

## **Gastrointestinal Simulation Based on the Advanced Compartmental Absorption and Transit (ACAT)**

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Founding Scientist  
Simulations Plus, Inc.

– GPEN, Kansas, 2006

## **GI Simulation Methods**

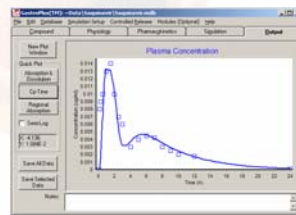
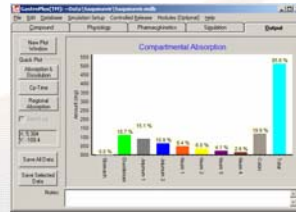
- Dispersion Model
  - Ho, NFH and Higuchi, WI - 1983
- Compartmental Absorption & Transit (CAT)
  - Yu, LX and Amidon, GL - 1996
- Heterogeneous Tube Model
  - Kalampokis, A and Macheras, P - 1999
- Advanced CAT Model (ACAT)
  - Simulations Plus, Inc. – 1998 - 2006

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# Data Integration Tool

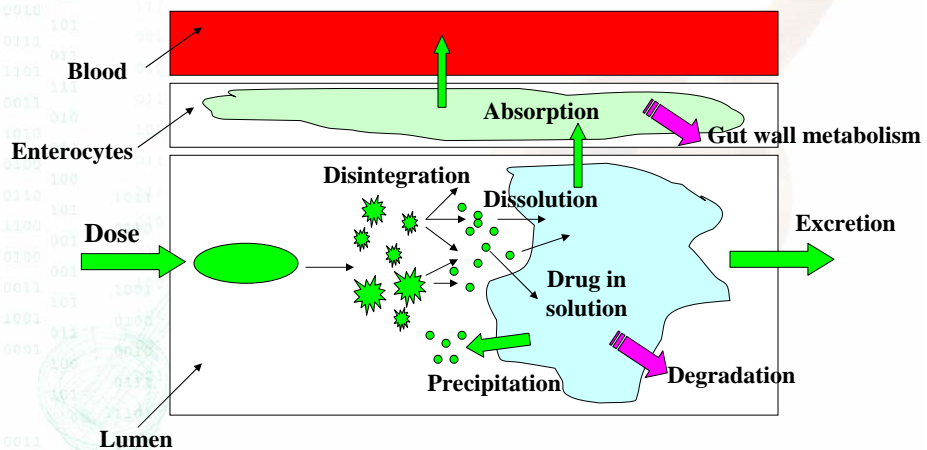
GastroPlus is a state-of-the-art database and simulation computer program that contains the following elements:

- Differential equations
  - Oral Absorption and related phenomena
    - Release, dissolution, precipitation
    - Transit
    - Absorption - passive diffusion and carrier-mediated transport
  - Pharmacokinetics
    - Gut and liver metabolism
    - Physiologically based pharmacokinetics
  - Pharmacodynamics
    - Direct and indirect models
- Solubility-pH calculation
- Selection of different physiologies
- Numerical integration
- Numerical optimization
- Plotting and file output
- Database and support files

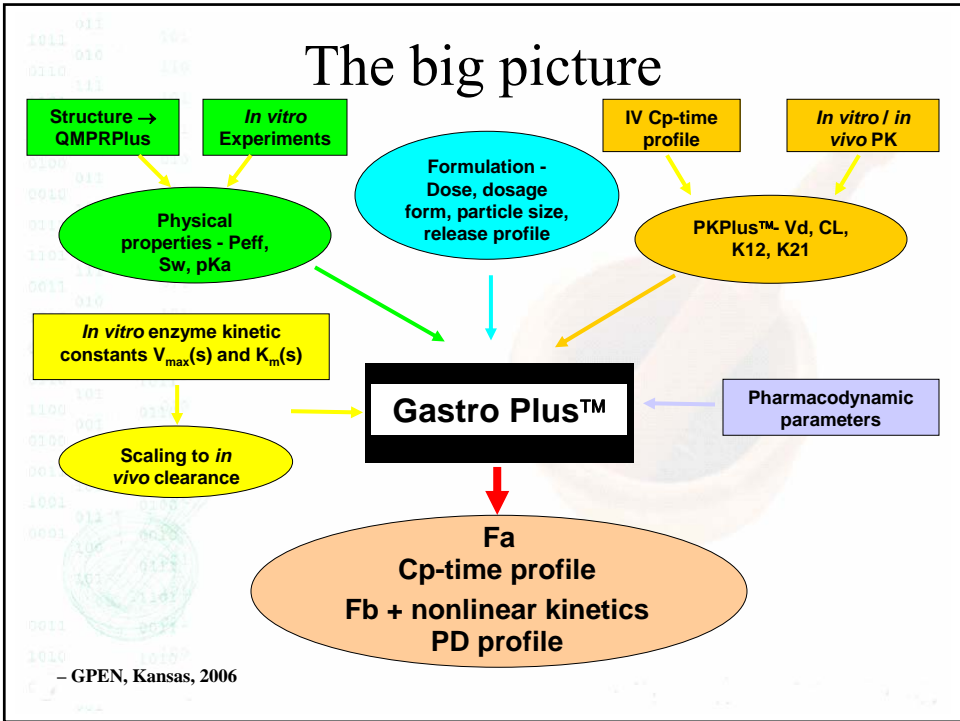
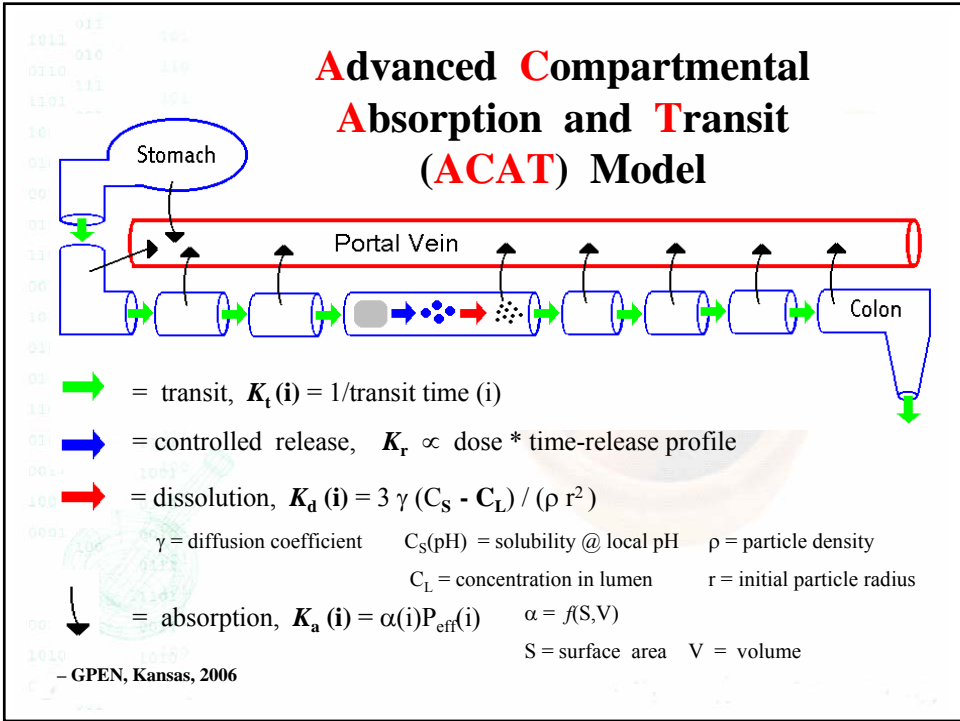


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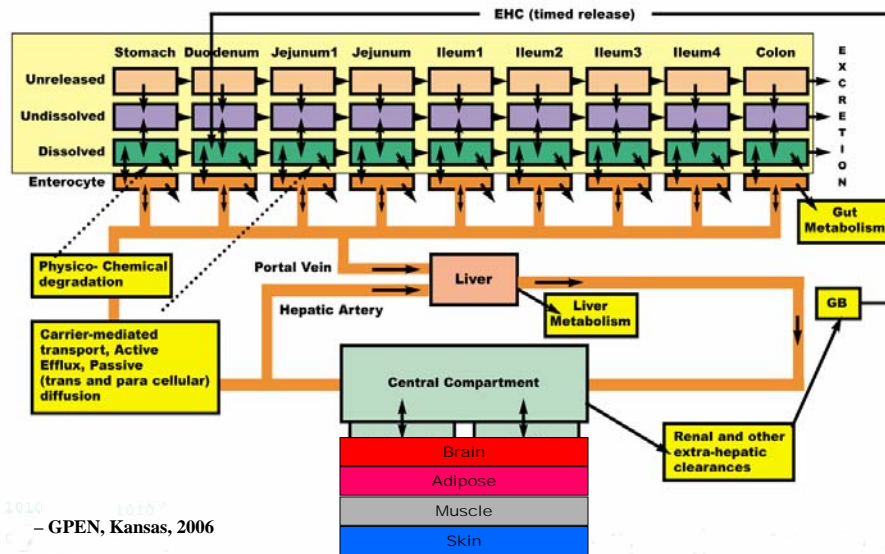
# Gastrointestinal Processes



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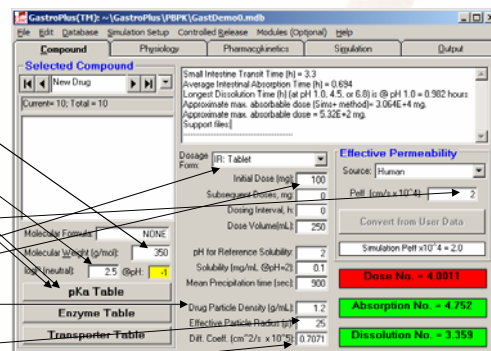


## Advanced Compartmental Absorption and Transit Model (ACAT)



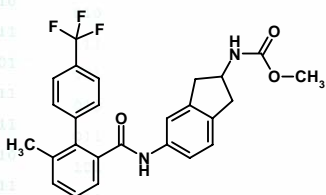
## Example 1 Inputs

- MWt = 350
- logP = 2.5
- pKa = acid 5.5
- Solubility = 0.1 mg/mL @ pH 2
- Solubility factor = 500
- Effective permeability =  $2E-4$  cm/s
- Dose = 100 mg tablet
- Particle density = 1.2 g/cc
- Particle radius = 25 micron
- Diffusion coefficient = ??



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## Oral Absorption of Ionizable Drugs



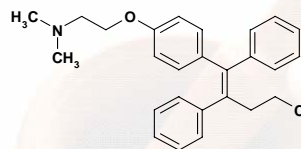
### LAB687

Log P = 4.7

Native Solubility = 0.17  $\mu\text{g/mL}$

\*Permeability =  $1.96 \times 10^{-4}$  cm/s

Fraction Absorbed: ~8%



### Toremifene

\*Log P = 6.57

\*Native Solubility = 0.069  $\mu\text{g/mL}$

\*Permeability =  $12 \times 10^{-4}$  cm/s

Fraction Absorbed = 100%

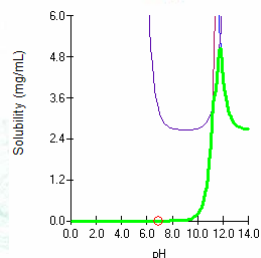
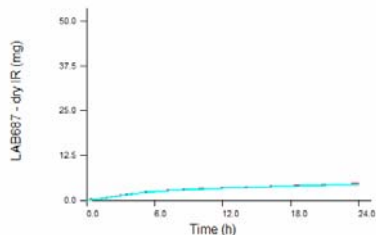
\*estimated by ADMET Predictor

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### LAB687

SolFactor =  $7.8 \times 10^4$

Amounts in Compartments  
Immediate Release Comp. C:\Documents and Settings\jgarity\Documents\SimPul\Gastro\LAB687\LAB687 - dry IR.app

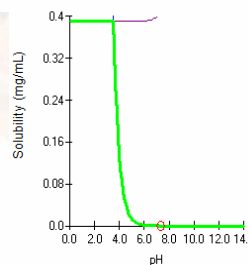
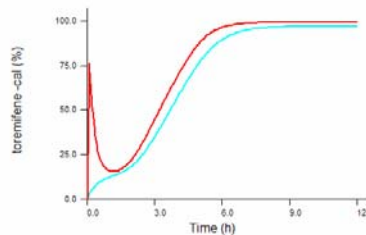


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### Toremifene

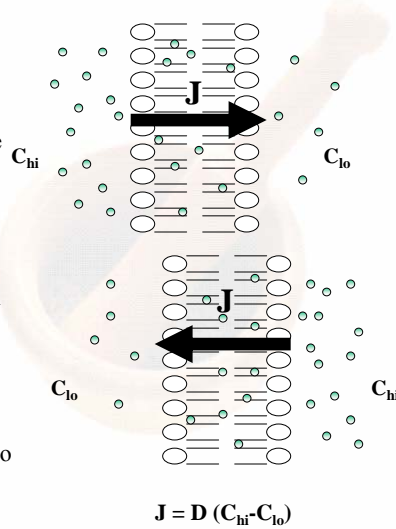
SolFactor =  $1.2 \times 10^5$

Amounts in Compartments  
Immediate Release



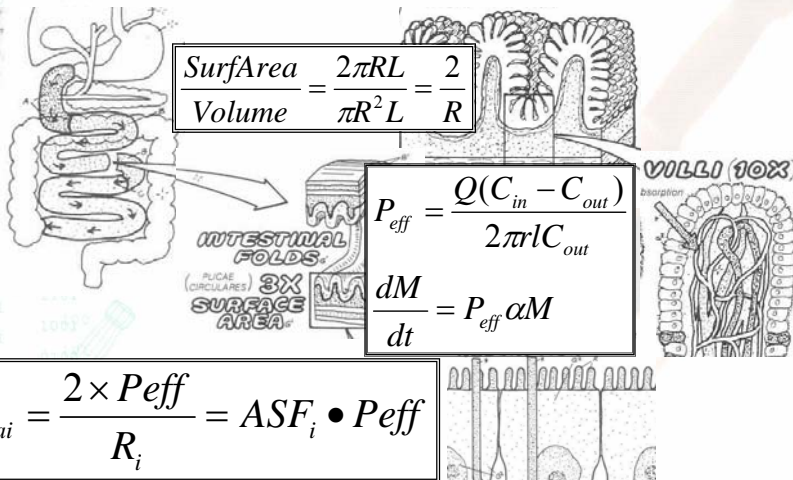
## Absorption - Fick's First Law

- Absorption means crossing the apical membrane of the enterocytes (not entering the portal vein)
- Diffusion of molecules through a membrane results from a difference in concentration across the membrane
- For passive diffusion, molecules move in both directions, but the net flux is from high to low concentration, and is proportional to the concentration difference (unless electrochemical charge is involved)
- For intestinal absorption, D is proportional to  $P_{eff}$  and the volume in the lumen compartment



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## Rate of absorption based on: Permeability = $f(\text{Surface Area, Physico-chemical Properties, Transporters, and Efflux})$



Kapit, W, et al. The Physiology Coloring Book, Harper Collins Publishers, Inc., NY, 1987  
 - GPEN, Kansas, 2006

# Absorption

Absorption term in compartment number  $i$ :

$$dM_{\text{diss}(i)}/dt = \underbrace{\alpha_{(i)} P_{\text{eff}(i)}}_{k_a'} \underbrace{V_{\text{lum}(i)}}_{M_{\text{diss}(i)}} (C(t)_{\text{lum}(i)} - C(t)_{\text{ent}(i)})$$

$\alpha_{(i)}$  = absorption scale factor in compartment  $i$  (nominal value is surface/volume, which is  $2/R_i$ )

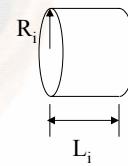
$R_i$  = radius of compartment  $i$

$P_{\text{eff}(i)}$  = permeability in compartment  $i^*$

$V_{\text{lum}(i)}$  = volume of lumen for compartment  $i$

$C(t)_{\text{lum}(i)}$  = lumen concentration in compartment  $i$

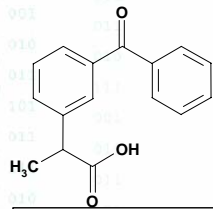
$C(t)_{\text{ent}(i)}$  = enterocyte concentration in compartment  $i$



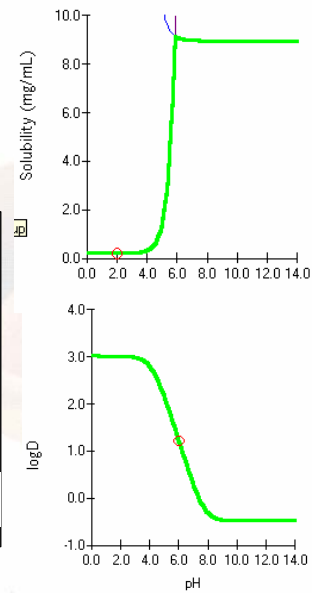
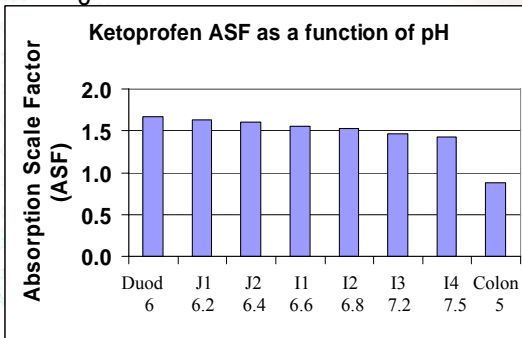
\* permeability may be net, or only passive component

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# Ketoprofen ASF Profile



**Fa = 100%**  
**logD(6.5) = 0.74**  
**Peff(7) = 8.7**  
**pKa = 4.3 (Acid)**



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## Simulations Plus log D Model

- $\text{Log}(P_{\text{eff}}) = a \Delta \log D_{\text{pH}} + \log(P_{\text{eff}}^0)$  (1)
- Where:  $\Delta \log D_{\text{pH}} = \log P - \log D_{\text{pH}}$

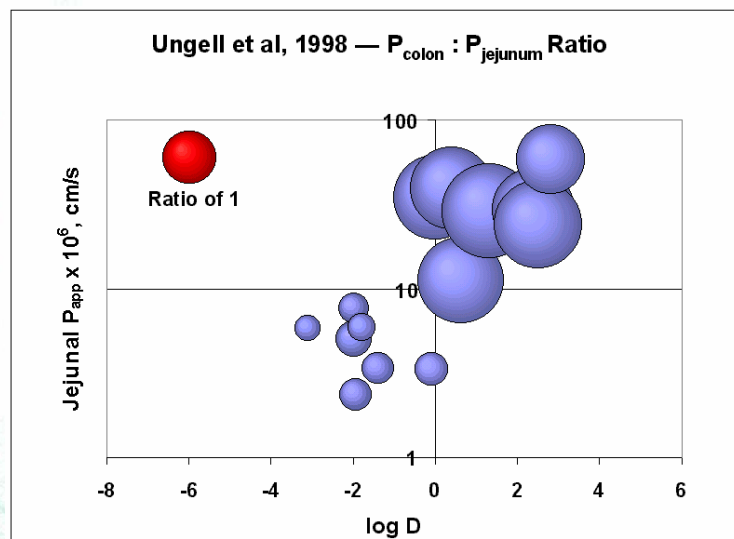
- Reference pH = 6.5 (Jejunal pH)

$$ASF_{SI} = C_2 10^{\left[ C_1 \left( \frac{\Delta \log D_{\text{pH}} - C}{\Delta \log D_{\text{pHref}} - C} \right) \right]} \quad (2)$$

C=6.26 (empirical estimation)

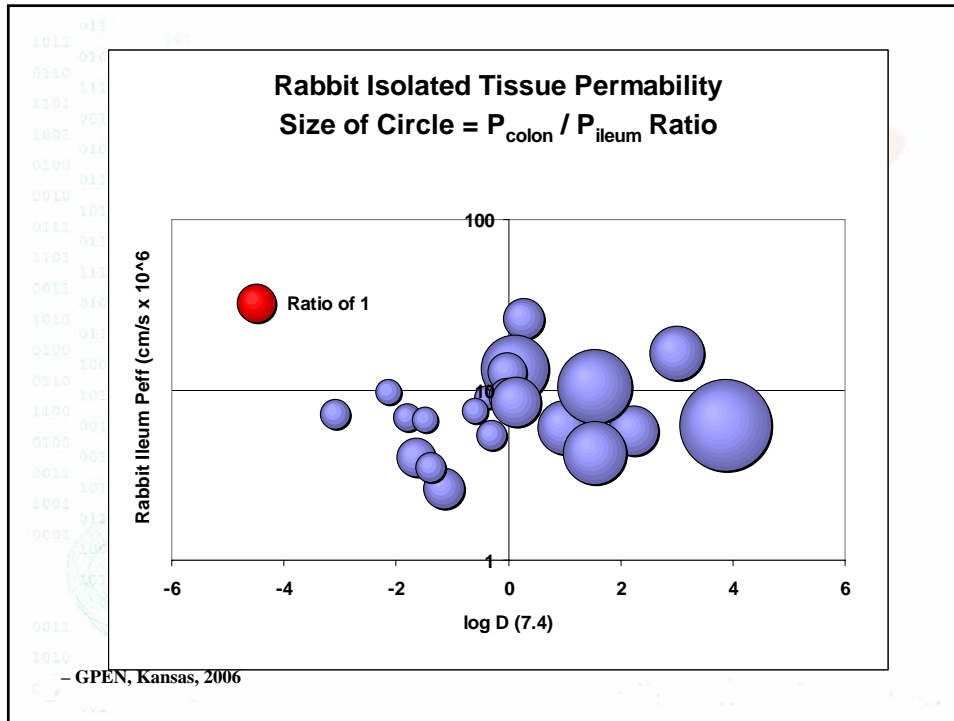
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Ungell, A.L., et al., 1998, J. Pharm. Sci. 87:360-366



– GPEN, Kansas, 2006



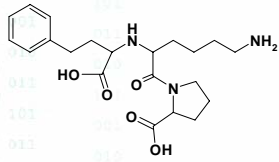


## Simulations Plus log D Model for Colon

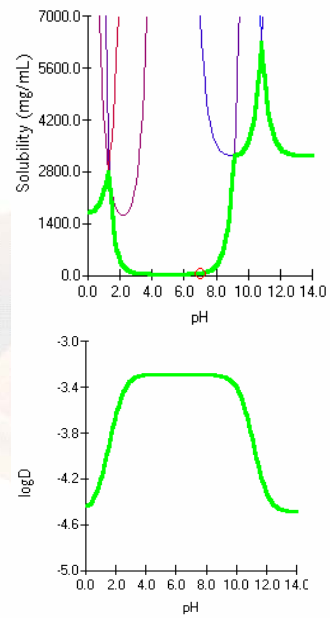
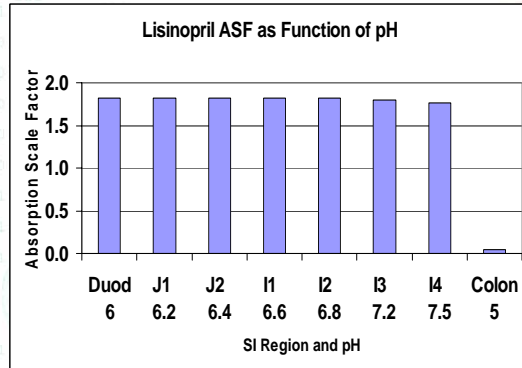
$$ASF_{\text{Colon}} = C_3 10^{C_4 \log D_{pH}}$$

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## Lisinopril ASF profile

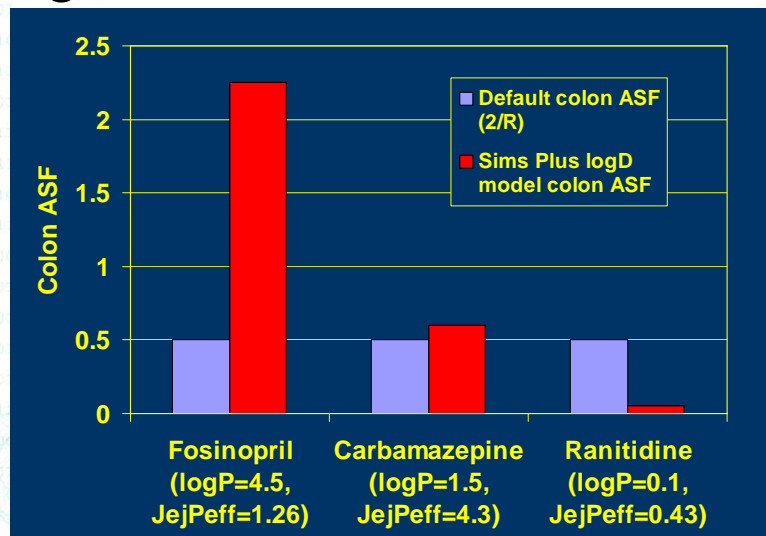


**Fa = 25%**  
**logD(6.5) = -3.3**  
**Peff(7)=0.12**



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## LogD model Colon ASF estimation



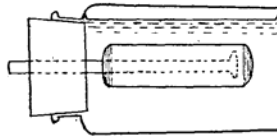
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## Rate of solution of solid substances in their own solution

Noyes, AA and Whitney, WR, J. Am. Chem. Soc. 19:930-934 (1897)

In conducting the experiments, exactly 100 cc. of distilled water were placed in each of the six bottles, and these were suspended in a thermostat kept at 25° C. within a few thousandths of a degree. After the temperature of the bath had been attained, the corks bearing the sticks of substance were inserted in the bottles so that the cylinders were in the middle of the bottle, and covered with water, as shown in the cut. The

$$\frac{dx}{dt} = C(S - x)$$



$x$  = Concn. at time  $t$   
 $S$  = Solubility  
 $C$  = Constant

“The rate at which a substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution.”

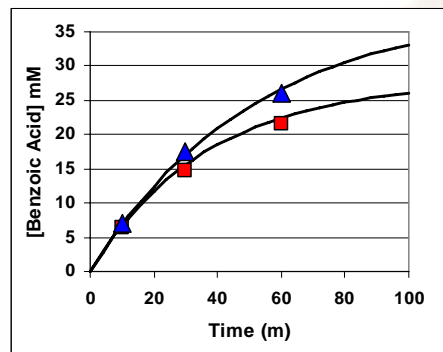
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## Noyes - Whitney Data

### Dissolution of:

-----  
 Benzoic Acid: ■  
 Solubility = 27.9 mM  
 $t_{1/2}$  = 25.4 m

-----  
 Lead Acetate: ▲  
 Solubility = 38.7 mM  
 $t_{1/2}$  = 35.6 m

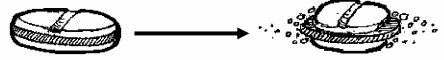


$$Y = S - (S \times e^{-k_d t})$$

$S$  = solubility     $k_d$  = dissolution rate constant ( $m^{-1}$ )

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## Dissolution and Precipitation Nernst & Brunner (1904)



Dissolution/precipitation processes are defined by the rate constants  $k(i)_d$  and  $k(i)_p$

$C_S > C_L \Rightarrow$  dissolution

↓ = Dissolution

$C_S < C_L \Rightarrow$  precipitation

↑ = Precipitation

$$k(i)_d = \frac{3\gamma(C_S - C_L)}{\rho r T}$$

$$k(i)_p = -1/t_p$$

$\gamma$  = diffusion coefficient

$\rho$  = particle density

$r$  = initial particle radius

$T$  = diffusion layer thickness

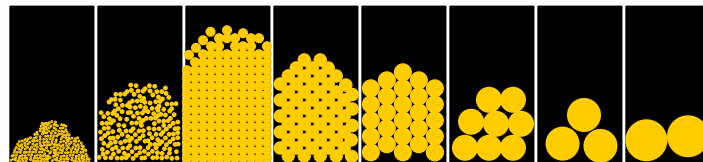
$C_S(\text{pH})$  = solubility @ local pH

$C_L$  = concentration in lumen

$t_p$  = mean precipitation time

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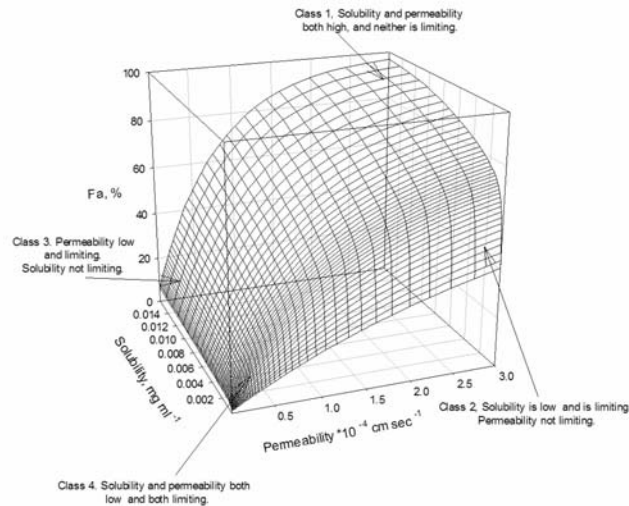
## Dissolution with Particle Size Distribution



- Particles are divided into  $n$  bins ( $n \leq 16$ )
- Each bin is represented with a mean radius and a fraction of the total mass of solid particles at any instant
- Distribution can be normal, log-normal, or user-provided (.psd file)
- Smaller particles dissolve faster, increasing drug concentration
- Particles in each bin become smaller with time
- Each ACAT gut compartment has  $n$  bins, so if 16 bins are used with 9 gut compartments, a total of  $9 \cdot 16 = 144$  differential equations for dissolution must be integrated – simulation runs slower
- Precipitation can cause particles to grow

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$$F_a = f(\text{Permeability and Solubility})$$



Hendriksen BA, Sanchez MF, and Bolger MB: (2003). AAPS Pharm. Sci. 5(1):Article 4, 2003  
 – GPEN, Kansas, 2006

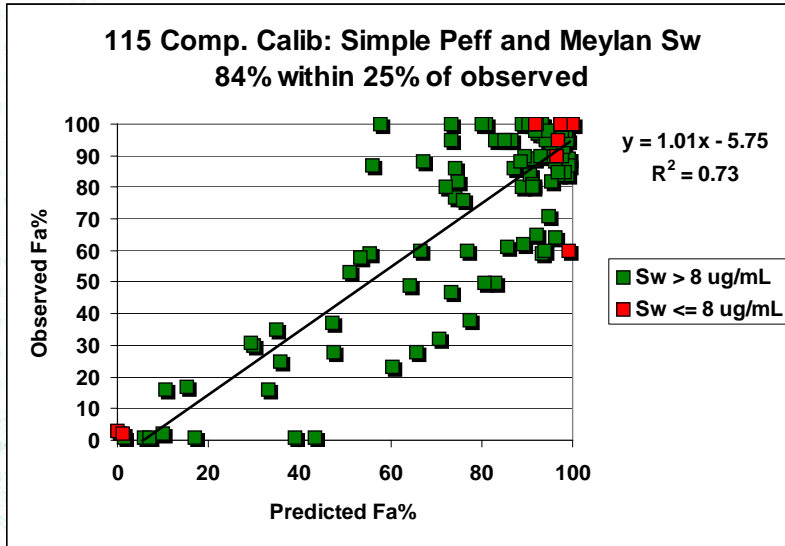
## Zhao & Abraham Dataset

- Selected 238 compounds and converted SMILES to 3D with CORINA.
- Used ADMET Predictor to generate pKas.
- Used ADMET Predictor to generate estimates for Permeability, Solubility, and Diffusivity.
- Sub-classified into groups for passive absorption and transport via influx or efflux transporters.
- Calculated fraction absorbed using GastroPlus.

Zhao Y.H., J. Pharm. Sci. 90(6):749 (2001)

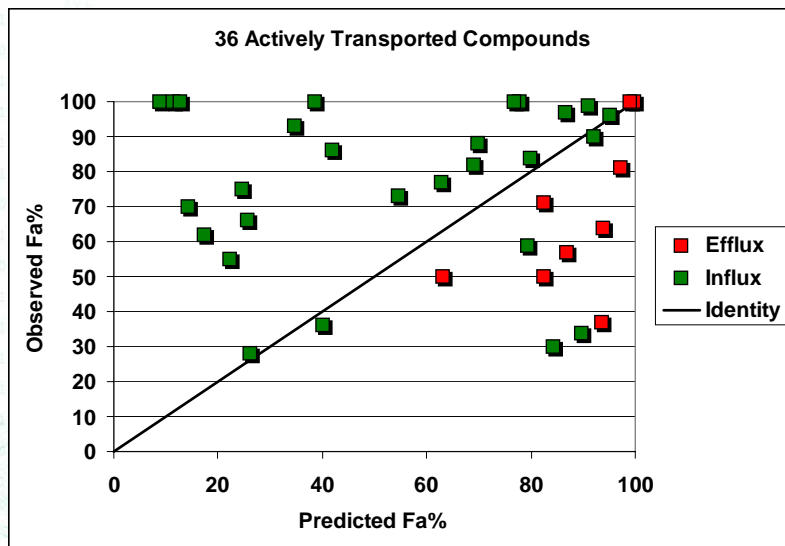
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# GastroPlus Simulation Results



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# 36 Active Transport



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## *GastroPlus Physiologies*

- Human Physiological Fasted
- Human Physiological Fed
- Human Equal Transit Time Fasted
- Human Equal Transit Time Fed
- Beagle Dog Fasted
- Beagle Dog Fed
- Rat Fasted
- Mouse Fasted
- Cynomolgous Monkey Fasted
- Rabbit Fasted
- Cat Fasted
- **User-defined**

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Each physiology includes default values for:

- pH's
- Transit times
- SI length & radius
- Stomach volume
- Colon volume
- Hepatic blood flow rate
- Gut enzyme and transporter distributions

## *Parameter Sensitivity Analysis*

**What experiments need to be run for a compound, and which ones can be skipped or delayed until we're sure we need them?**

– Sensitivity analysis identifies critical experimental parameters

- pKa measurements (vs predictions)
- permeability measurements – PAMPA, Caco-2, MDCK
- solubility measurements (vs predictions) – PBS vs FASSIF, FESSIF

– Toxicity experiments

- no need to run if compound can be eliminated for other reasons
- if needed, what dose levels to use (and which can be eliminated) in dose escalation studies in animals

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## Parameter Sensitivity Analysis (PSA)

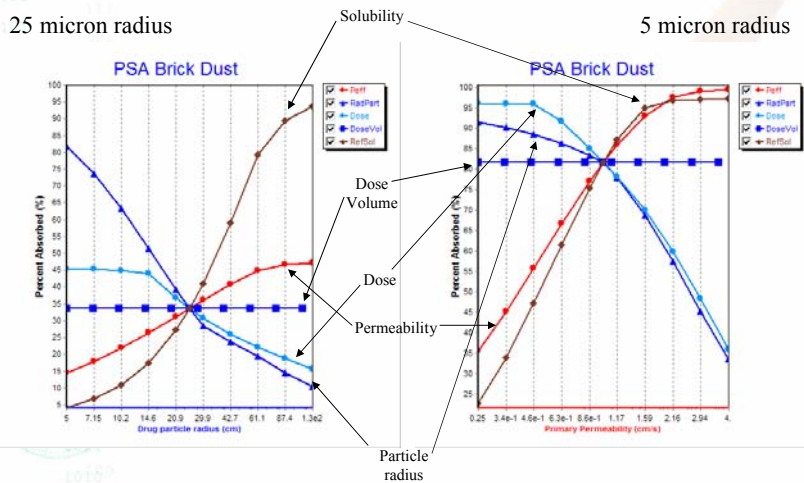
What parameters have a significant effect for this drug?

- pKa?
- Dose?
- Dose volume?
- Particle radius?
- Solubility?
- Diffusion coefficient?
- Permeability?
- Transit times?
- Hepatic blood flow?



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## "Brick Dust"



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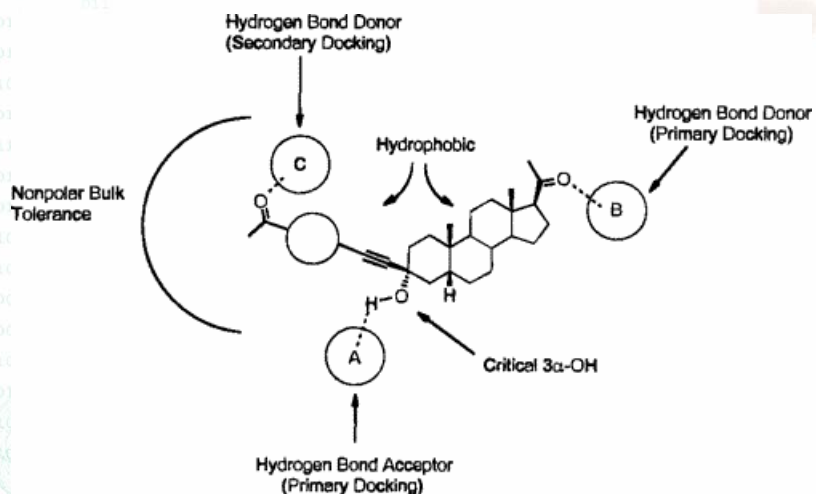


## Neurosteroid *Sim/PK/PD* Methods

- ADMET Predictor™ - 3D strucs. used to estimate:
  - Peff, Solubility, pKa, Diffusivity, log P
- GastroPlus™ used to simulate:
  - Fraction absorbed
  - Plasma concentration vs. time profile
  - Pharmacodynamic response vs. time profile
- MS-Excel pivot table used to create 3D plot of log IC<sub>50</sub> vs. log S<sub>w</sub> vs. Maximal Response

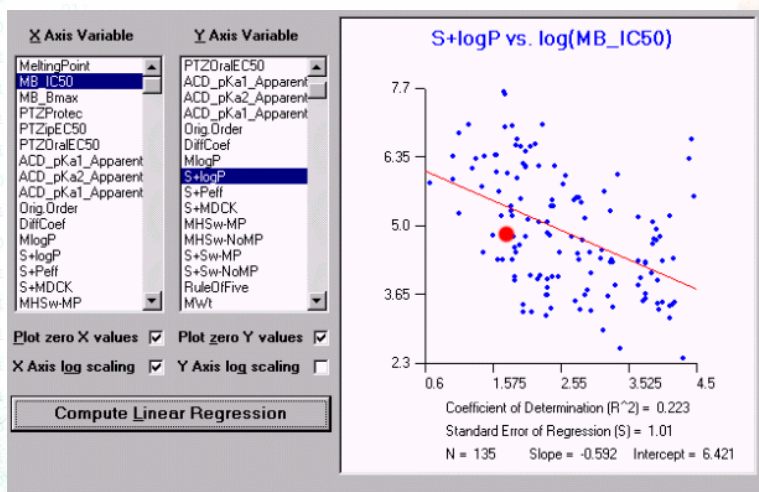
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## Neuroactive Steroid SAR



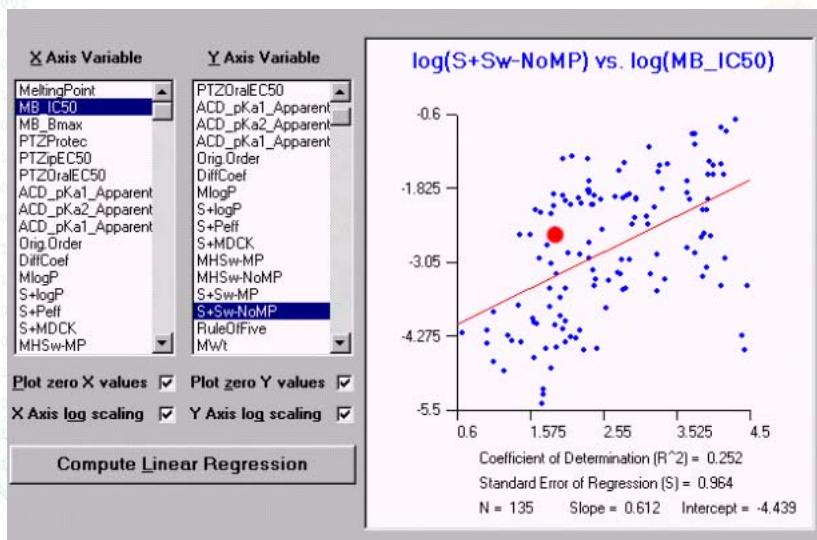
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# Activity vs. BioPharm.



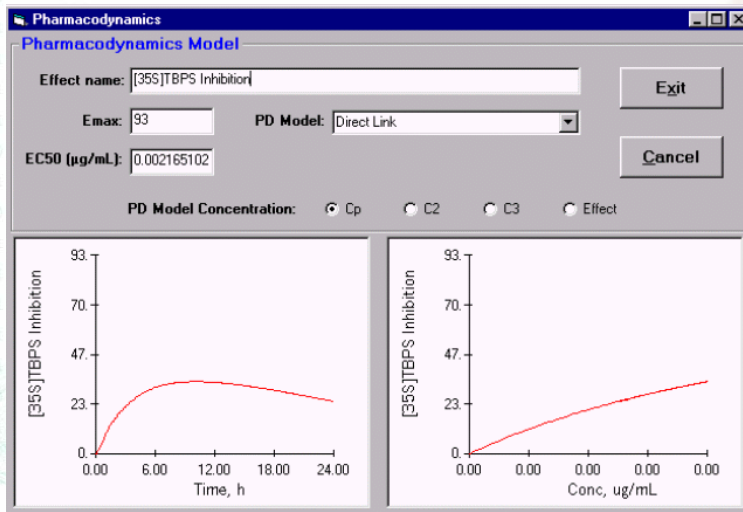
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# Activity vs. BioPharm.



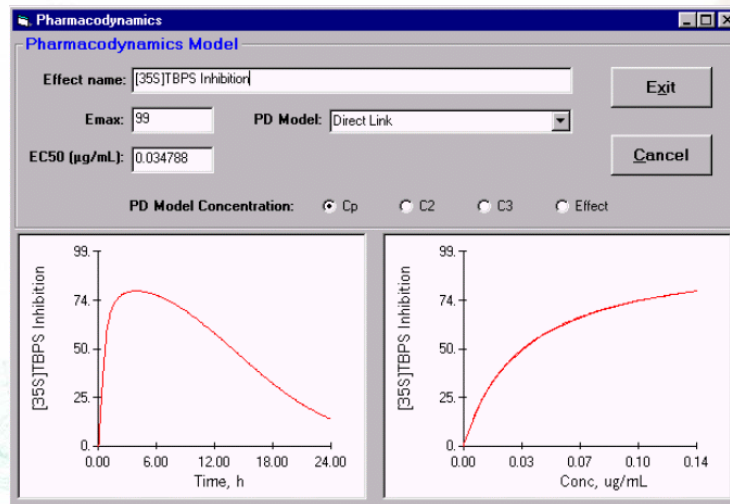
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**PD Profile for most potent drug**  
**IC<sub>50</sub> = 4.7 nM Sol. = 0.000058 mg/mL**

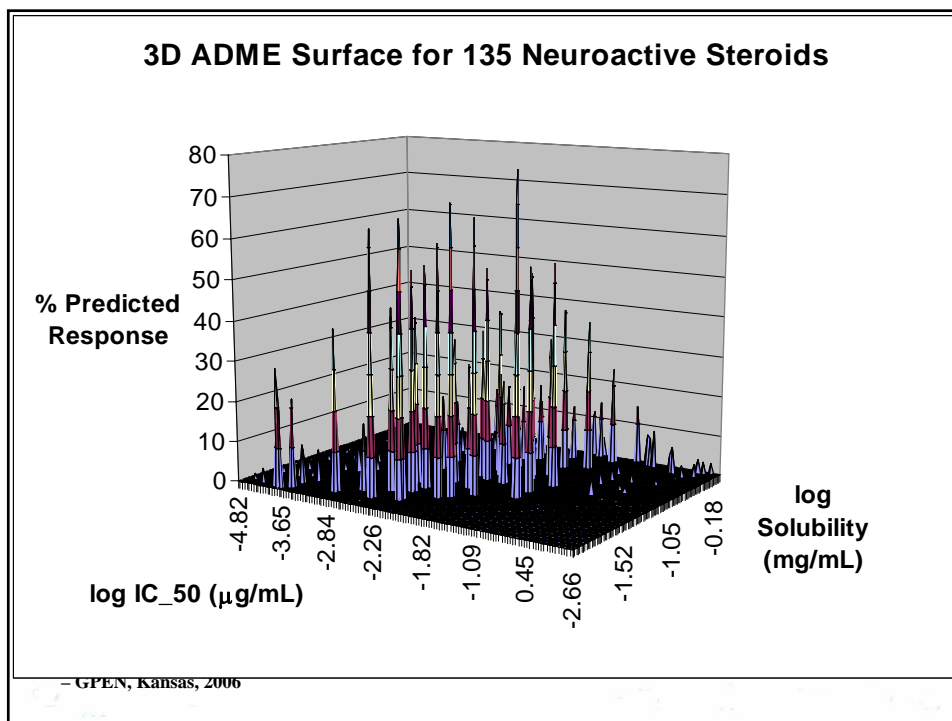


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**PD Profile for most effective drug**  
**IC<sub>50</sub> = 104 nM Sol. = 0.046 mg/mL**



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## Conclusions

- Data integration is a key factor in drug discovery and development.
- Gastrointestinal simulation provides us with a mechanistic understanding of preclinical and clinical data.
- Parameter sensitivity is more important than the exact solution.
- Most potent compound is not always the best drug.

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