Predicting Oral Absorption with ADME Models & PBPK Simulations

2023 Gulf Coast Consortium Future of ADME Symposium

Houston, Texas

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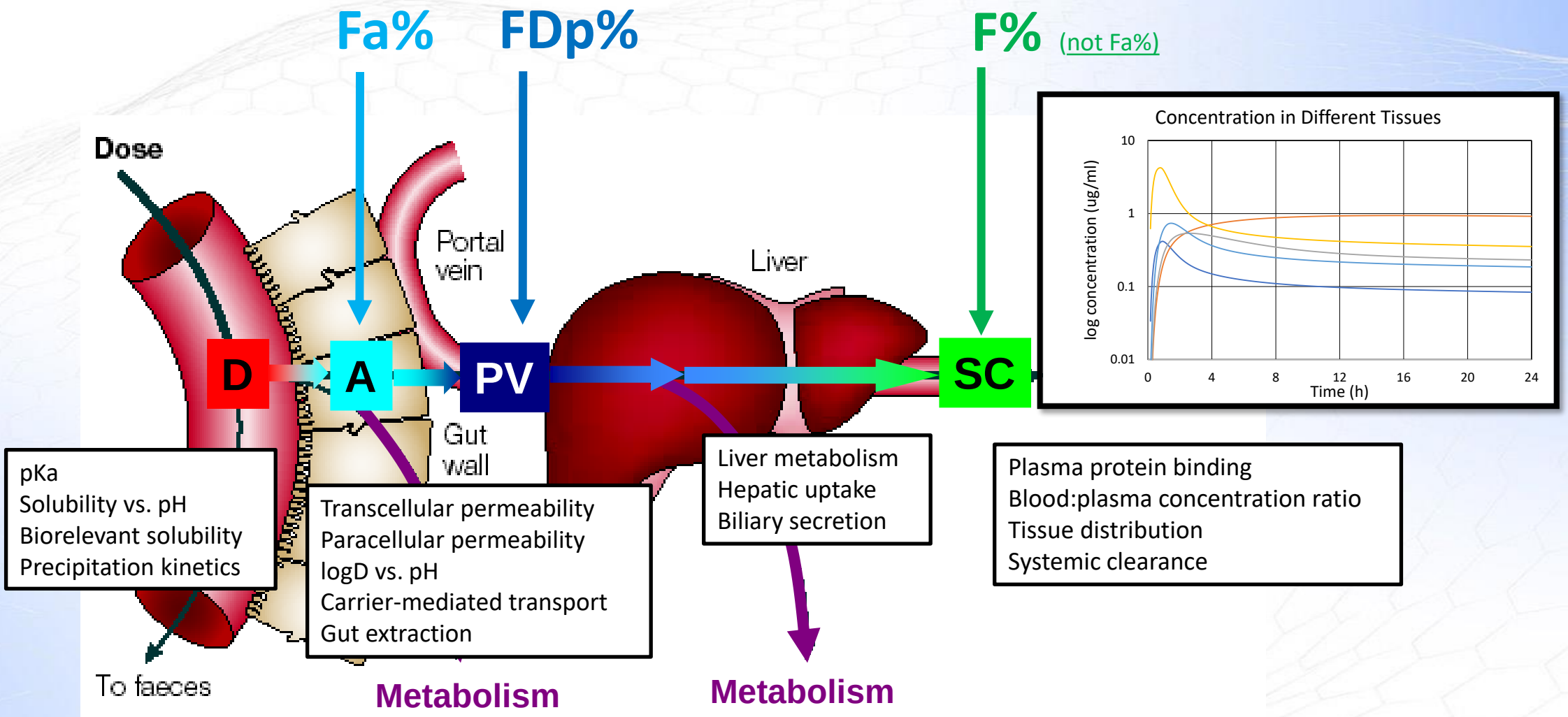
SimulationsPlus

Predicting Oral Absorption

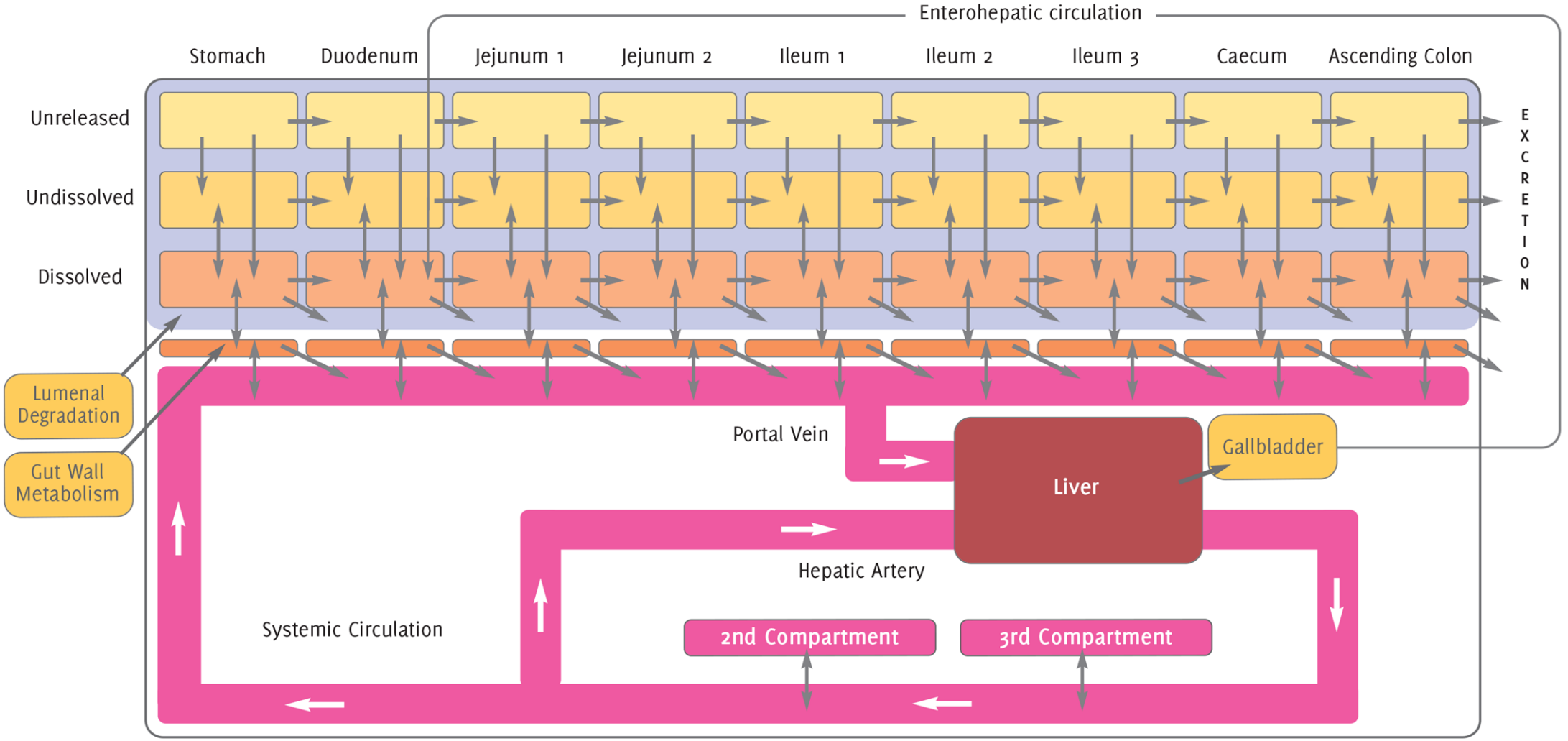
- What is happening *in vivo* to an orally delivered tablet?
- Gastrointestinal (GI) tract physiology
- ADME parameters in physiologically based pharmacokinetic (PBPK) models
- Ionization, partition coefficient, permeability, and solubility models
- Simulations of low solubility, ionizable compounds

What is happening *in-vivo*?



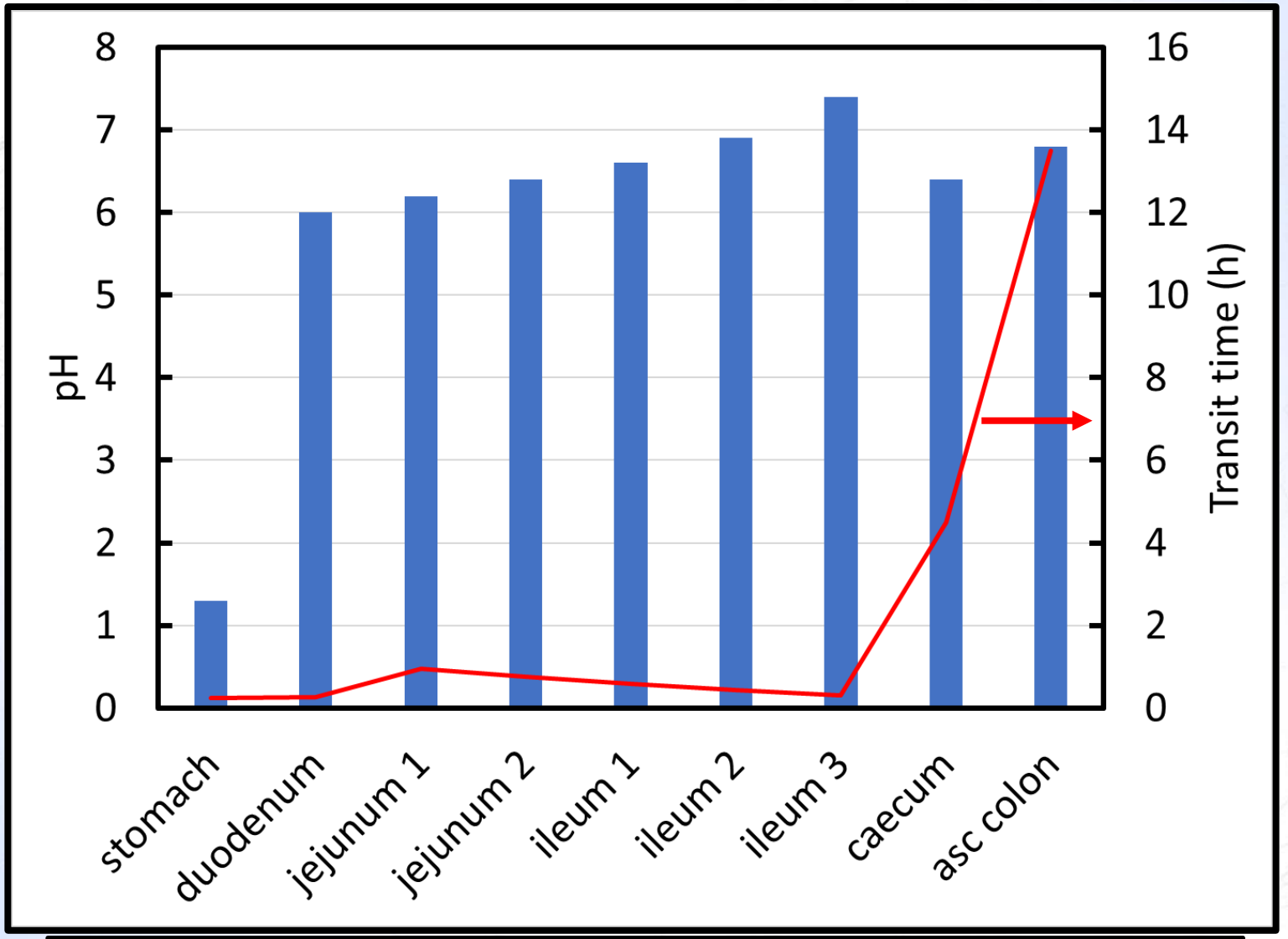
* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

Advanced Compartmental Absorption and Transit Model (ACAT™)*



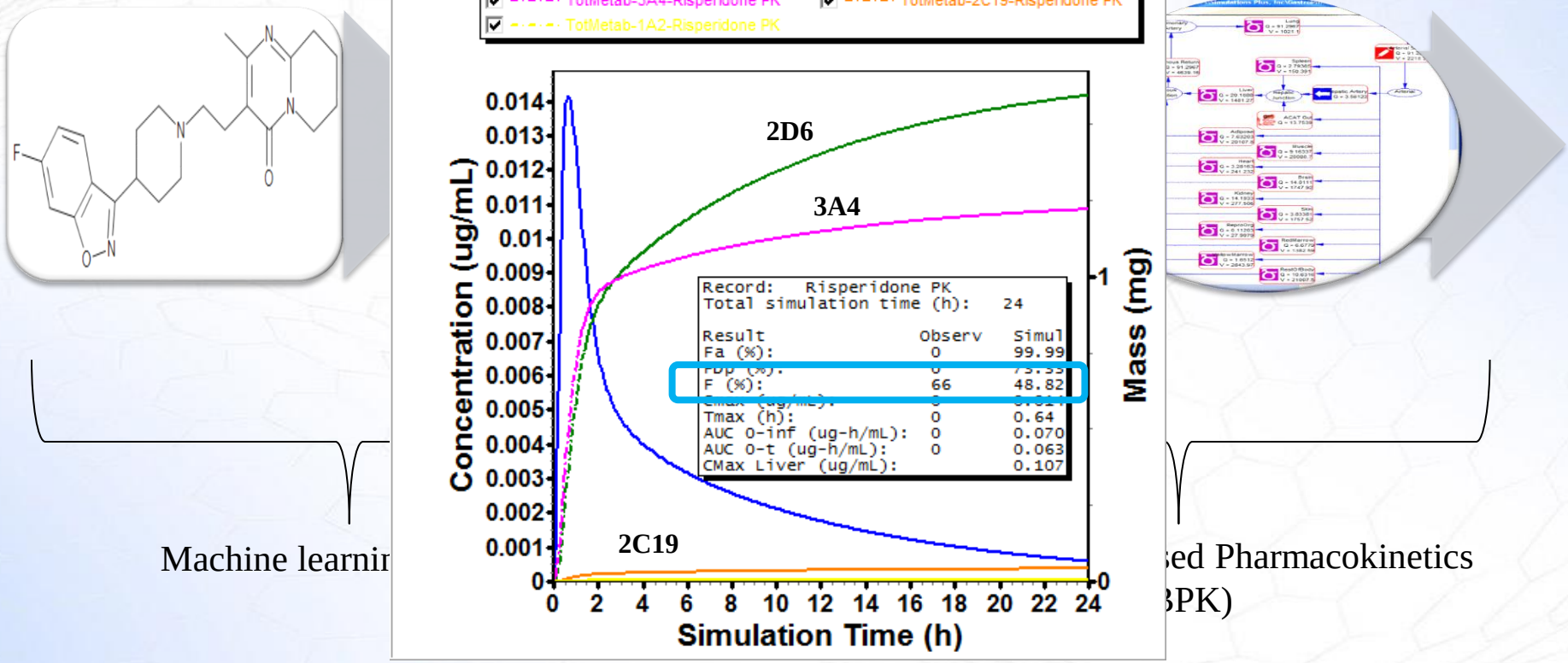
*GastroPlus®, Simulations Plus, Inc. Lancaster CA 93534.

pH and transit time along GI Tract



Fasted Physiology for a 25-year-old, 85 kg American male in GastroPlus

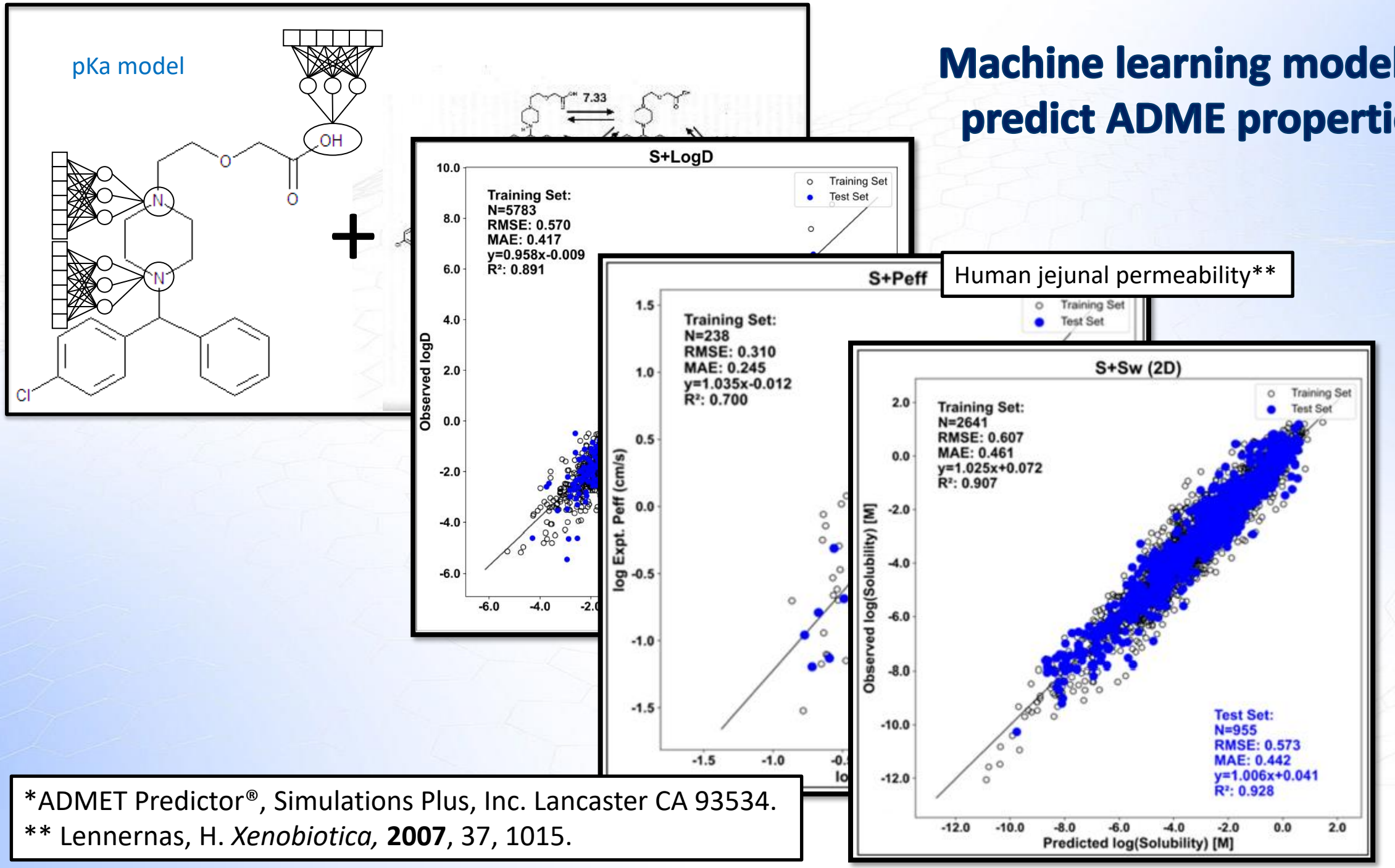
Machine Learning Models as Parameters in PBPK Simulations



Machine learnir

sed Pharmacokinetics
BPK)

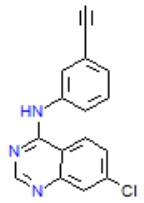
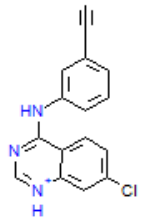
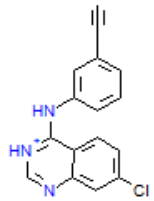
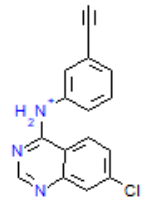
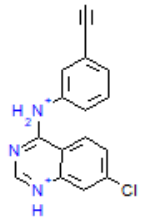
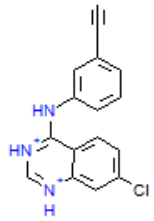
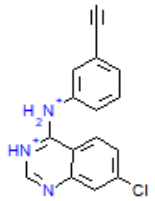
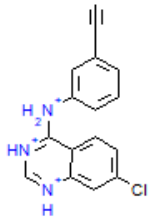
Machine learning models to predict ADME properties*

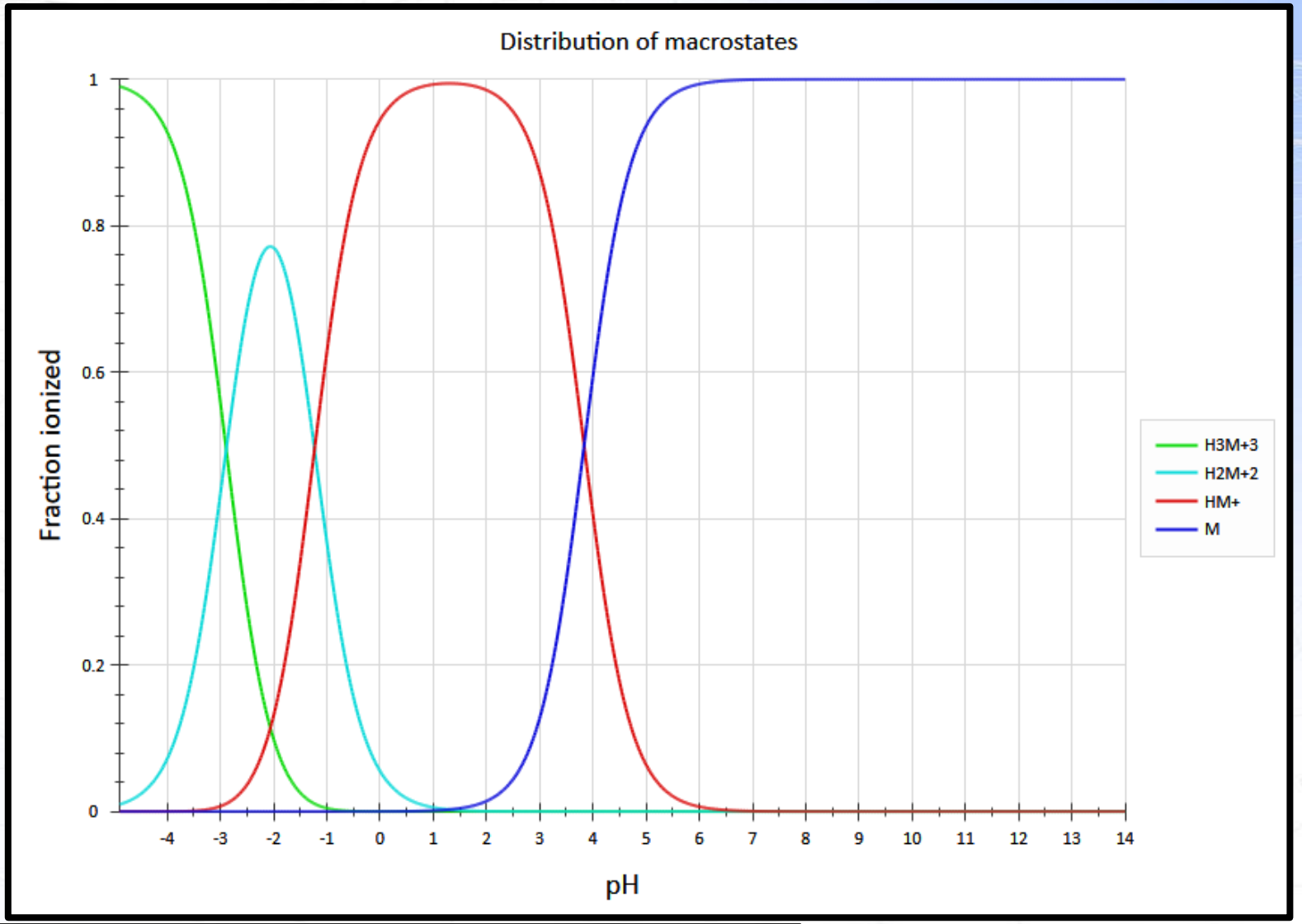


*ADMET Predictor®, Simulations Plus, Inc. Lancaster CA 93534.

** Lennernas, H. *Xenobiotica,* **2007**, 37, 1015.

S+pKa*

pKa	Macrostates	
	M	100.0% 
3.83		
	HM^{+}	95.1%  4.9%  0.0% 
-1.23		
	H_2M^{+2}	82.9%  16.4%  0.7% 
-2.89		
	H_3M^{+3}	100.0% 



*Fraczkiewicz R, et al. *J. Chem. Inf. Model.* **2015**, 55, 389-397.

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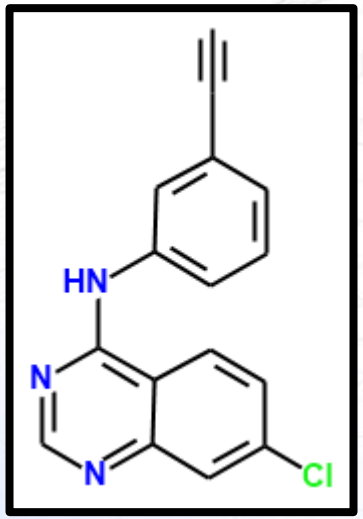
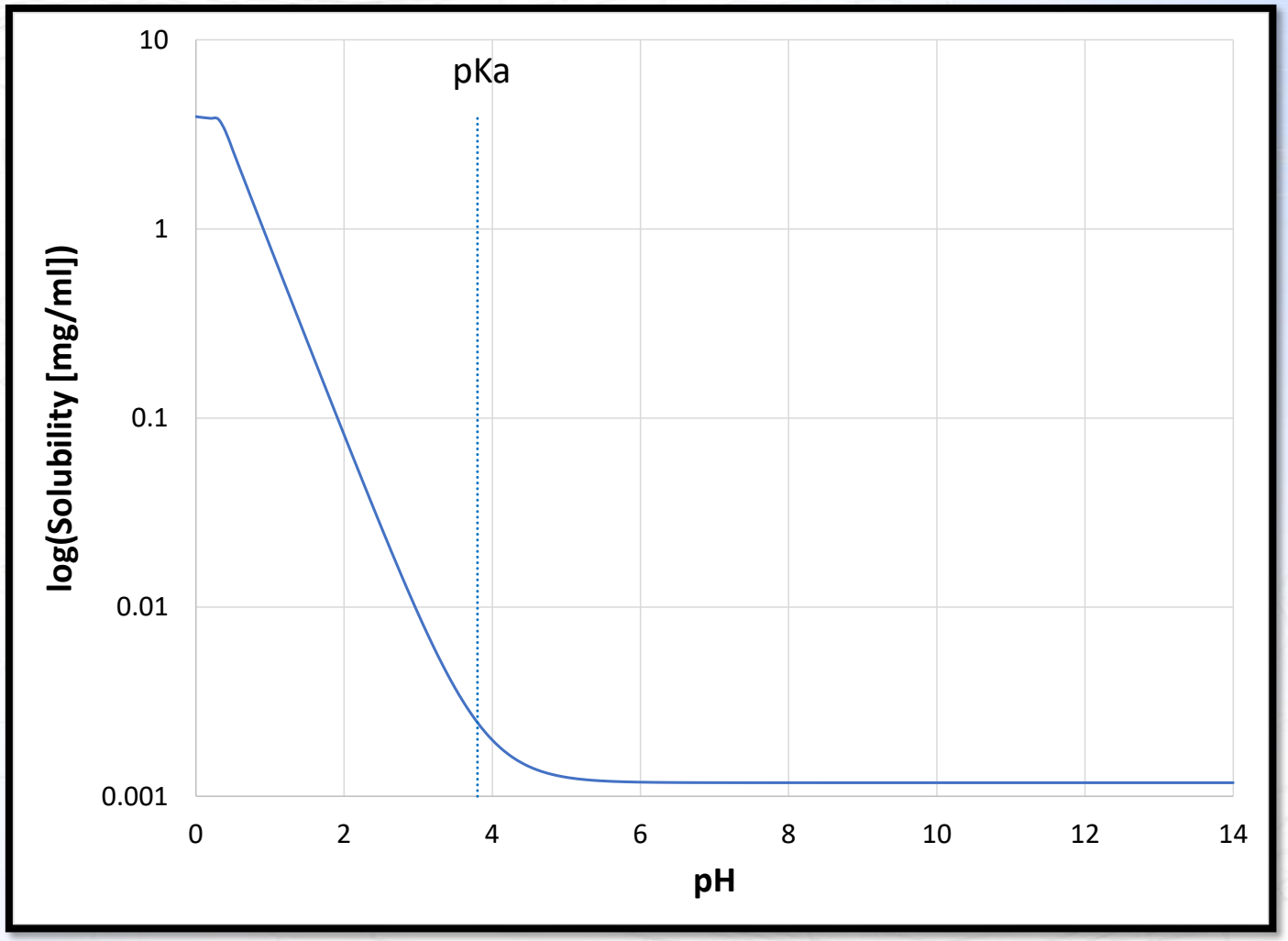
Solubility vs. pH

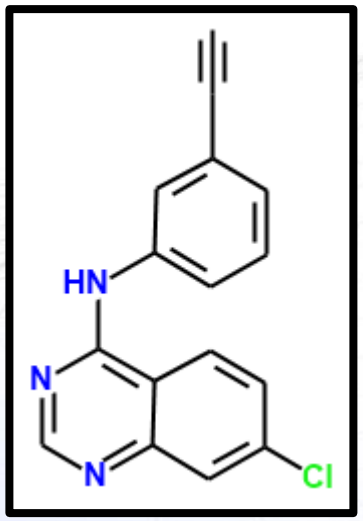
In general, solubility increases with increasing ionization



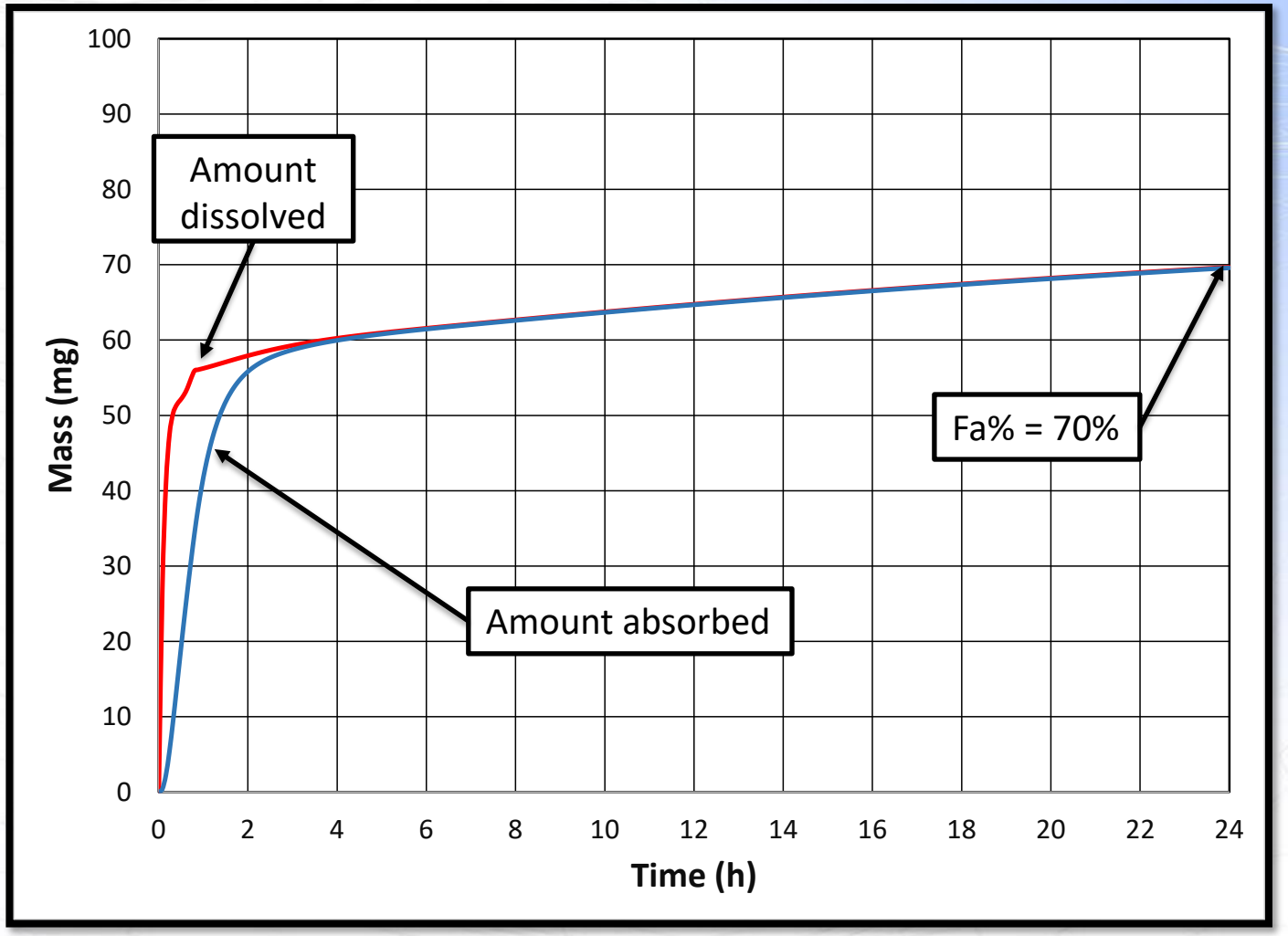
S+Sw = 1.18 x 10^{-3} mg/ml



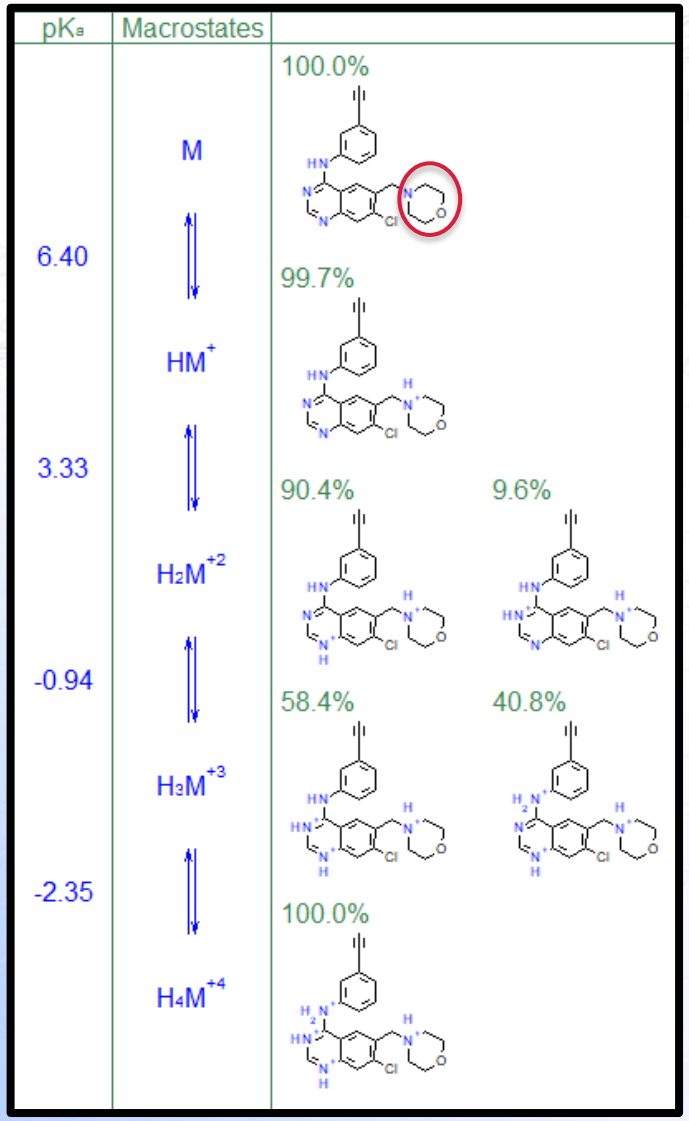
PBPK Simulation of 100 mg dose

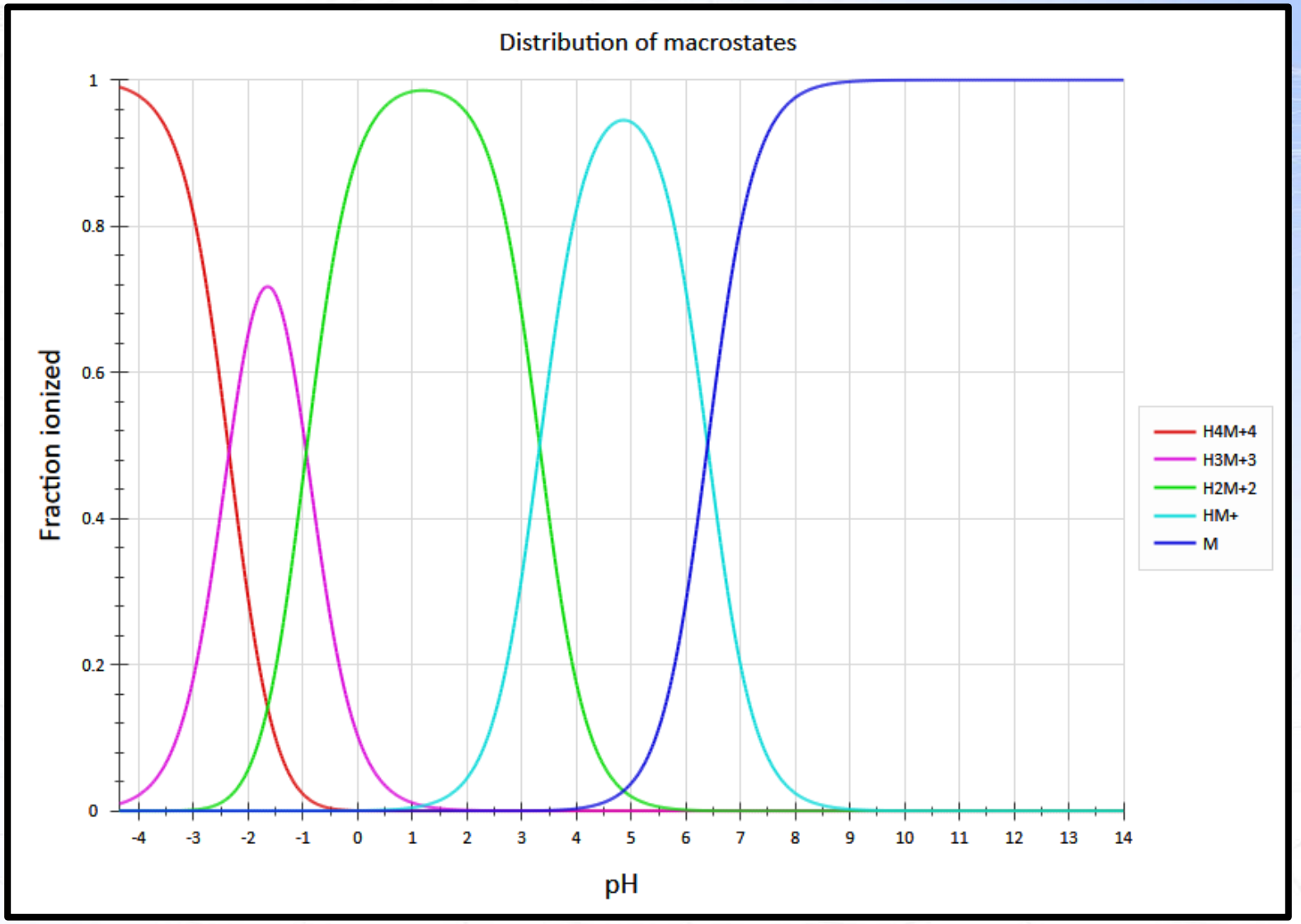


Solubility at stomach pH (0.406 mg/ml) is less than concentration in stomach so the whole dose is not dissolved.

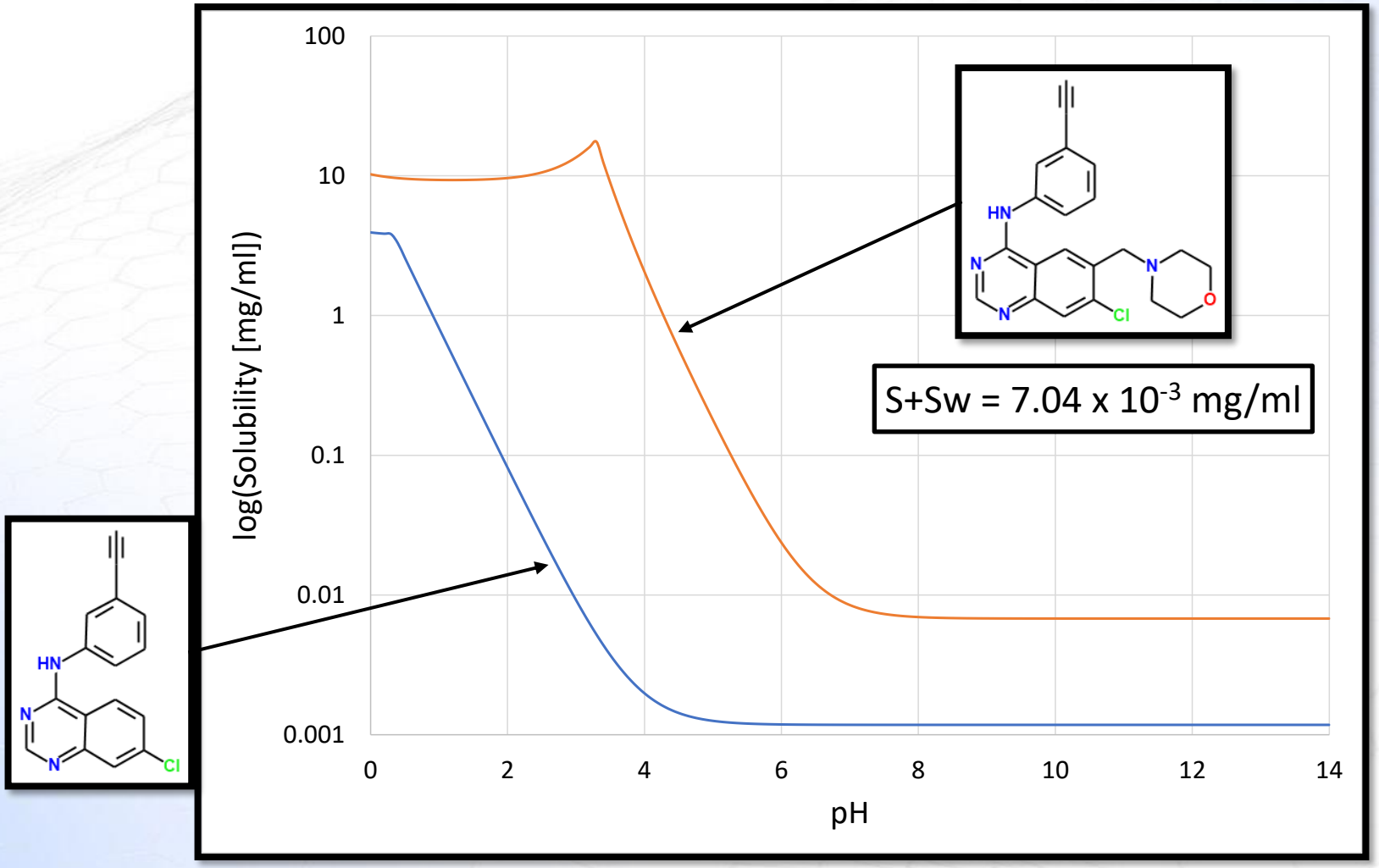


Add a morpholine group

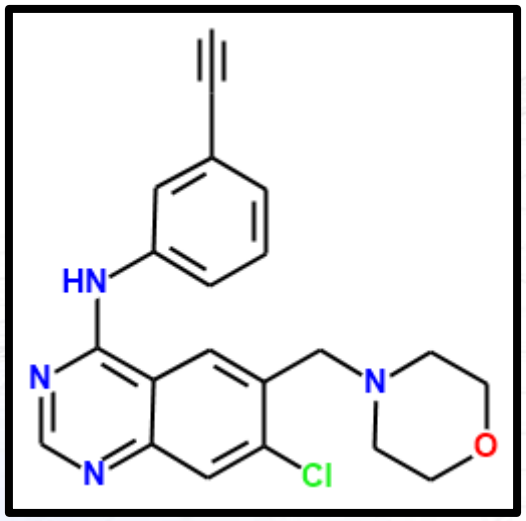




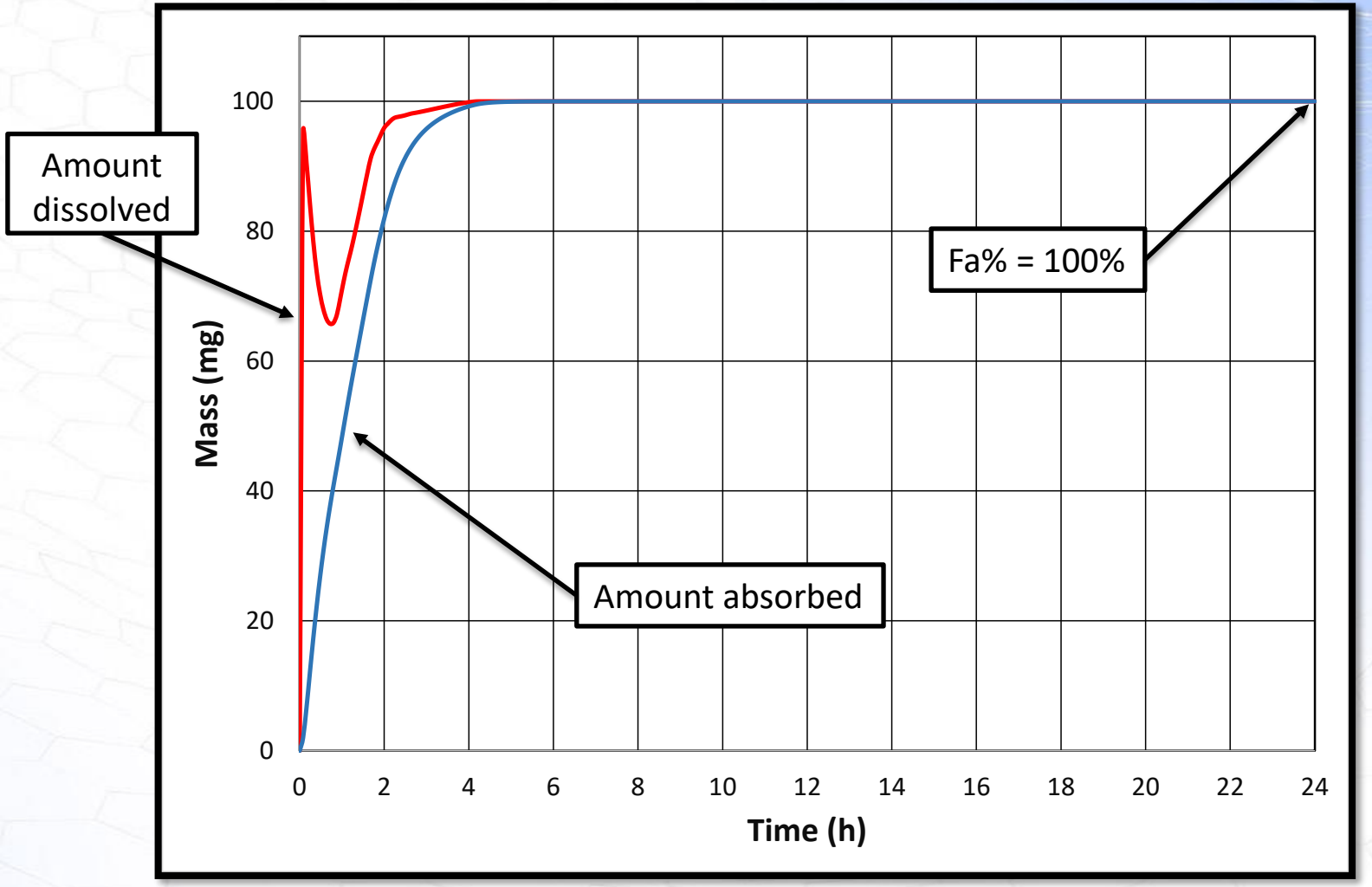
Morpholine group increases solubility



PBPK Simulation of 100 mg dose of morpholine containing compound



The compound dissolves in the stomach at pH = 1.3 but re-crystallizes in duodenum and jejunum because the pH increases so the solubility drops.



Summary

- Machine learning models can be developed to predict ADME properties
- *In silico* predictions can be used to parametrize PBPK simulations
- Solubility is ionization dependent
- The stomach and compartments in the gastrointestinal (GI) tract have different pH values
  - Thus, the solubility of compounds with ionizable groups can vary along the GI tract
- Examples were shown that illustrate how ionization affects oral absorption