NATIONAL CHEMISTRY WEEK

Chemistry in Drug Design and Delivery: Use of Chemical Principles to Make Better Drugs

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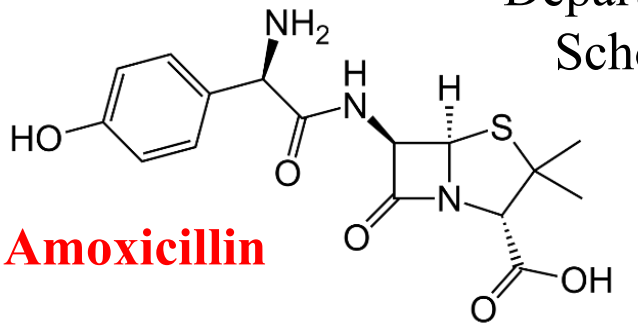
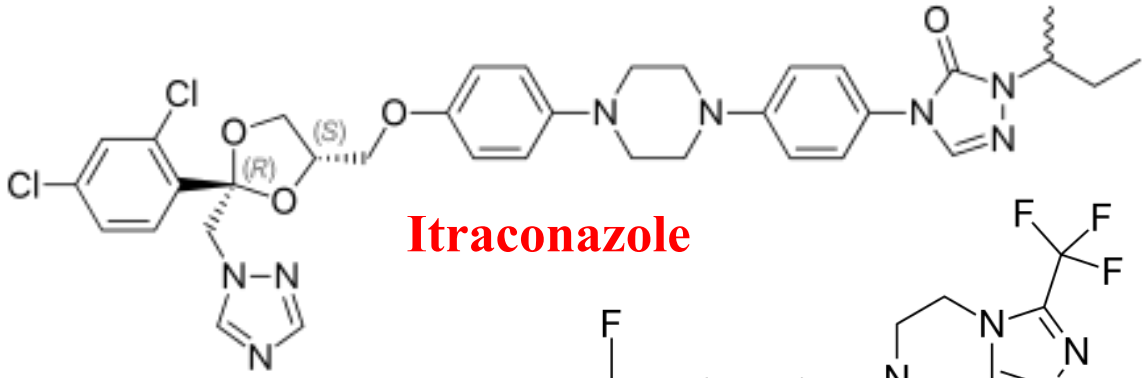
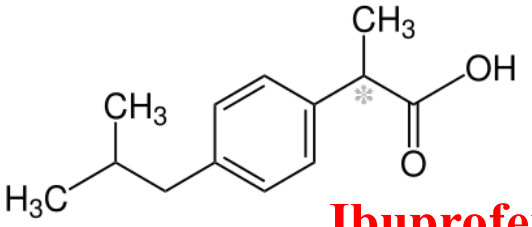
School of Pharmacy, University of Southern California



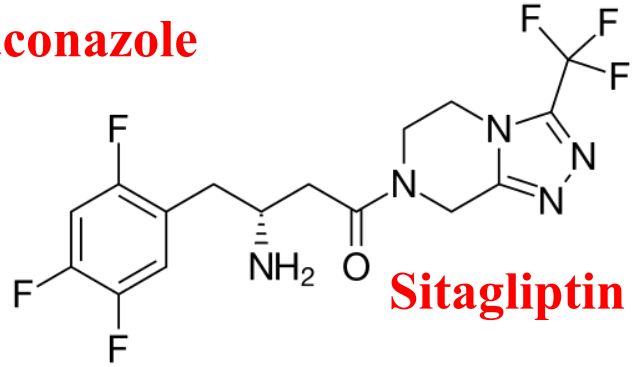
Amoxicillin



Itraconazole



Ibuprofen



Sitagliptin

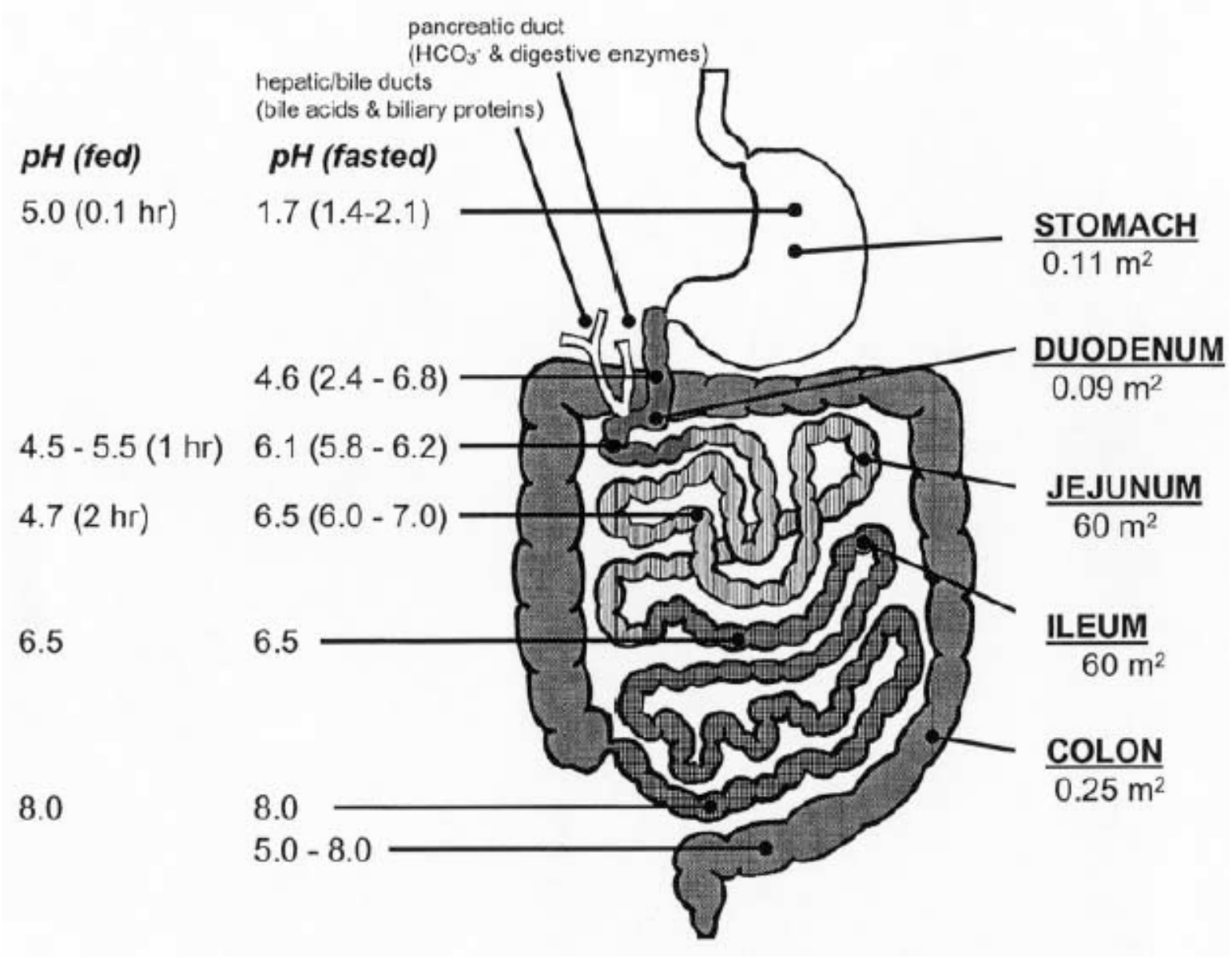
STICKING WITH CHEMISTRY

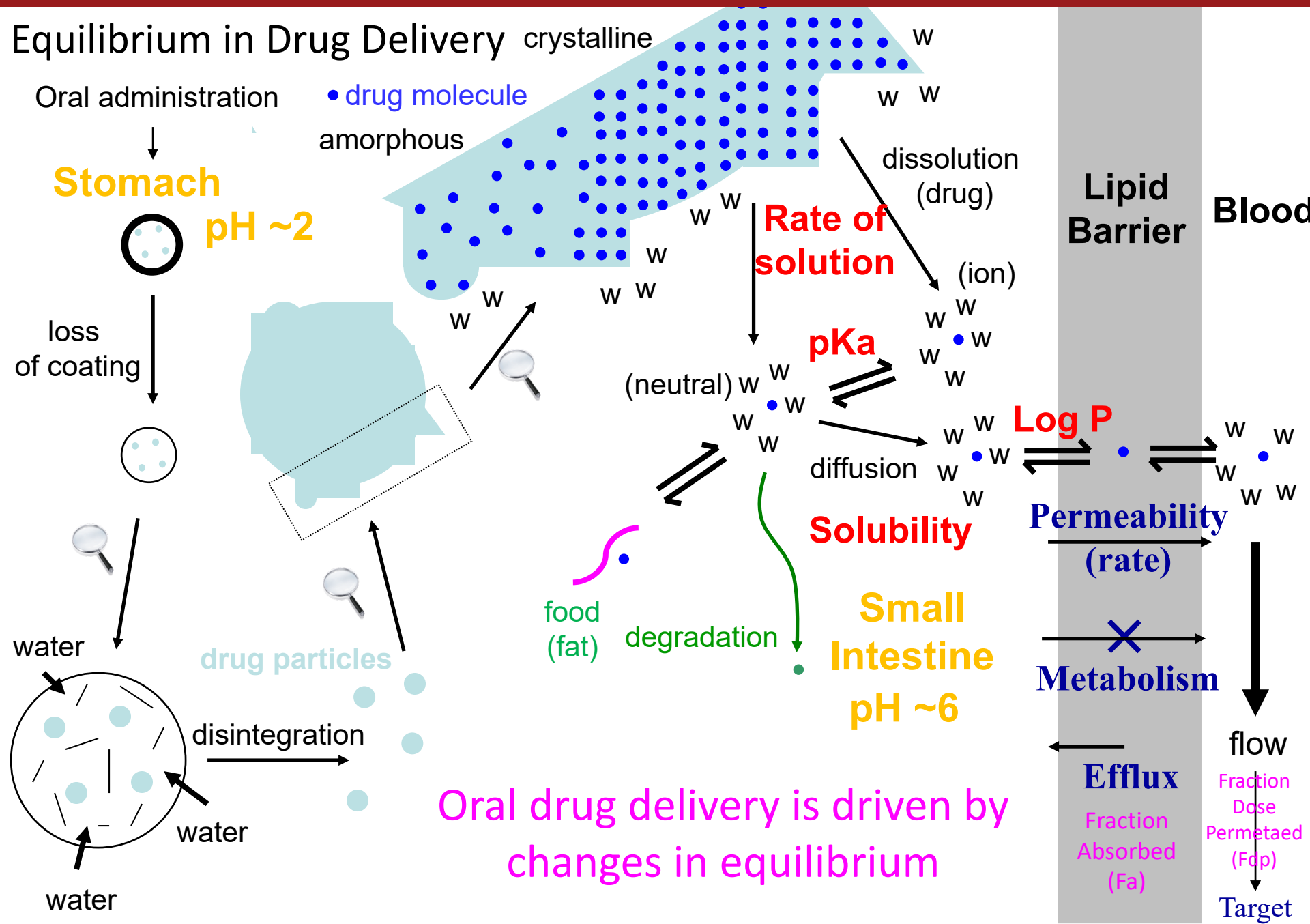
ACS Chemistry for Life™

AIAA SHAPING THE FUTURE OF AEROSPACE
AIAA LOS ANGELES - LAS VEGAS SECTION

USC School of Pharmacy

pH Values of Different Parts of the Gastrointestinal Tract




Equilibrium in Drug Delivery
crystalline
Oral administration
drug molecule
amorphous
Stomach
pH ~2
dissolution (drug)
Lipid Barrier
Blood
Rate of solution
(ion)
loss of coating
pKa
(neutral)
Log P
diffusion
Solubility
Permeability (rate)
food (fat)
degradation
Small Intestine pH ~6
Metabolism
water
drug particles
disintegration
water
water
Efflux
Fraction Absorbed (Fa)
flow
Fraction Dose Permetaed (Fdp)
Target
Oral drug delivery is driven by changes in equilibrium

Lipinski's Rule of Five

- Molecular Weight <= 500 - Size
- # Hydrogen Bond Acceptors <=10
  - Sum of N and O
- # Hydrogen Bond Donors <= 5
  - Sum of NH and OH

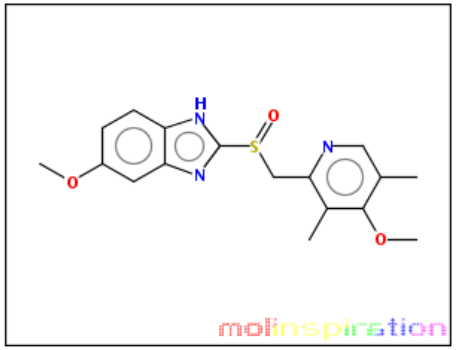
Pharmacophoric Properties

- -2 < CLog P < 5. - Solubility
- # Rotatable Bonds <= 10 - Molecular Flexibility

Lipinski et al. Adv Drug Deliv Rev 1997; 23: 3-25.

molinspiration

SMILES COc3ccc2[nH]c(S(=O)Cc1ncc(C)c(OC)c1C)nc2c3



miLogP	2.411
TPSA	77.114
natoms	24
MW	345.424
nON	6
nOHNH	1
nviolations	0
nrotb	5
volume	302.808

Get data as text (for copy

This was request 1 out of 100 available this month for your site 76.167.147.238.

www.molinspiration.com/cgi-bin/properties

Pubchem: http://pubchem.ncbi.nlm.nih.gov/

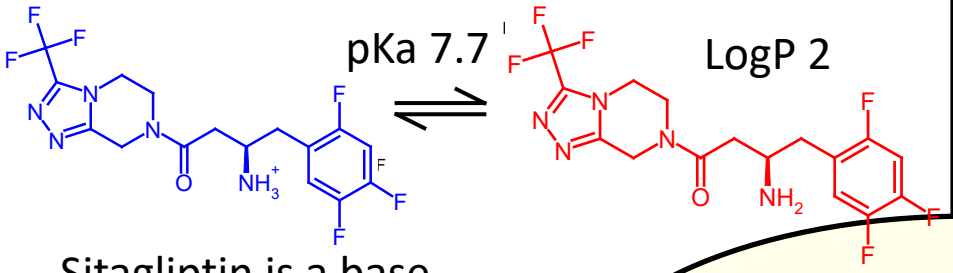
Oral bioavailability (F) in rat

quartile	%F range (rat)	MW	no. of rotatable bonds	C log P[b]	H-bond donor count	H-bond acceptor count	H-bond total count
			Full Data Set, MW range 220–770, n = 1117				
4	>42.7–100	*431.6*	*6.17*	4.45	*1.75*	*5.81*	*7.56*
3	>15.5–42.7	483.9	8.15	*4.78*	2.03	6.60	*8.63*
2	>4.3–15.5	492.3	*9.00*	4.38	2.40	7.12	9.52
1	<4.3	*511.1*	*10.22*	*3.49*	*2.99*	*8.06*	*11.05*
all	av 28.7	479.8	8.39	4.27	2.29	6.90	9.20
	r with %F	−0.35	−0.39	0.10	−0.32	−0.35	−0.39

Physicochemical and Pharmacokinetic Properties of Sitagliptin

SMILES String

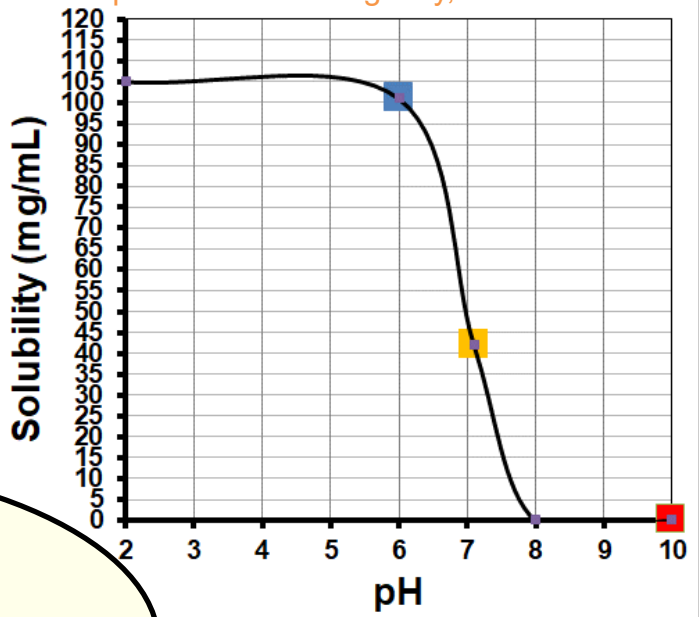
C(F)(F)(F)C1=NN=C2N1CCN(C2)C(=O)C[C@H](N)Cc3c(F)cc(F)c(F)c3



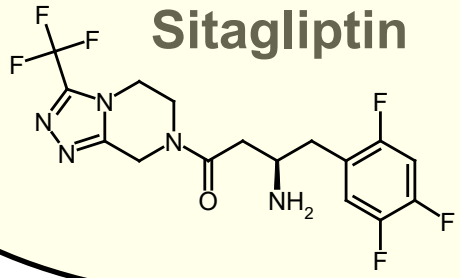
Sitagliptin is a base

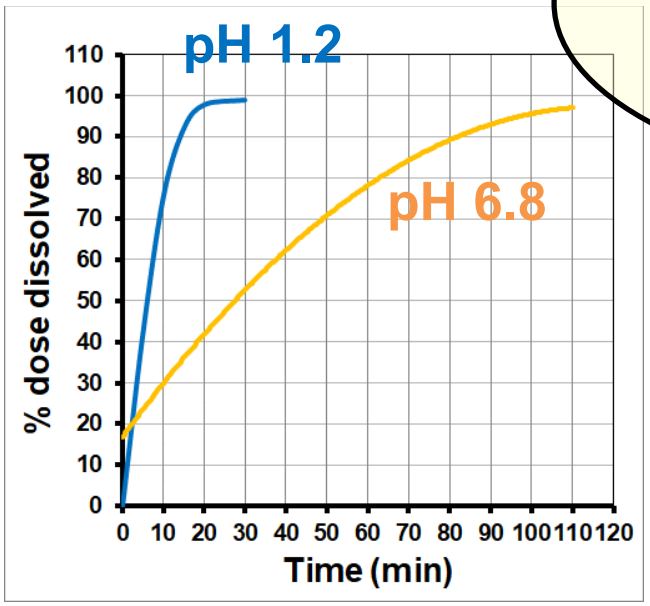
Selleckchem.com European Medicines Agency, 2009 ALOGPS

101 mg/mL in water (pH 6)
42.1 mg/mL at pH 7.1
Intrinsic sol. 0.034 mg/mL



Sitagliptin

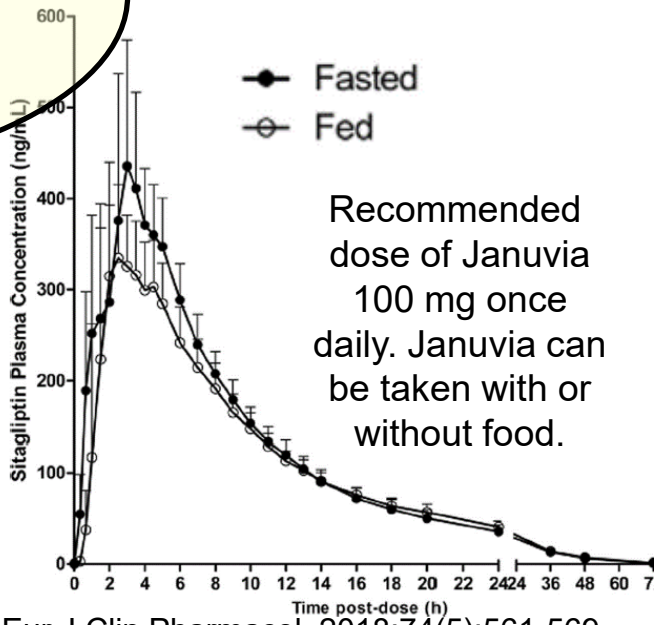




Januvia (Sitagliptin phosphate)
50 mg
pH 1.2
900 ml
100 rpm
37±0.5°C

Kumar et al. Int J Pharm. 2012;2(2):64-81.

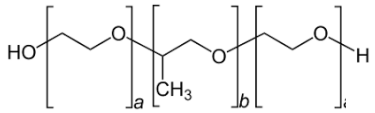
Single oral dose
100 mg sitagliptin.in healthy male subjects



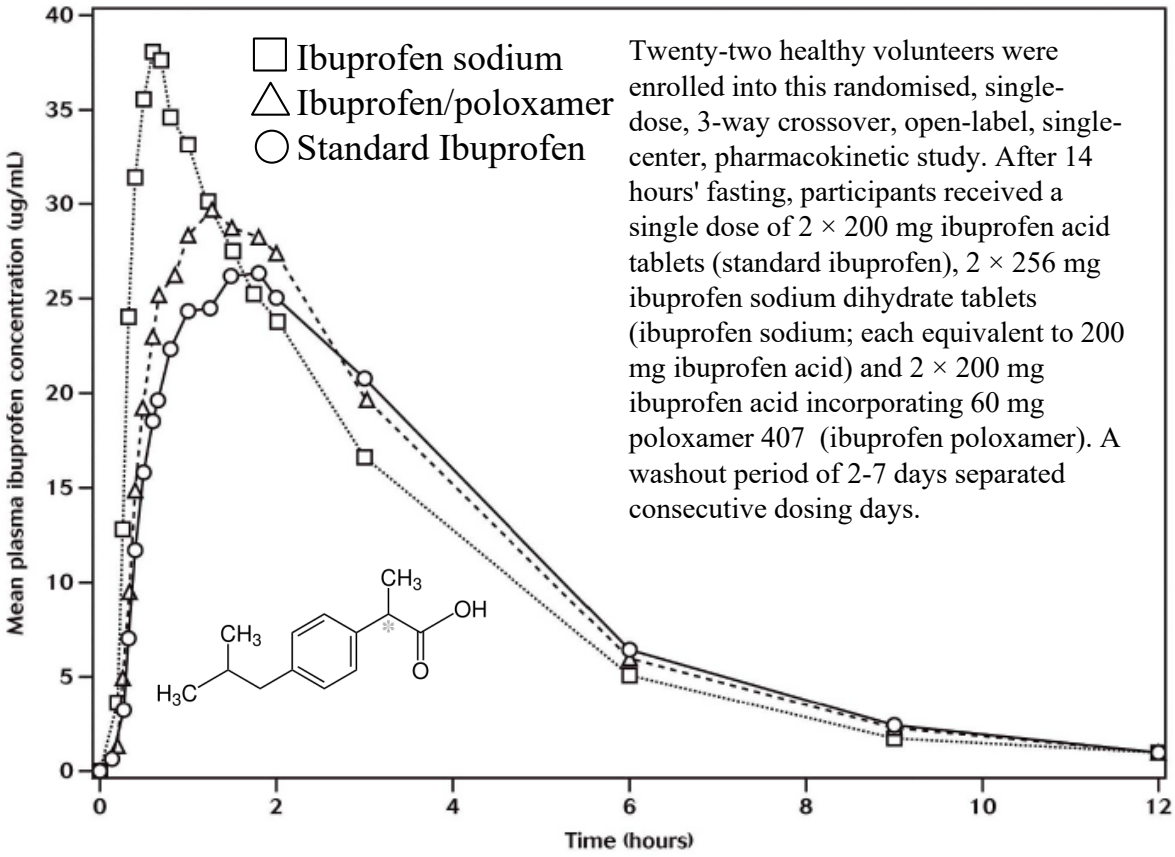
Recommended dose of Januvia 100 mg once daily. Januvia can be taken with or without food.

Sangle et al. Eur J Clin Pharmacol. 2018;74(5):561-569.

Dependence of Ibuprofen Pharmacokinetics on Rate of Solution

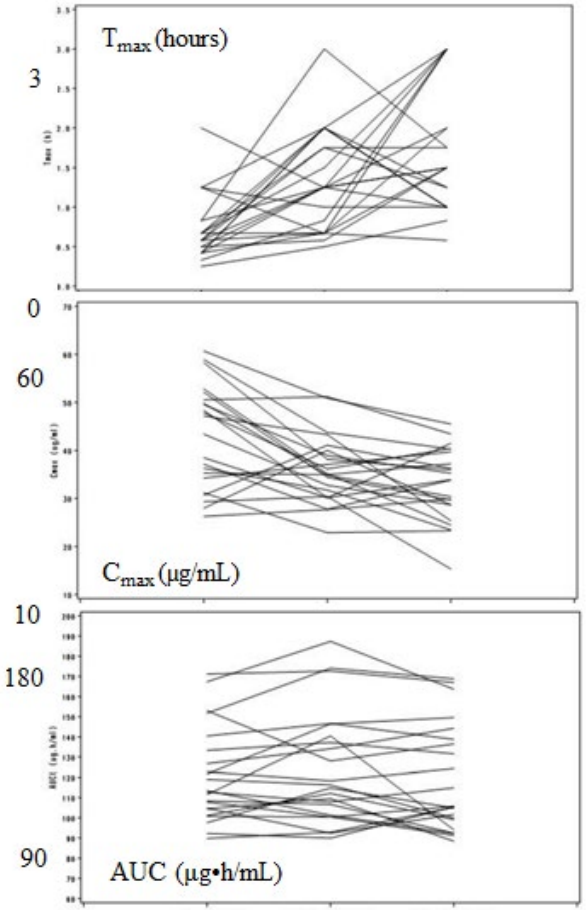


Poloxamer 407



Twenty-two healthy volunteers were enrolled into this randomised, single-dose, 3-way crossover, open-label, single-center, pharmacokinetic study. After 14 hours' fasting, participants received a single dose of 2 × 200 mg ibuprofen acid tablets (standard ibuprofen), 2 × 256 mg ibuprofen sodium dihydrate tablets (ibuprofen sodium; each equivalent to 200 mg ibuprofen acid) and 2 × 200 mg ibuprofen acid incorporating 60 mg poloxamer 407 (ibuprofen poloxamer). A washout period of 2-7 days separated consecutive dosing days.

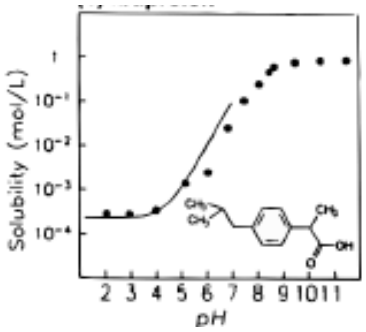
Individual responses

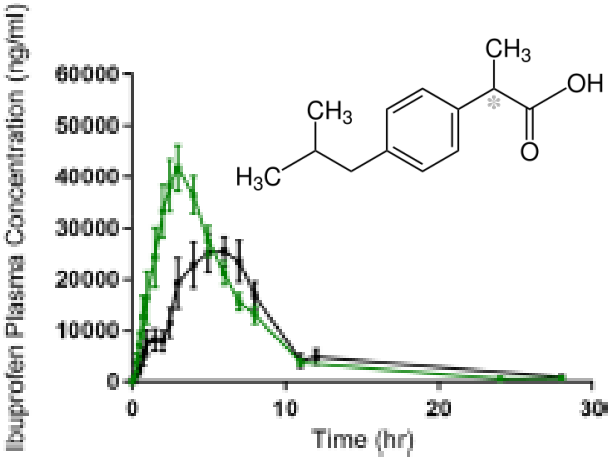


T_{max}	The time to the first occurrence of the maximum plasma concentration	(minutes)	35	75	90
C_{max}	The observed maximum plasma concentration		43.01	36.06	32.84
AUC_{0-t}	AUC to the last measurable plasma concentration (Cp), calculated by the linear trapezoidal rule		120.57	124.10	119.10

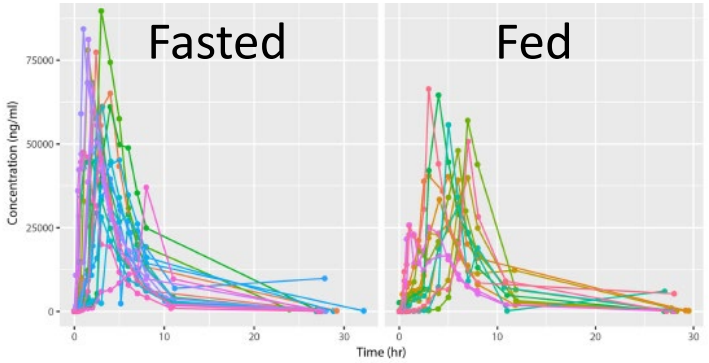
Dewland et al. BMC Clinical Pharmacology 2009, 9:19

Dependence of Ibuprofen Pharmacokinetics on Fasted or Fed Conditions

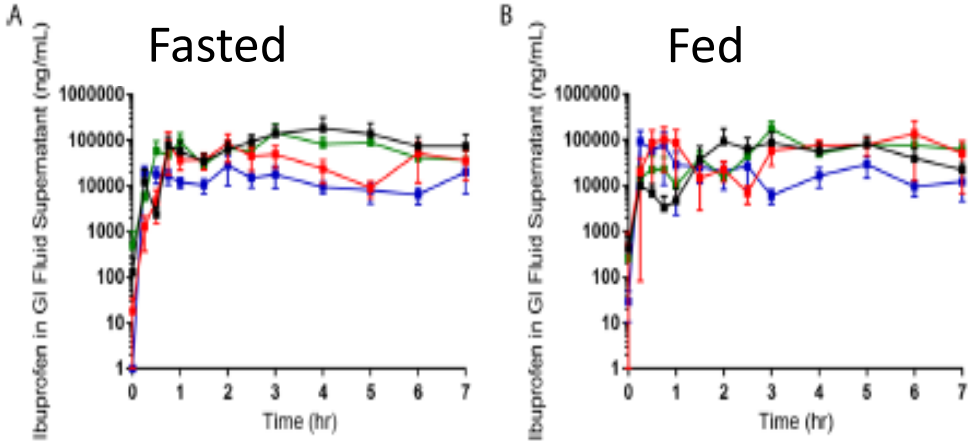




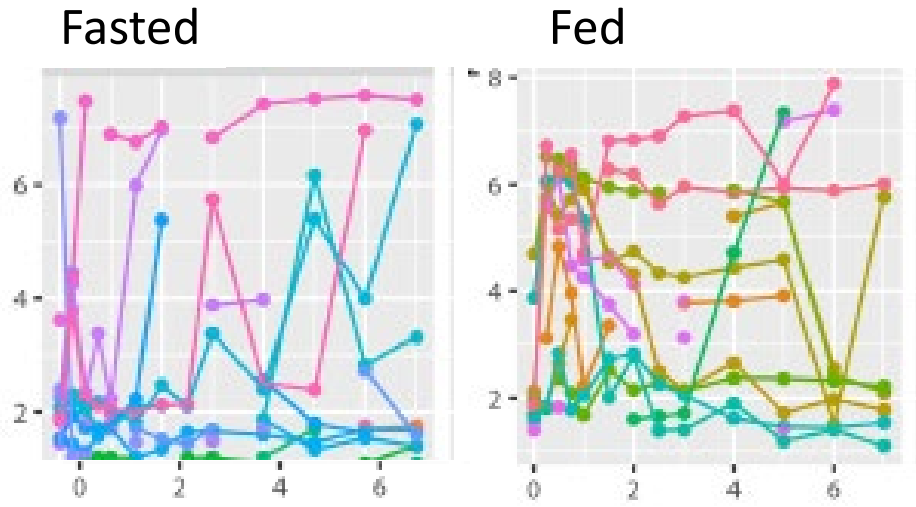
Average plasma concentration vs time profiles of ibuprofen. Fasted (n = 20, green line) and fed (n = 14, black line) conditions plotted in (A) logarithmic and (B) linear scale. Error bars indicate the standard error of the mean (SEM). Data from fasted subjects (n = 20) and fed subjects (n = 14) are shown.



Individual plasma concentration vs. time profiles of ibuprofen under fasted and fed conditions. Each line represents an individual subject. given an 800 mg tablet of ibuprofen swallowed with 250 mL of water.



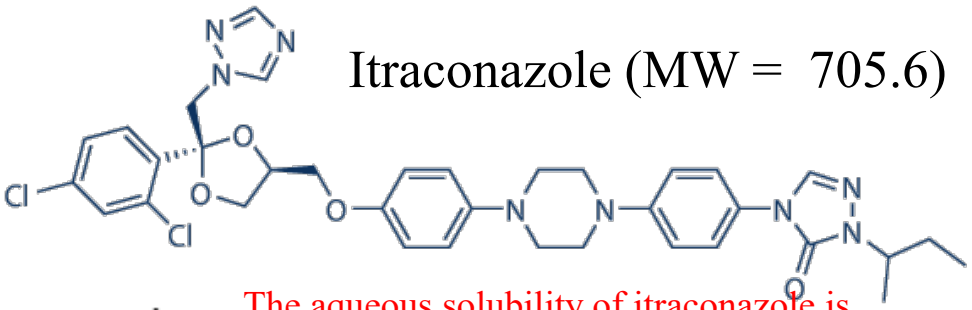
Average concentration of ibuprofen in luminal GI fluid supernatant through the GI tract.in fasted or fed states. Mid jejunum (black line), proximal jejunum (red line), duodenum (green line), and stomach (blue line).



Individual pH values in the stomach over time in fasted or fed states

Koenigsknecht et al. Mol. Pharmaceutics 2017;14: 4295−4304

Itraconazole: A Very Insoluble Drug



The aqueous solubility of itraconazole is about 1 ng/mL at pH 7 and 4 µg/mL at pH 1.

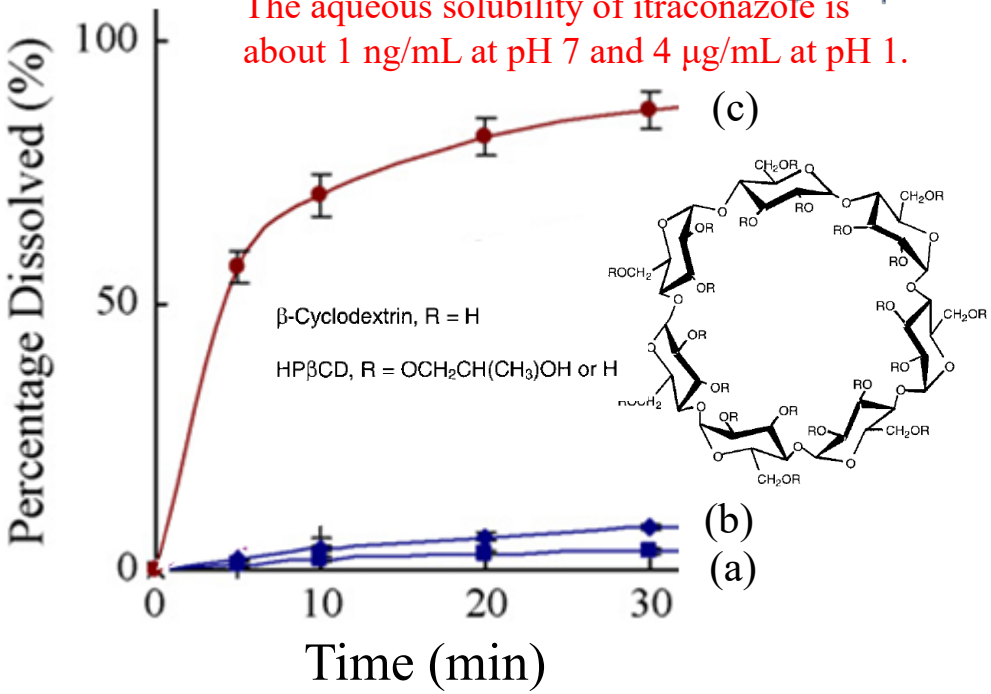
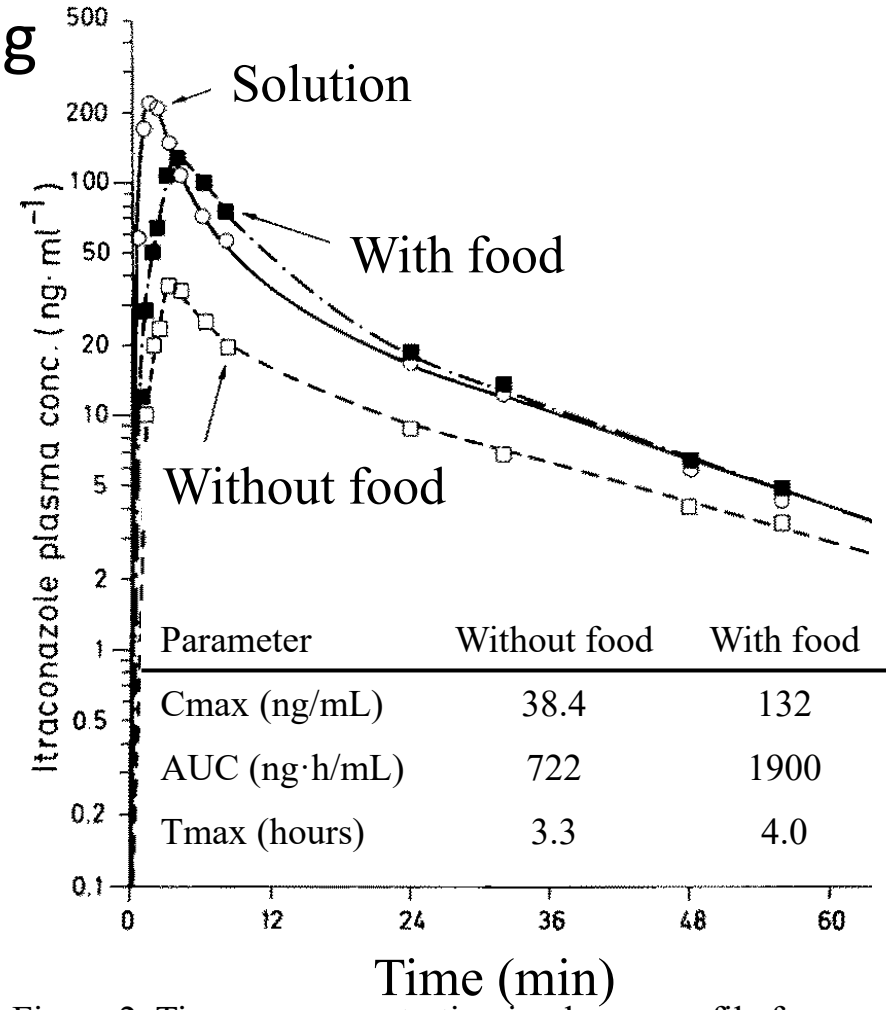


Figure 1. Dissolution profiles of (a) 100 mg itraconazole, (b) 100 mg of itraconazole HCl, and (c) 100 mg of itraconazole HCl with beta-cyclodextrin in 900 mL of simulated gastric fluid (pH 1.2) at a stirring rate of 100 rpm

Tao et al. Int J Pharm. 2009;367:109-14.

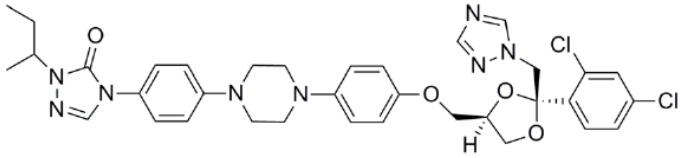


Parameter	Without food	With food
Cmax (ng/mL)	38.4	132
AUC (ng·h/mL)	722	1900
Tmax (hours)	3.3	4.0

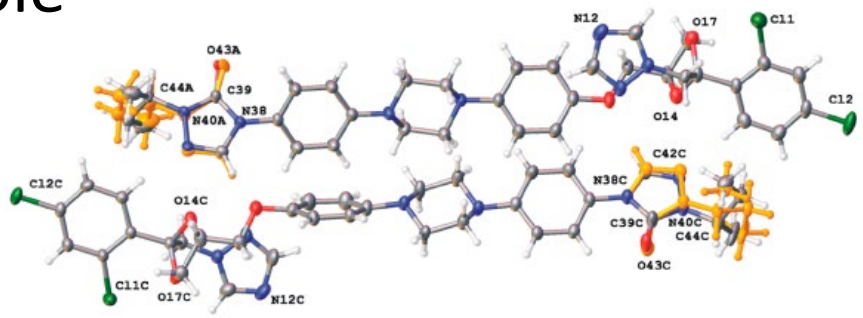
Figure 2. Time vs, concentration in plasma profile for a single dose of itraconazole capsules (100 mg dose) in healthy volunteers after fasting and after eating a meal. Parameters are given for these two experiments. A curve is also shown for a solution of itraconazole (100 mg, also containing cyclodextrin) given under fasted conditions.

Van Peer et al. Eur J Clin Pharmacol. 1989;36:423-6.

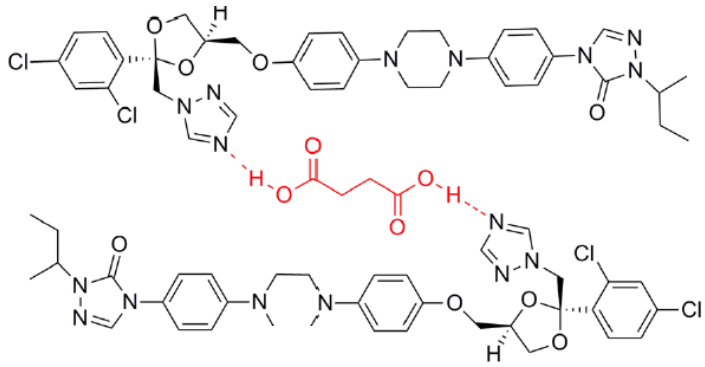
Crystal Engineering for Itraconazole

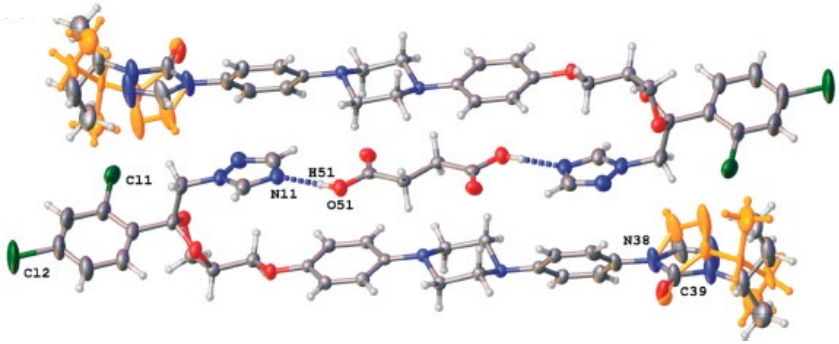


Itraconazole

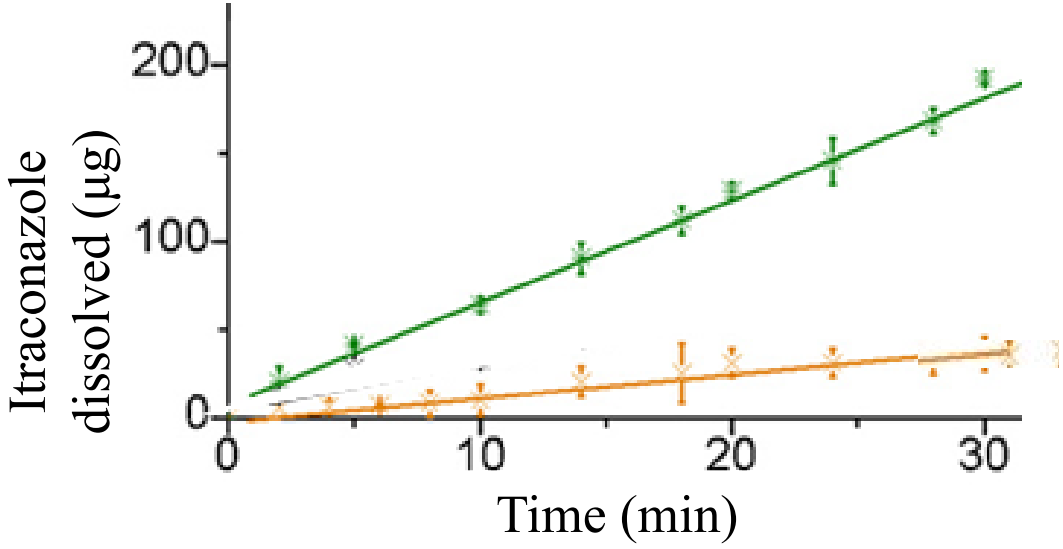


Itraconazole-Succinic Acid Co-Crystal





Dissolution profiles for 100 mg of intraconazole (orange) and 100 mg of intraconazole succinic acide (green) dissolving in 500 mL of water at pH 1.2 (hydrochloric acid buffer) at a stirring rate of 100 rpm.

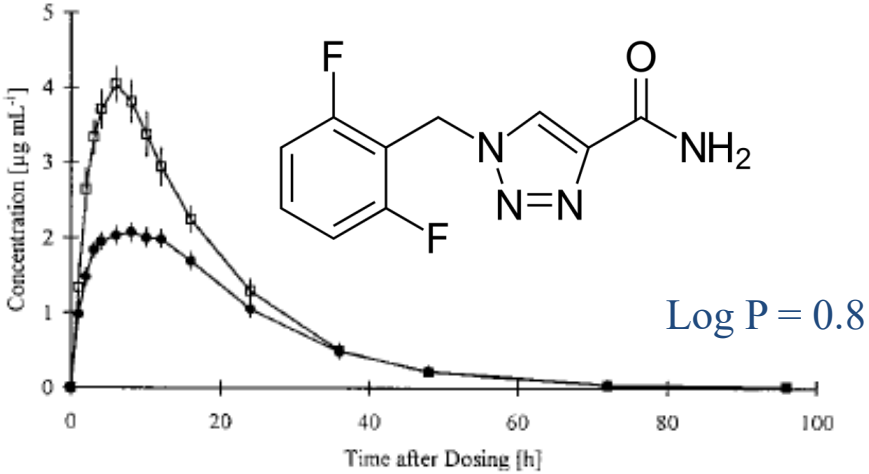


Itraconazole-Succinic Acid Co-Crystal

Itraconazole

Nonappa et al. Cryst Growth Des. 2013;13:346−51. (reference added after talk)

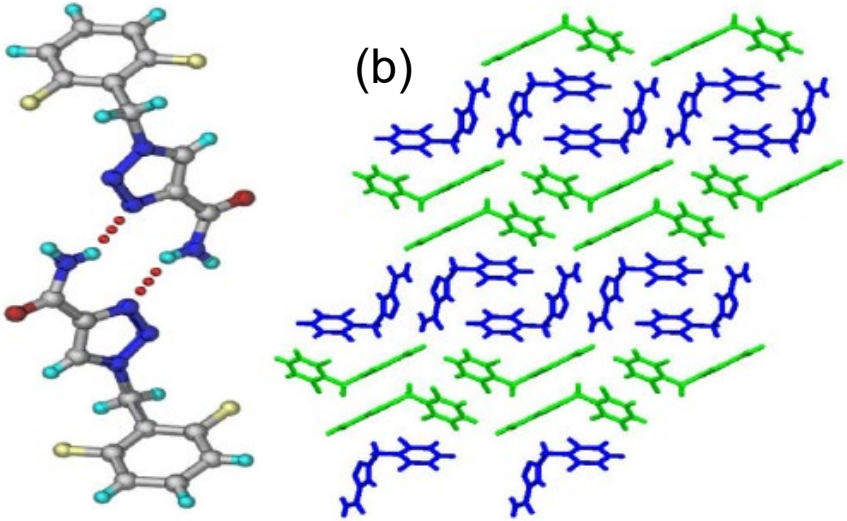
Effect of Food on Pharmacokinetics and Crystal Packing of Rufinamide



Log P = 0.8

Mean plasma concentrations of rufinamide in healthy volunteers treated with a single oral dose of 600 mg without (●) and with (○) food

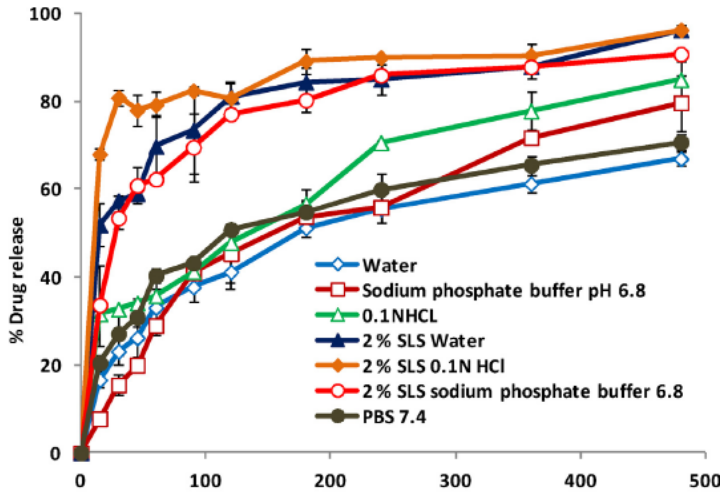
Cardot et al. Biopharm Drug Dispos. 1998;19:259-62.



(a) H-bonded dimer with ring motif

(b) Arrangement of molecules in the crystal structure

Salunke et al. J Pharm Biomed Analysis 2018;149:185–92.



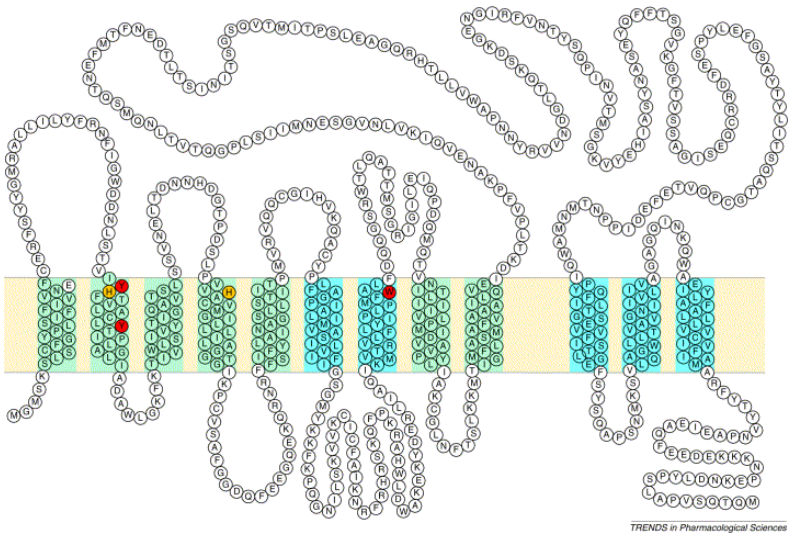
Dissolution profiles of rufinamide

Solubility profile of R (n = 3).

Media	pH	Conc. ± SD (µg/ml)
Water	7	30.56 ± 3.64
0.1 N HCl	1.4	30.26 ± 4.47
0.01 N HCl	2.15	31.91 ± 4.93
0.001 N HCl	3	25.97 ± 2.16
0.1 N KCl	5.3	31.32 ± 2.15
Citrate buffer	3	29.28 ± 3.71
Citrate buffer	5	28.08 ± 3.53
Acetate buffer	4.5	29.36 ± 2.93
Sodium phosphate buffer	6.85	28.50 ± 1.99
Phosphate buffer (PBS)	7.41	28.12 ± 1.67
1% Tween 80 0.1 N HCl	1.5	80.84 ± 7.2
2% Tween 80 0.1 N HCl	1.51	75.96 ± 1.61
1% SLS 0.1 N HCl	1.65	92.84 ± 0.63
2% SLS 0.1 N HCl	1.69	144.84 ± 2.94
1% Tween 80 PBS 7.4	8.03	62.06 ± 4.3
2% Tween 80 PBS 7.4	8.05	59.18 ± 5.86
1% Tween 80 Water	6.5	67.53 ± 1.57
2% Tween 80 Water	6.5	99.94 ± 5.13
1% SLS Water	8.23	56.07 ± 8.24
2% SLS Water	8.87	139.63 ± 4.58
1% Tween 80 sodium phosphate buffer 6.8	7.15	45.68 ± 2.88
2% Tween 80 sodium phosphate buffer 6.8	7.14	47.61 ± 4.35
1% SLS sodium phosphate buffer 6.8	7.11	158.58 ± 2.75
2% SLS sodium phosphate buffer 6.8	7.15	184.22 ± 7.56

Transporter-Mediated Drug Absorption

Human Dipeptide Transporter (hPEPT1)



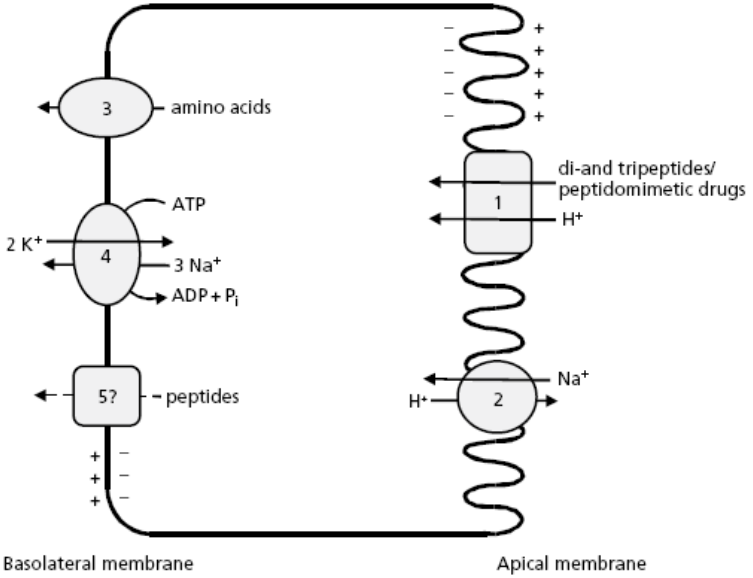
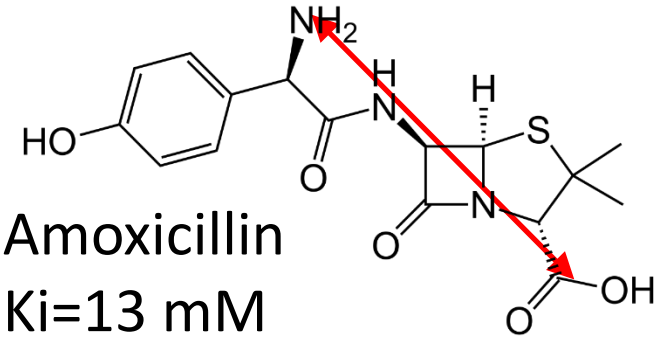


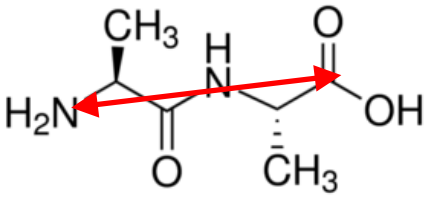
Table 2 Classification of affinity constants at PEPT1

Category (K_i range)	Substrate/inhibitor	K_i (mM)[a]
High affinity (< 0.5 mM)	Lys[Z(NO_2)]-Val	0.002 ± 0.001[b]
	Alafosfalin	0.19 ± 0.01
	Ala-Lys	0.21 ± 0.02
	Ceftibuten	0.34 ± 0.03
	Valaciclovir	0.49 ± 0.04
Medium affinity (0.5–5 mM)	Gly-Sar	1.1 ± 0.1
	Pro-Pro	1.2 ± 0.1
	δ-Aminolevulinic acid	1.5 ± 0.1
	Cloxacillin	3.0 ± 1.0
	Lys-Lys	3.4 ± 0.7
Low affinity (5–15 mM)	D-Ala-Lys	7.0 ± 0.6
	Cefadroxil	7.2 ± 0.8
	Pro-Ala	9.5 ± 0.4
	4-Aminophenylacetic acid	14 ± 1
	Cephalexin	14 ± 2



Amoxicillin
Ki=13 mM

Ala-Ala
Ki=0.08 mM



Brandsch et al. J Pharm Pharmacol. 2008;60:543–585.

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J Chem Educ. 2020;97:2212–2220

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Article

Teaching of Biopharmaceutics in a Drug Design Course: Use of GastroPlus as Educational Software

Rebecca M. Romero, Michael B. Bolger, Noam Morningstar-Kywi, and Ian S. Haworth*

Cite This: https://dx.doi.org/10.1021/acs.jchemed.0c00401

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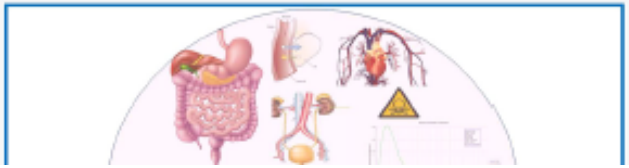
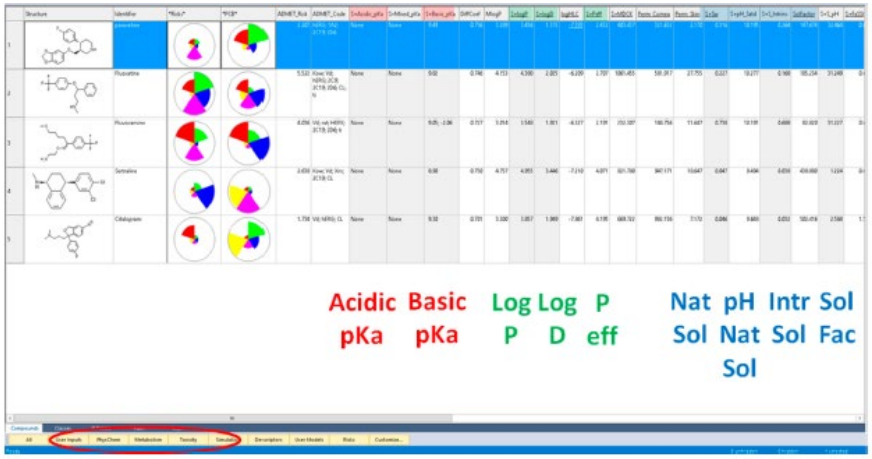
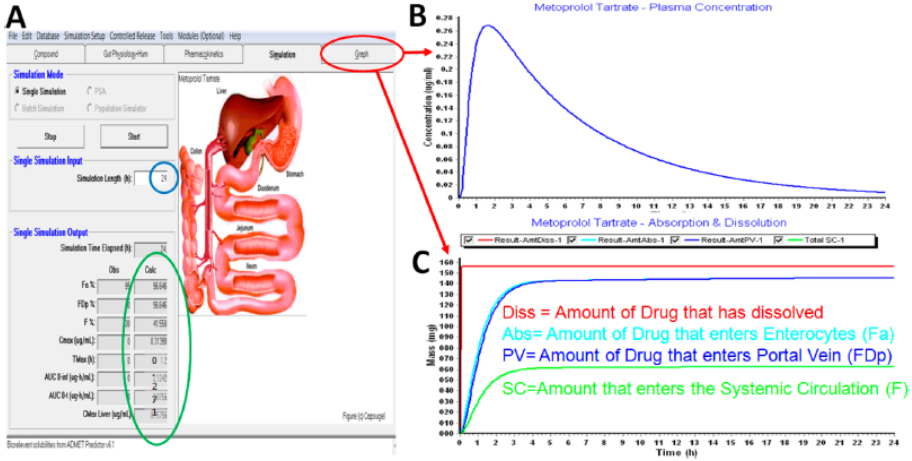
ABSTRACT: Drug design and development requires collaboration among scientists with diverse expertise. In early-stage drug design, establishment of promising drug candidates requires integration of structure-based molecular design with biopharmaceutics and ADMET (absorption, distribution, metabolism, excretion, and toxicity) principles.







Conclusions

1. Good oral absorption requires a drug with a mixture of hydrophilic and hydrophobic properties
2. Physicochemical data collected in vitro can be used to predict aspects of drug delivery in vivo
3. Drug delivery can be sensitive to the environment of the gastrointestinal tract
4. The solid-state form of the drug can influence its potential for oral delivery
5. Drug delivery can be simulated using physicochemical and biochemical data in physiologically-based pharmacokinetic (PB/PK) models