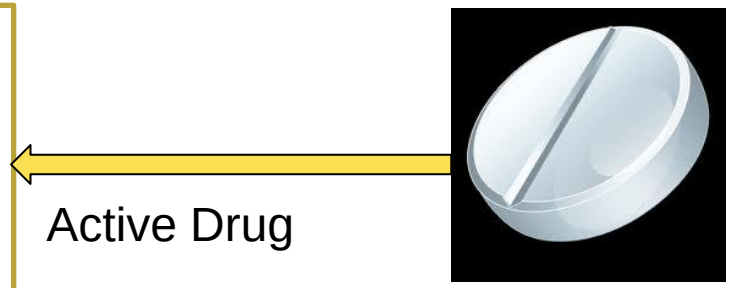


- Dissolution model combines Unreleased & Undissolved layers

Case Study – Cimetidine (or Tagamet)

- Treatment of duodenal and gastric ulcers, gastro esophageal reflux disease (GERD/acid reflux or heart burn)
- Drug inhibits stomach acid production by inhibiting the secretion of gastric glands





Active Drug

Aqueous solubility = 6 mg/ml
Bioavailability = 60 – 70%
Human permeability = 0.35 x 10^{-4} cm/sec

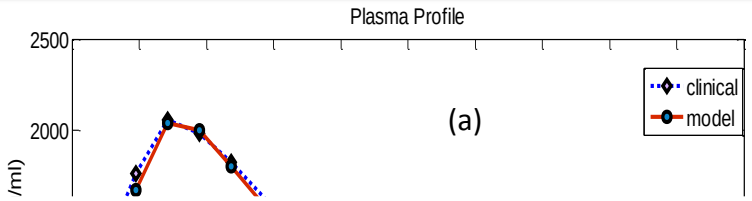
$$\underset{T}{Min}\ J = \int_0^{t_f} \left[C^{model}(t) - C^{exp}(t) \right]^2 dt \ \Leftrightarrow\ AUC$$

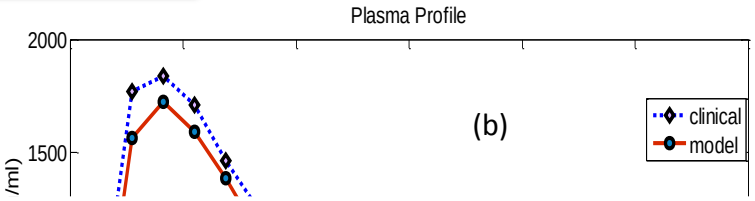
$s.t.$

Pharmacokinetic Model

Jantratid, E., Prakongpan, S., Amidon, G.L., Dressman, J.B., 2006. Clinical Pharmacokinetics 45, 385-399.

PLASMA PROFILES (AUC)





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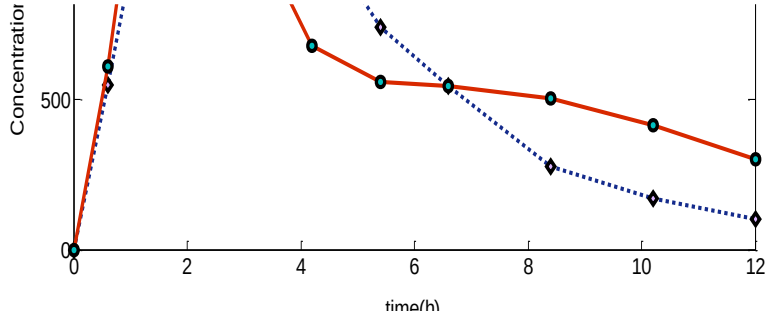

(b) 15% methacrylate copolymer cimetidine tablet
(c) 26% methacrylate copolymer cimetidine tablet

To Discuss

- Area of research
- Findings to date
- Specific ways/ideas that research can contribute towards the mission of CAR
- Current working relationships with resources available
- Collaborations and resources needed for multidisciplinary research