BCS Class 3 Biowaivers and Transporter Considerations

James E. Polli

jpolli@rx.umaryland.edu

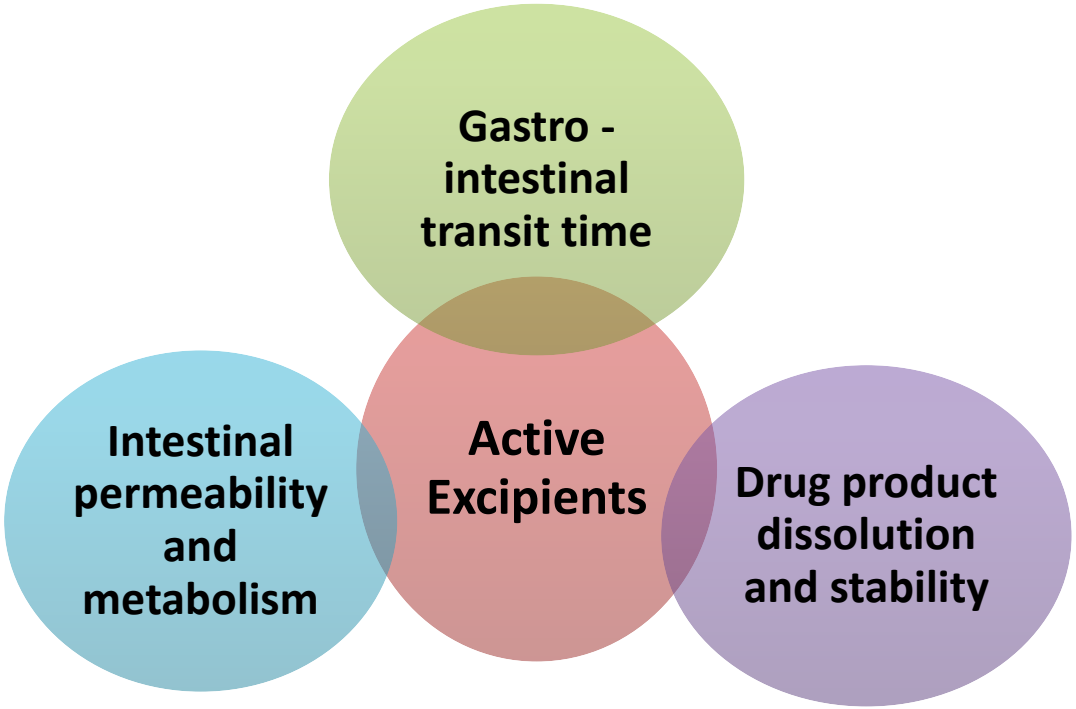
October 27, 2015

Outline

- Background
  - Prior human in vivo studies
- Recent series of in vivo human studies of 14 common excipients
- Potential transporter (or enzyme or nuclear receptor) x excipient interaction concern
- Conclusions

Excipient Effects

- Class 3 Biowaivers: Excipients should not modulate the rate and extent of drug absorption
- Class 3/low permeation compounds: essentially site-dependent absorption properties



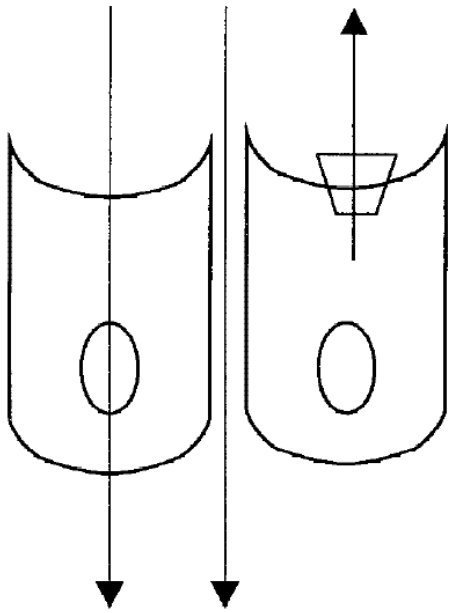
Chen ML, Straughn AB, Sadrieh SN, et al. (2006). Pharm Res. 24(1):73-80.
Pham AT, Lee PI. (1994). Pharm Res.11(10):1379-1384.; Rege BD, Yu LX, Hussain AS, Polli JE. (2001). J Pharm Sci. 90(11):1776-1786.

General importance of passive permeability

- “While our results do not completely refute the transporters-only hypothesis, they demonstrate that it is unlikely for transporters alone to explain most observations in transcellular drug transport, …”
- Matsson P, Fenu LA, Lundquist P, Wiśniewski JR, Kansy M, Artursson P. Quantifying the impact of transporters on cellular drug permeability. Trends Pharmacol Sci. 2015 May;36:255-62.

Need for moderate or low permeability for a material transporter effect

Apical Surface

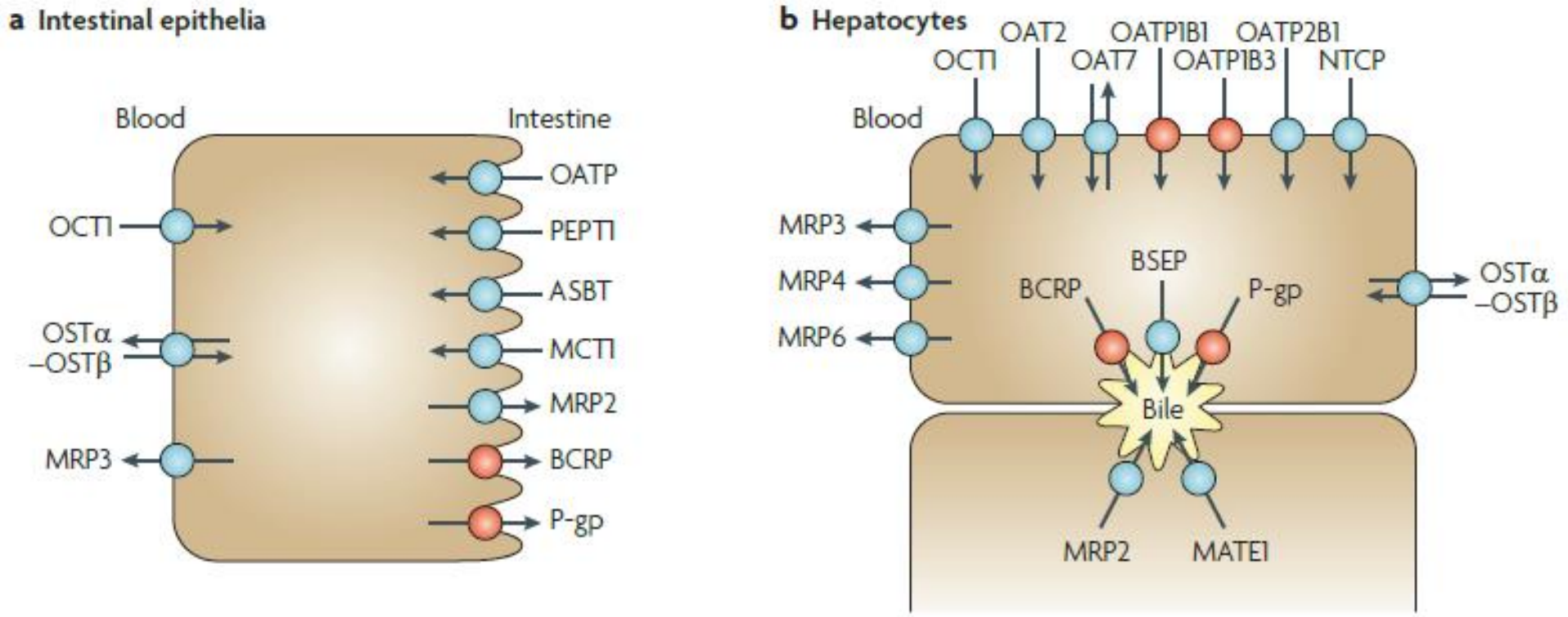


$$J_{AP-BL} = (P_{trans} + P_{para})C_d - \frac{V_{max}C_{cyto}}{K_m + C_{cyto}}$$

Basolateral Surface

- Lentz KA, Polli JW, Wring SA, Humphreys JE, Polli JE. 2000. Influence of passive permeability on apparent P-glycoprotein kinetics. Pharm Res 17(12): 1456-1460.

Tissue localization of transporters and their role in drug disposition



Giacomini KM et al. Membrane transporters in drug development. Nature Rev Drug Discov. 2010;9:215–236.

FDA Guidance for Industry

- Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations
- Draft, February 2012
- Content
  - General Strategies (i.e. in vitro studies, special in vivo clinical investigations, population pharmacokinetic screens)
  - Design of *In Vivo* Drug-Drug Interaction Studies
  - Labeling Recommendations
  - Appendicies: “Models for Determining When *In Vivo* Transporter-Mediated Drug Interaction Studies Are Needed”
    - P-gp, BRCP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 interaction decision trees

FDA Guidance for Industry

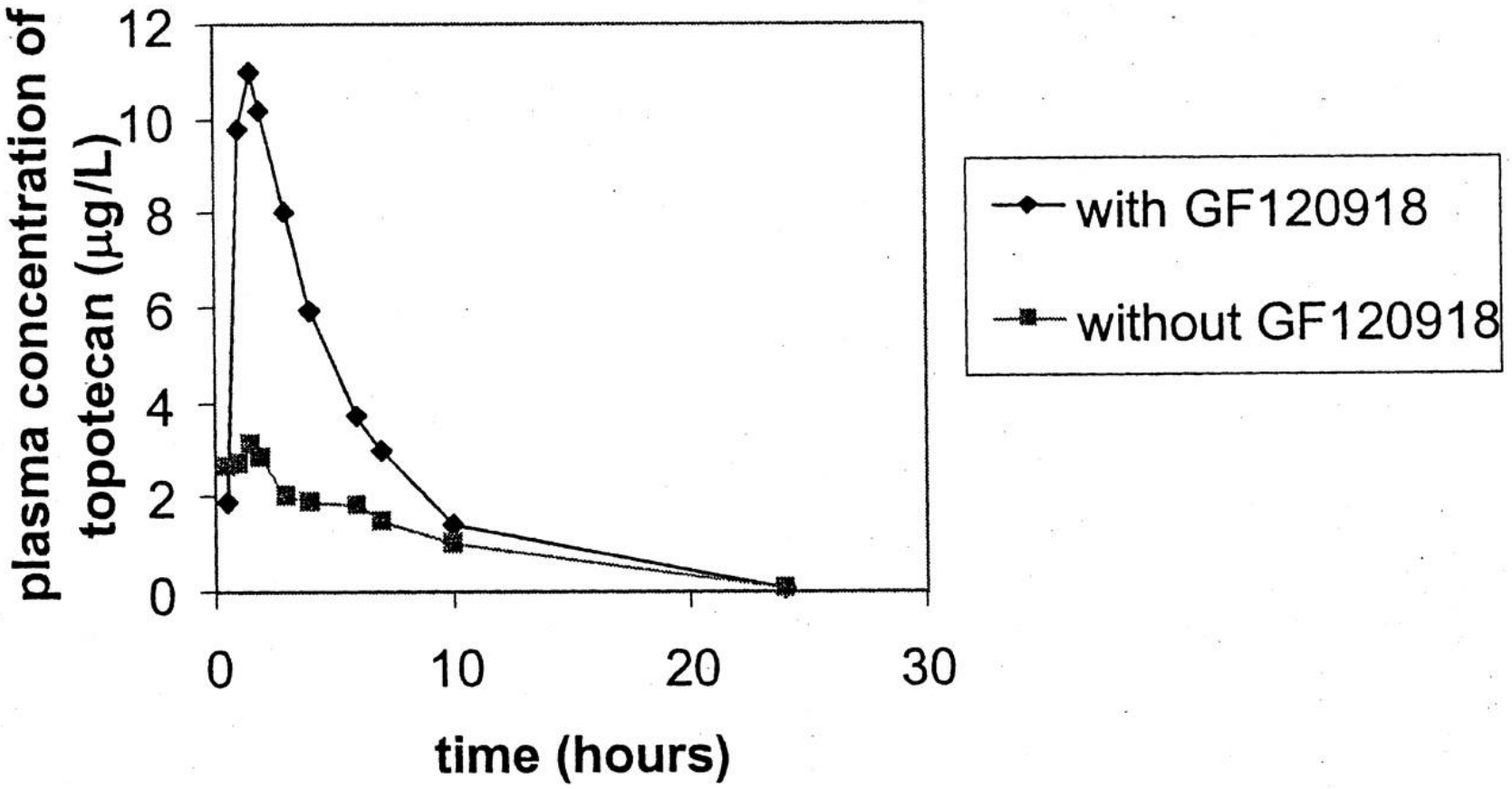
- Linear PK (i.e. relationship between dose and AUC) implies passive transport

- BCS class 1 biowaiver requires no excipient that affects rate or extent
- BCS class 3 biowaiver requires excipients to be qualitatively the same and quantitatively very similar (i.e. within SUPAC composition level 1 and 2)

Topotecan and GF120918

- CMF Kruijtzer et al. Increased Oral Bioavailability of Topotecan in Combination With the Breast Cancer Resistance Protein and P-Glycoprotein Inhibitor GF120918. Journal of Clinical Oncology 20:2943-2950, 2002.
- Motivation: Breast cancer resistance protein (BCRP) substantially limits the oral bioavailability of topotecan in mdr1a/1b(-/-) P-glycoprotein (P-gp) knockout and wild-type mice.
- Conclusion: Coadministration of the BCRP and P-gp inhibitor GF120918 resulted in a significant increase of the systemic exposure of oral topotecan. The apparent oral bioavailability increased from 40.0% without to 97.1% with GF120918.

Topotecan and GF120918

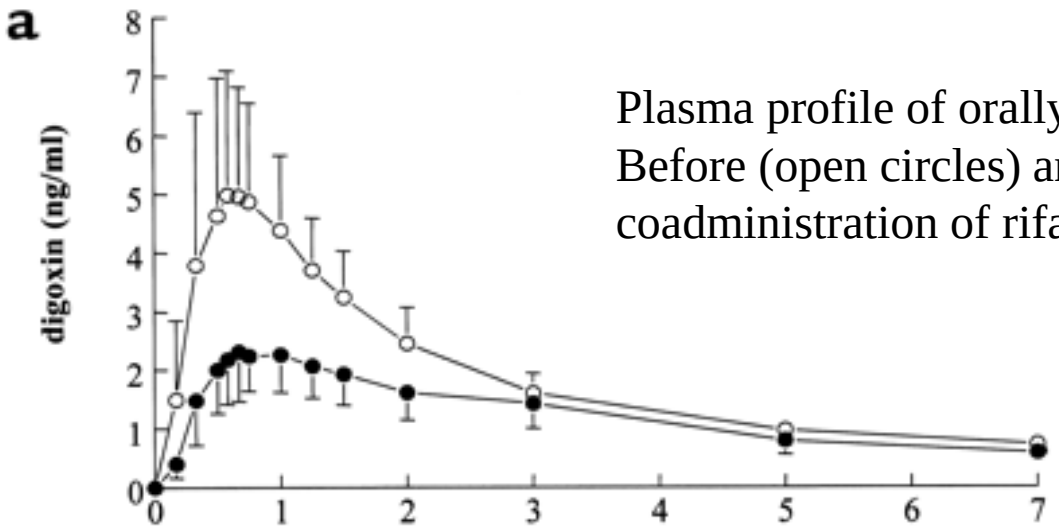


Representative plasma profiles of topotecan in a patient of cohort A. The dose of oral GF120918 was 1,000 mg.

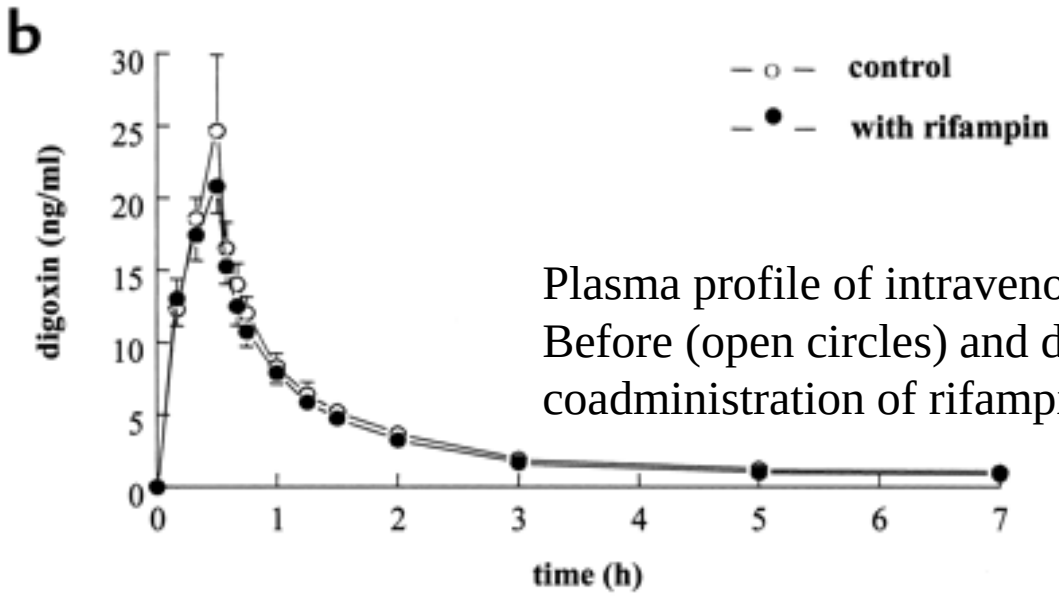
Interaction of Digoxin and Rifampin

- B. Greiner et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J. Clin. Invest. 104:147-153, 1999.
- Conclusion: Oral digoxin plasma profiles were lower after co-administration with rifampin, which increased intestinal P-gp content. Intraveneous digoxin plasma profiles were largely unchanged after co-administration with rifampin. The digoxin-rifampin interaction occurs at the level of the intestine (i.e. induction of P-gp by rifampin).

Interaction of Digoxin and Rifampin



Plasma profile of orally administered 1mg digoxin
Before (open circles) and during (filled circles) coadministration of rifampin.



Plasma profile of intravenously administered 1mg digoxin
Before (open circles) and during (filled circles) coadministration of rifampin.

Outline

- Background
  - Prior human in vivo studies
- Recent series of in vivo human studies of 14 common excipients
- Potential transporter (or enzyme or nuclear receptor) x excipient interaction concern
- Conclusions

Vaithianathan,S., Haidar, S.H., Zhang, X., Jiang, W., Avon, C., Dowling, T.C., Kane, M.A., Hoag, S.W., Flasar, M.H., Ting, T.Y., and Polli, J.E. (2015): Lack of In Vivo Impact of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. DOI: 10.1002/jps.24643. In press in *J. Pharm. Sci*.

Study Design

- Cimetidine and acyclovir
- 14 common excipients

- Fasted, single-dose, four-way crossover bioequivalence studies (n=24) in healthy human volunteers
  - Three test formulations and commercial oral liquid reference
  - Commercial solution of cimetidine HCl (eq 300mg base per 5ml) from Hi Tech Pharmacal
  - Commercial suspension of acyclovir (200mg per 5ml) from Hi Tech Pharmacal

Top 20 excipients in BCS Class 3 drugs

- Magnesium Stearate
- Microcrystalline Cellulose
- Lactose
- Starch
- Sodium Starch Glycolate
- Silicon Dioxide
- Povidone
- Sodium Lauryl Sulfate
- Croscarmellose Sodium
- Stearic Acid
- Pregelatinized Starch
- Hydroxypropylmethyl Cellulose
- Opadry
- Crospovidone
- Talc
- Calcium Phosphate
- Citric Acid
- Sucrose
- Methyl Cellulose
- Titanium Dioxide

Study 1A: Test capsule formulations with 100mg cimetidine per capsule

formulation	Excipient 1	Excipient 2	Excipient 3
CimTest-1	Microcrystalline Cellulose (300mg)	Hydroxypropyl-methyl Cellulose (45mg)	Sodium Lauryl Sulfate (25mg)
CimTest-2	Corn Starch (450mg)	Sodium Starch Glycolate (100mg)	Colloidal Silicon Dioxide (20mg)
CimTest-3	Dibasic Calcium Phosphate (300mg)	Sodium Lauryl Sulfate (25mg)	Crospovidone (50mg)

Formulation CimTest-1 and AcyTest-1 employed the same excipients.

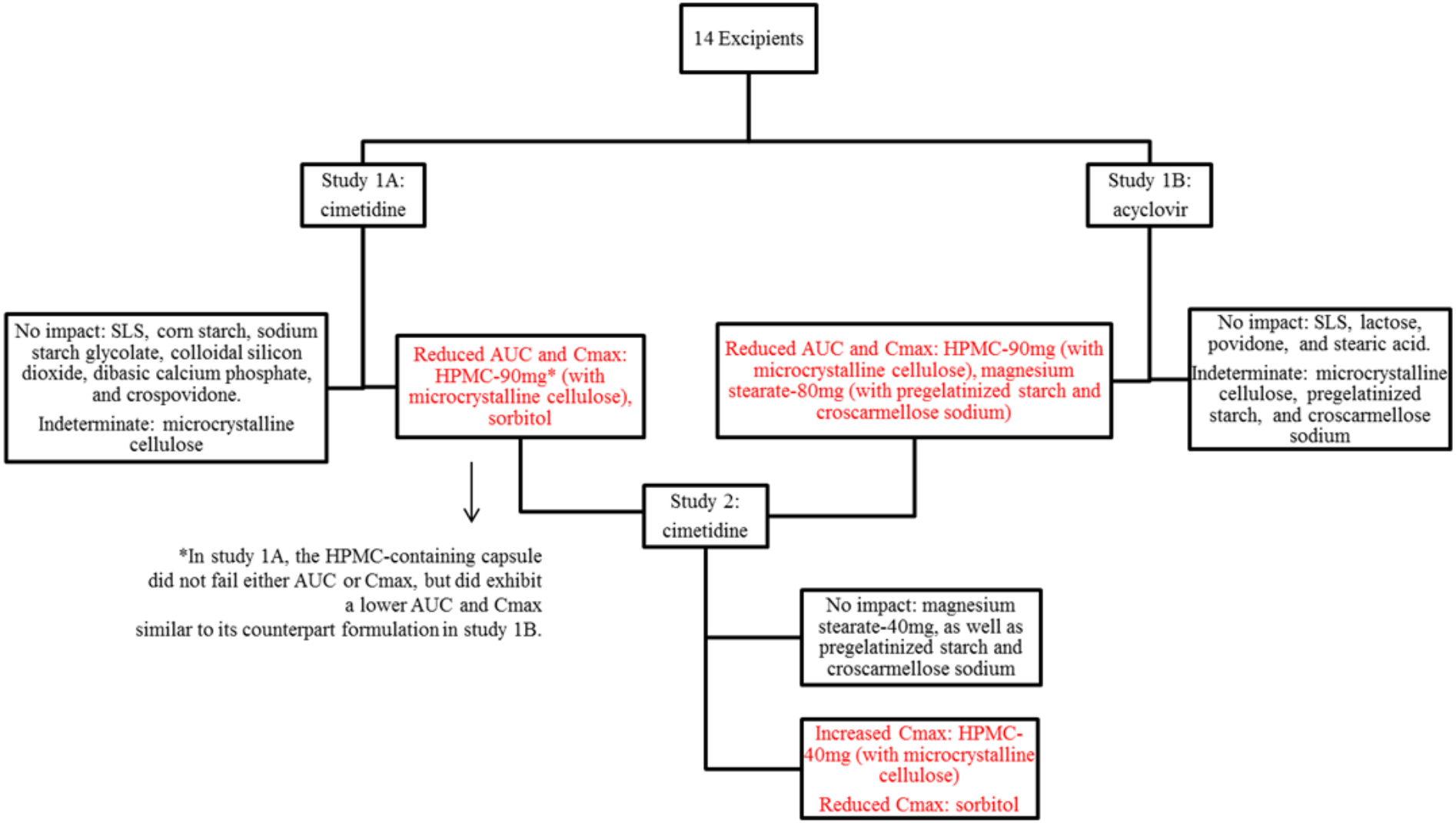
Sodium lauryl sulfate was included in formulations CimTest-1, CimTest-3, and AcyTest-1.

In the in vivo study of each formulation, two capsules were administered as a single dose of 200mg of drug.

Study 1A: Test capsule formulations with 100mg acyclovir per capsule

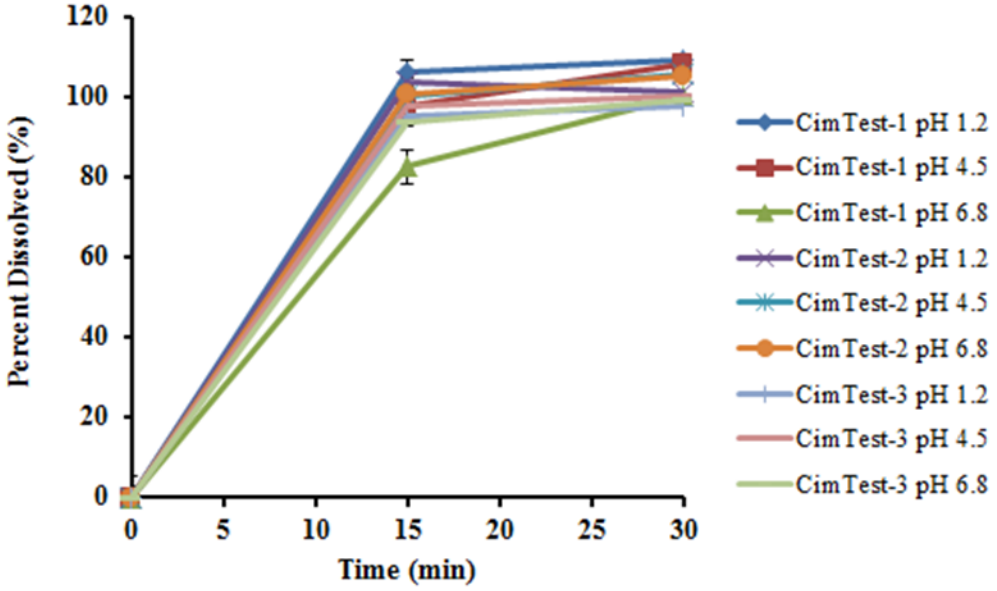
formulation	Excipient 1	Excipient 2	Excipient 3
AcyTest-1	Microcrystalline Cellulose (300mg)	Hydroxypropyl-methyl Cellulose (45mg)	Sodium Lauryl Sulfate (25mg)
AcyTest-2	Lactose (450mg)	Povidone (35mg)	Stearic Acid (40mg)
AcyTest-3	Pregelatinized Starch (100mg)	Croscarmellose Sodium (60mg)	Magnesium Stearate (40mg)

Flowchart of excipient influences across studies 1 and 2



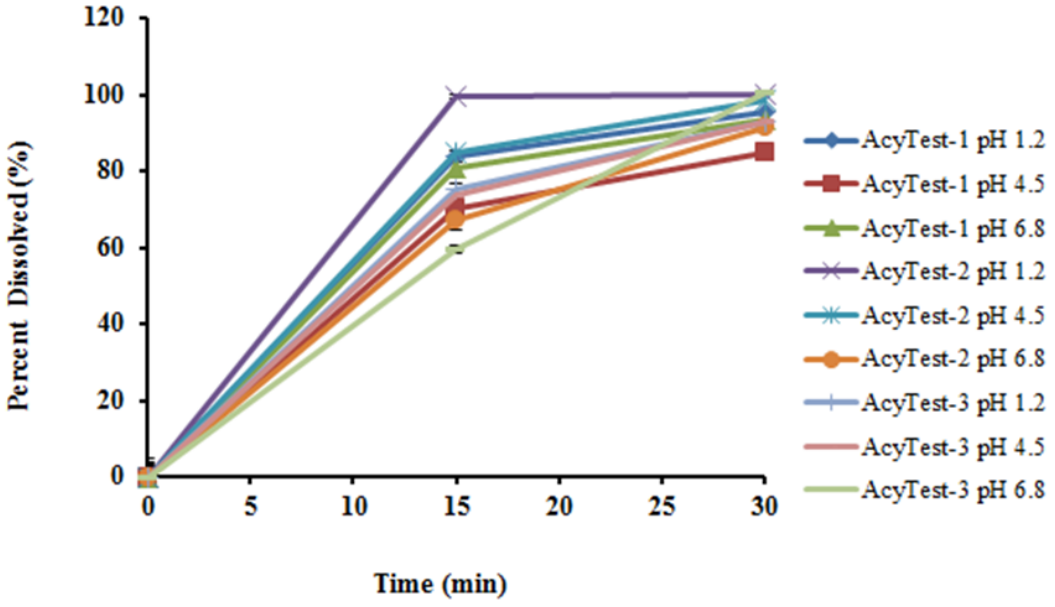
Study 1A: Cimetidine test capsule dissolution profiles

- All very rapidly dissolving except CimTest-1 at pH 6.8
- Appearance and identification, assay, impurity, content uniformity, and dissolution
- Assay was within 2% of target label dose
- Prototype formulations with higher HPMC amounts were slow

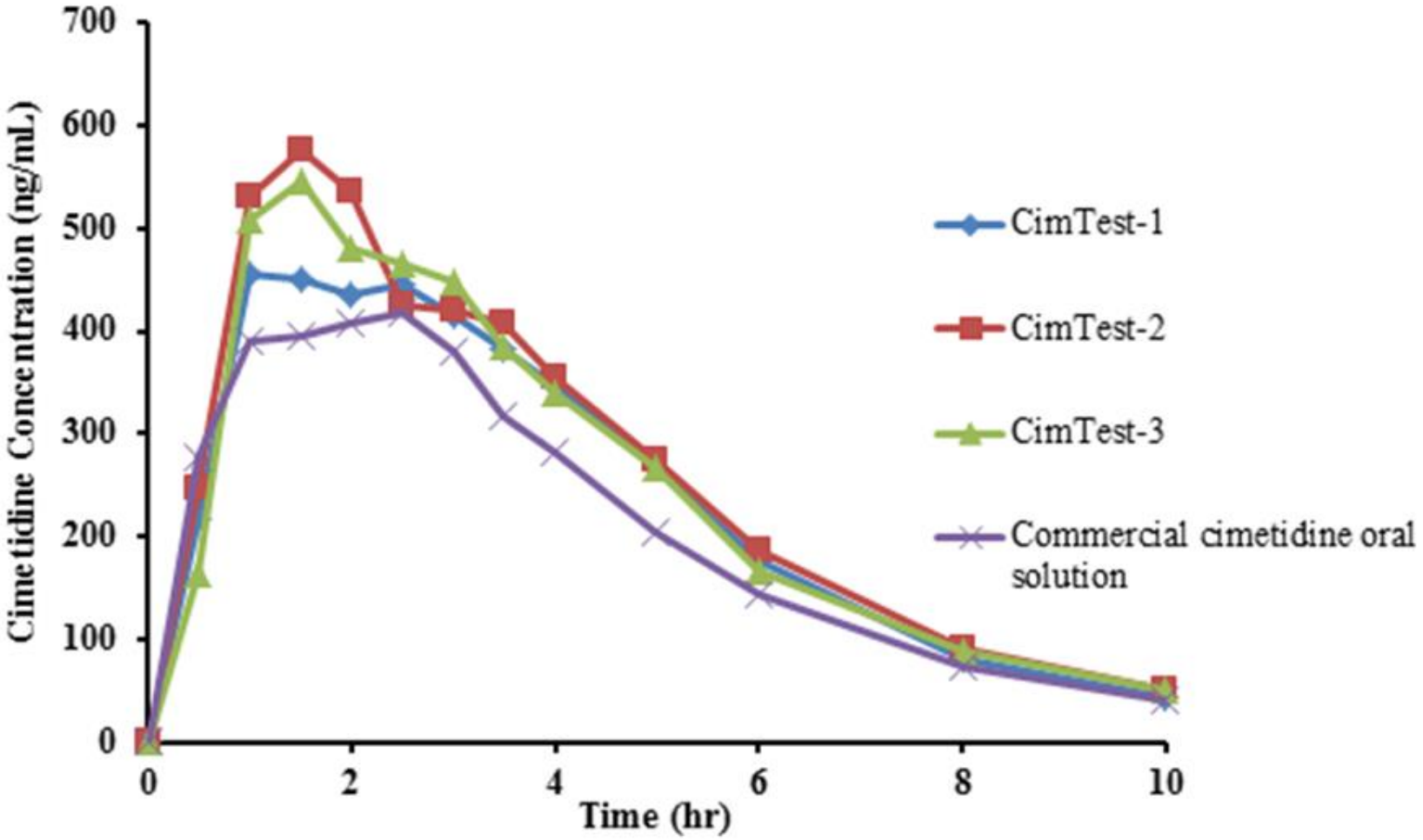


Study 1B: Acyclovir test capsule dissolution profiles

- Only AcyTest-2 in pH 1.2 and pH 4.5 was very rapidly dissolving
- Appearance and identification, assay, impurity and guanine, and content uniformity
- Assay was within 4.1% of target label dose



Study 1A: Cimetidine plasma concentration-time profiles



Study 1A: Cimetidine BE analysis

Formulation (vs solution)	Cmax point estimate	Cmax 90% CI	AUCt point estimate	AUCt 90% CI
Test1	120.4	107.7-134.6	112.0	104.6-119.8
Test2	132.9	118.9-148.6	123.3	115.2-131.9
Test3	134.9	120.7-150.8	117.1	109.3-125.3

Study 1A: Cimetidine BE analysis

Formulation (vs CimTest-2)	Cmax point estimate	Cmax 90% CI	AUCt point estimate	AUCt 90% CI
CimTest-1	90.6	81.0-101.3	90.9	84.9-97.2
CimTest-3	101.5	90.8-113.4	95.0	88.8-101.6
Solution	75.2	67.3-84.1	81.1	75.8-86.8

Cimetidine solution

- Reference
  - Commercial solution of cimetidine HCl (eq 300mg base per 5ml)
  - Hi Tech Pharmacal (Amityville, NY 11701)
- Each 5 ml (1 teaspoonful) contains cimetidine hydrochloride equivalent to 300mg; alcohol, 2.8%. In addition, the oral solution contains the following inactive ingredients: FD&C Yellow No. 6, flavor hydrochloric acid, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin, sodium, sodium chloride, dibasic sodium phosphate anhydrous, sorbitol and water. The pH range is 5.1 to 5.7.
- HiTech's cimetidine oral solution (per 5 mL):
  - Sorbitol: measured 2355(±8) mg/5mL or 1568(±5) mg/3.33mL

Sorbitol effect

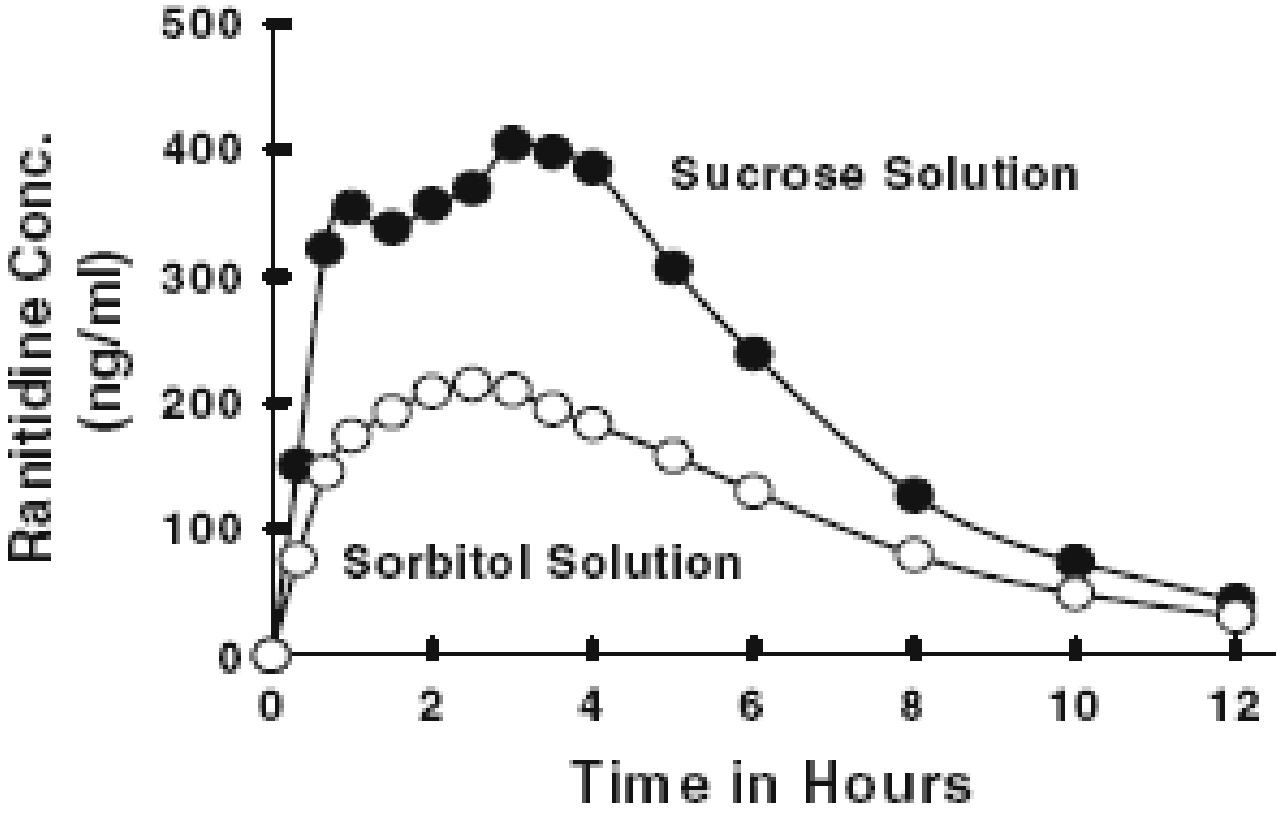


Fig. 1. Mean plasma concentrations of ranitidine in 20 healthy volunteers after administration of 150 mg ranitidine solution with addition of 5 Gm of sorbitol (*open circle*) or 5 Gm of sucrose (*solid circle*).

Chen, M.-L. et al. Pharm Res. 24:73- 80(2007)

Sorbitol effect

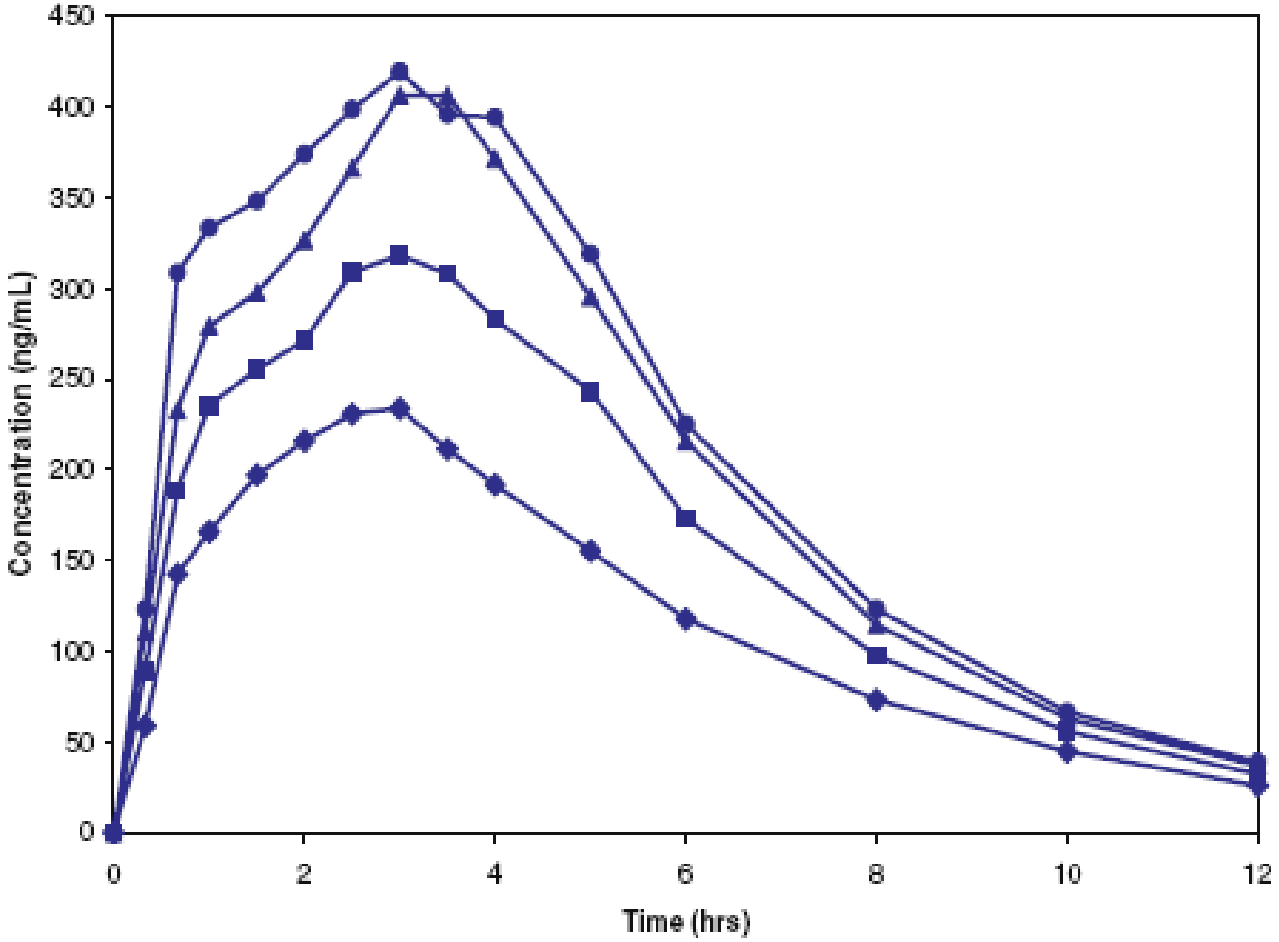
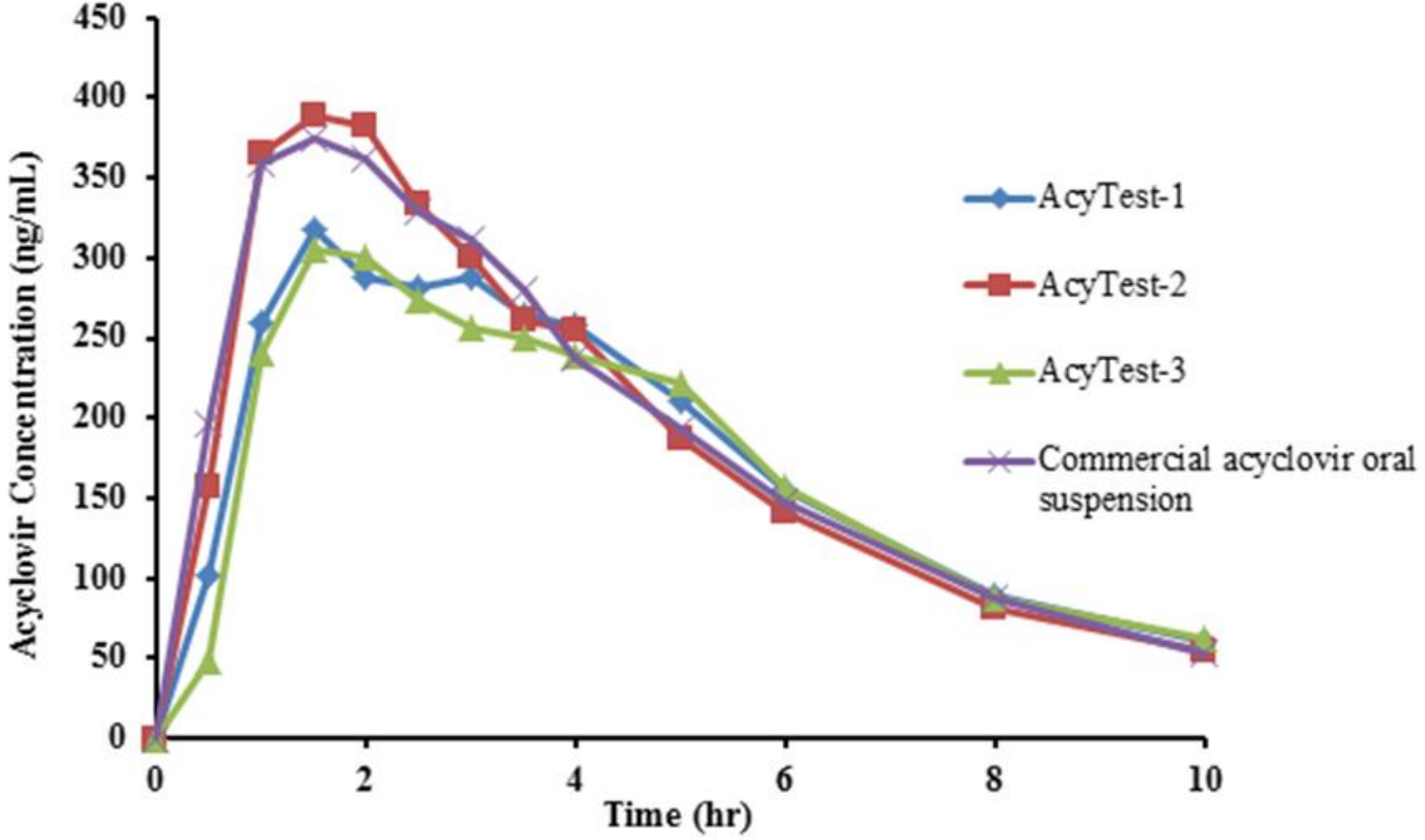


Fig. 4. Mean plasma concentrations of ranitidine in 24 healthy volunteers after administration of 150 mg ranitidine solution with addition of 0 (*closed circle*), 1.25 (*triangle*), 2.5 (*square*), and 5 Gm (*diamond*) of sorbitol.

Chen, M.-L. et al. Pharm Res. 24:73- 80(2007)

Study 1B: Acyclovir plasma concentration-time profiles



Study 1B: Acyclovir BE analysis

Formulation (vs suspension)	Cmax point estimate	Cmax 90% CI	AUCt point estimate	AUCt 90% CI
AcyTest-1	82.7	72.1-94.9	91.7	80.4-104.7
AcyTest-2	102.9	89.7-118.1	97.4	85.3-111.2
AcyTest-3	87.1	75.9-99.9	87.6	76.7-99.9

Study 1B: Acyclovir BE analysis

Formulation (vs AcyTest-2)	Cmax point estimate	Cmax 90% CI	AUCt point estimate	AUCt 90% CI
AcyTest-1	80.3	70.0-92.1	94.2	82.5-107.5
AcyTest-3	84.6	73.7-97.0	89.9	78.7-102.6
Suspension	97.1	84.7-111.4	102.7	89.9-117.2

Acyclovir suspension

- Reference
  - Commercial suspension of acyclovir (200mg per 5ml)
  - Hi Tech Pharmacal (Amityville, NY 11701)
- Each teaspoonful (5 ml) of acyclovir suspension , USP, for oral administration contains 200mg of acyclovir and the inactive ingredients artificial banana flavor carboxymethylcellulose sodium, glycerin, methylparaben, 0.1%, microcrystalline cellulose, propylparaben 0.02%, purified water and sorbitol.
- HiTech's suspension of acyclovir (per 5 mL):
  - Sorbitol: measured 1503(±21) mg /5mL

Study 2: Test capsule formulations with 100mg cimetidine per capsule

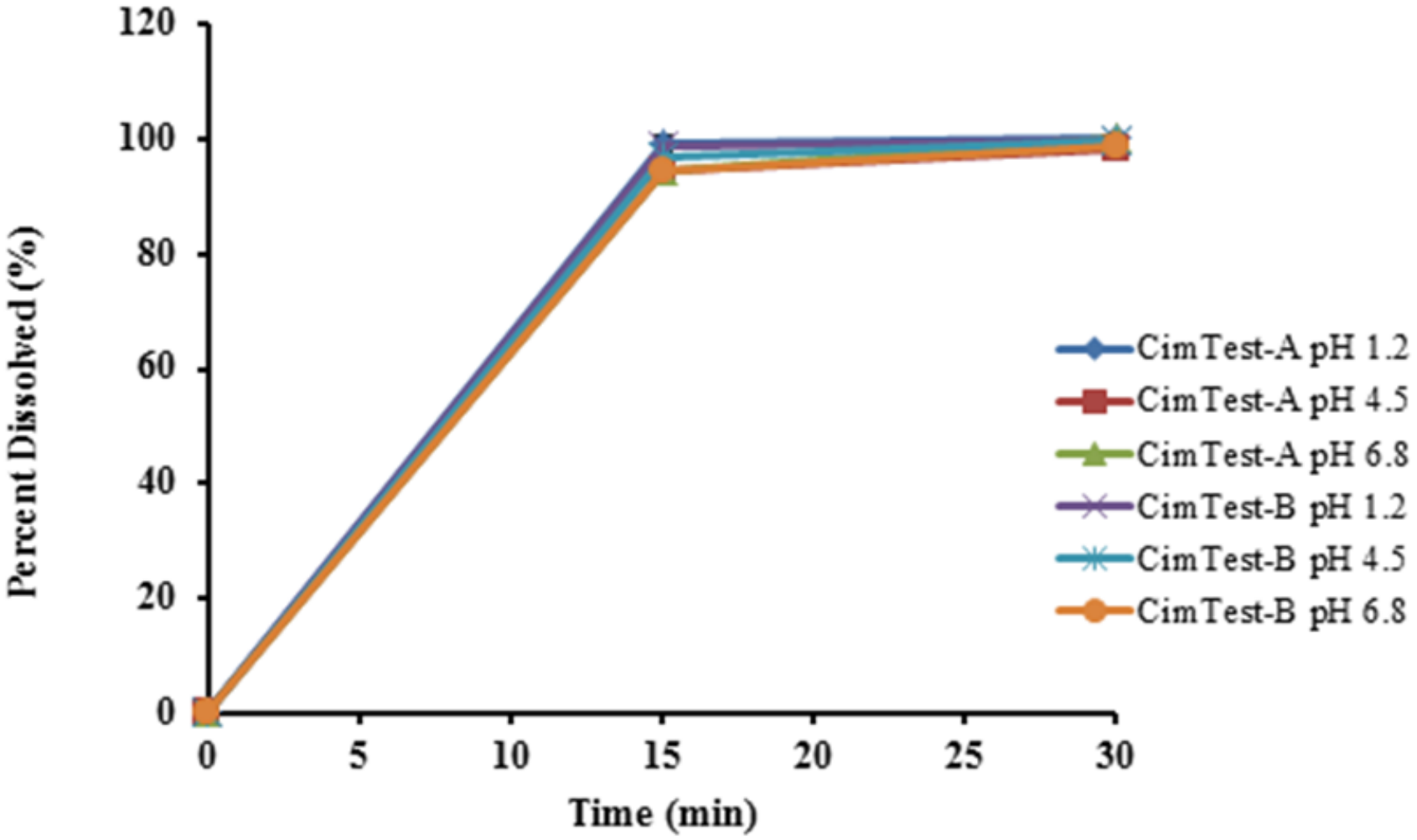
formulation	Excipient 1	Excipient 2	Excipient 3
CimTest-A	Microcrystalline Cellulose (300mg)	Hydroxypropyl-methyl Cellulose (20mg)	Sodium Lauryl Sulfate (25mg)
CimTest-B	Pregelatinized Starch (100mg)	Croscarmellose Sodium (60mg)	Magnesium Stearate (40mg)

CimTest-A is CimTest-1 (and AcyTest-1) but reduced HPMC from 45mg to 20mg per capsule.

CimTest-B is AcyTest-3 but reduced magnesium stearate from 40mg to 20mg per capsule. Also changed from Turbula mixer to V-blender.

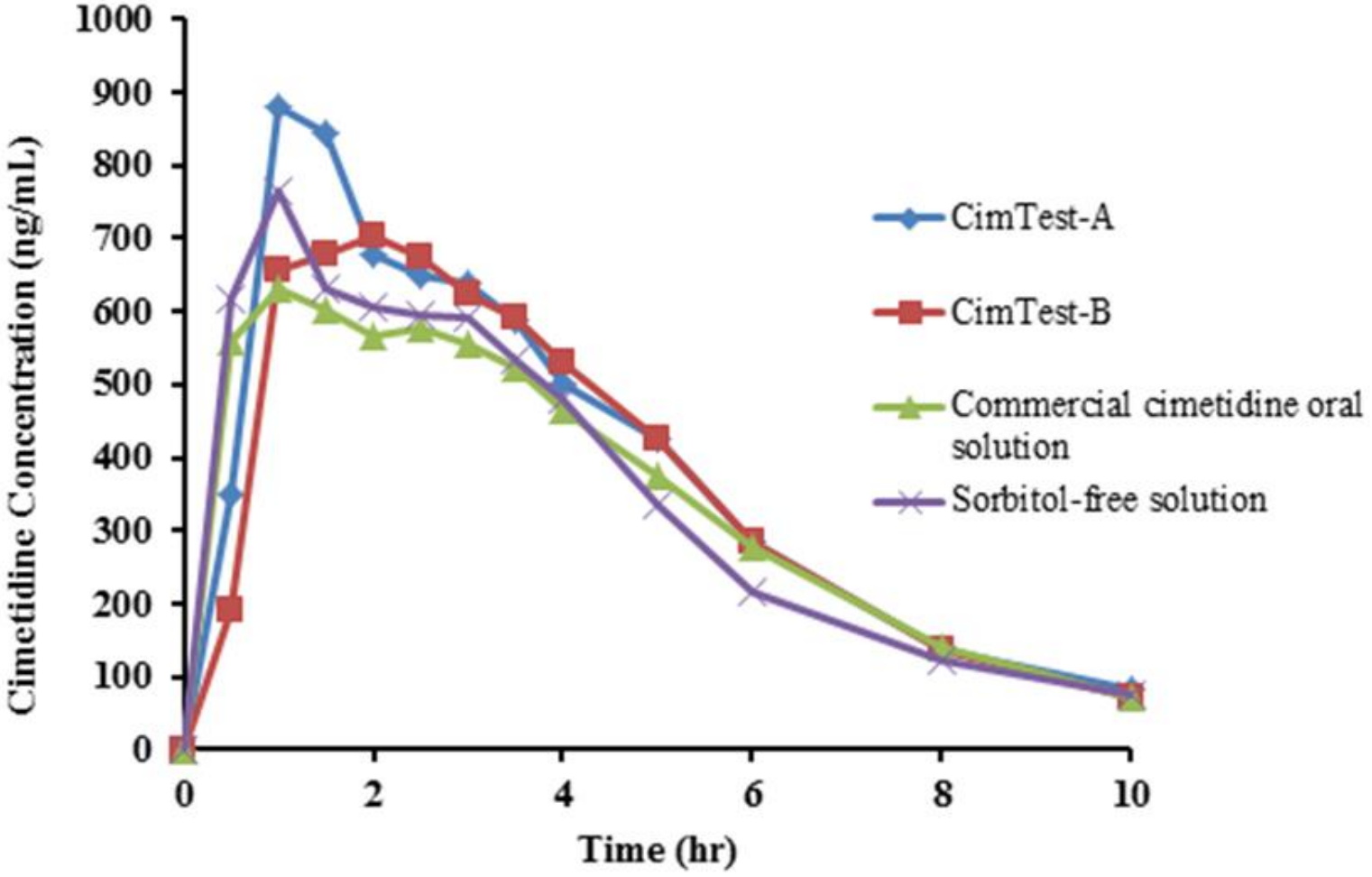
In the in vivo study of each formulation, two capsules were administered as a single dose of 200mg of drug.

Study 2: Cimetidine test capsule dissolution profiles



All profiles were very rapidly dissolving.

Study 2: Cimetidine plasma concentration-time profiles



Study 2: Cimetidine BE analysis

Formulation (vs sorbitol-free solution)	Cmax point estimate	Cmax 90% CI	AUCt point estimate	AUCt 90% CI
CimTest-A	122.1	109.4-136.2	112.2	104.4-120.6
CimTest-B	105.0	94.1-117.2	105.2	97.6-113.0
Commercial solution	86.9	77.9-97.0	100.2	93.2-107.7

Max amount of excipients that BCS class 3 biowaivers can accommodate

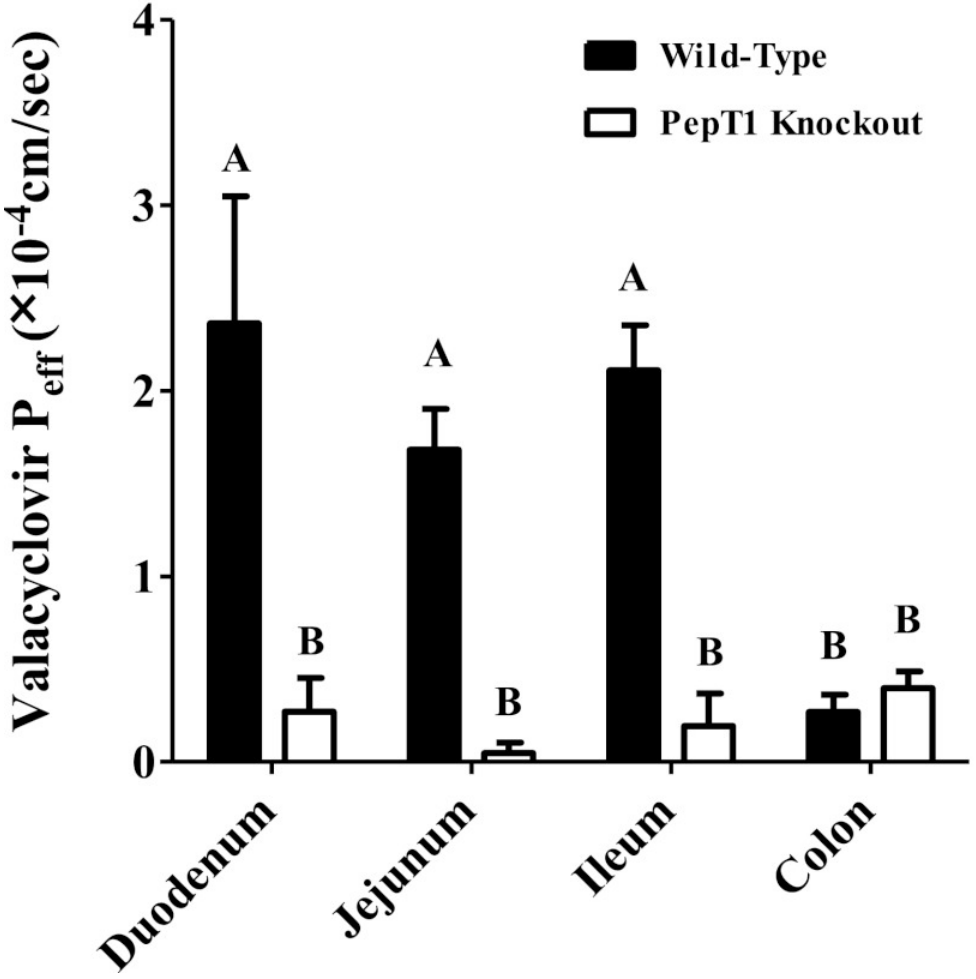
Excipient	Max (mg)
Microcrystalline Cellulose	Q1 and Q2
HPMC	Q1 and Q2
Sodium Lauryl Sulfate	50
Corn Starch	900
Sodium Starch Glycolate	200
Colloidal Silicon Dioxide	40
Dibasic Calcium Phosphate	600

Excipient	Max (mg)
Crospovidone	100
Lactose	900
Povidone	70
Stearic Acid	80
Pregelatinized Starch	200
Croscarmellose Sodium	120
Magnesium Stearate	40

Outline

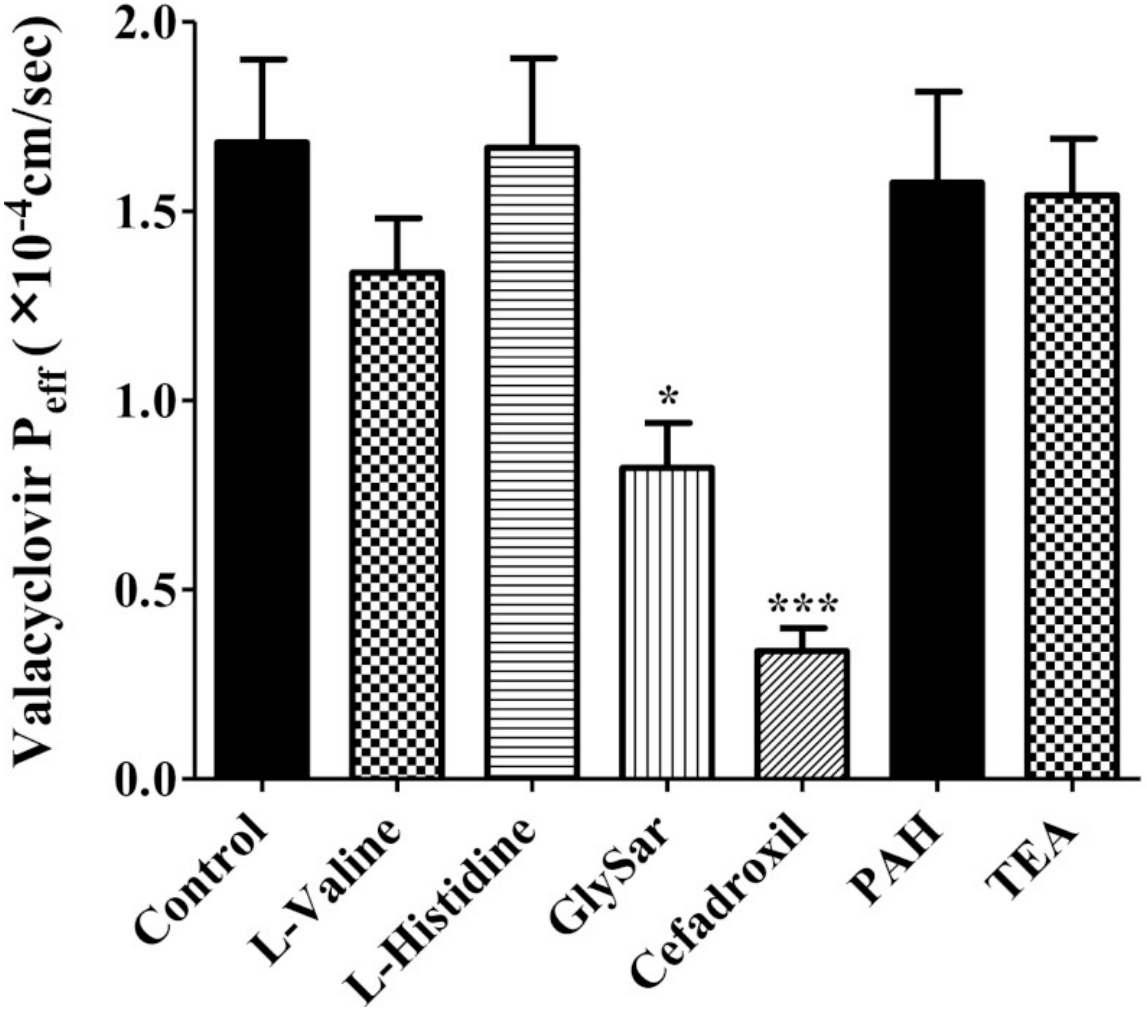
- Background
  - Prior human in vivo studies
- Recent series of in vivo human studies of 14 common excipients
- Potential transporter (or enzyme or nuclear receptor) x excipient interaction concern
- Conclusions

Permeability of valacyclovir in different intestinal segments of wild-type and *PepT1* knockout mice



Bei Yang and David E. Smith. Significance of Peptide Transporter 1 in the Intestinal Permeability of Valacyclovir in Wild-Type and PepT1 Knockout Mice. Drug Metab Dispos. 2013 Mar; 41: 608–14.

Effect of potential inhibitors on valacyclovir jejunal perfusion permeability in wild-type mice



Tompkins, L., Lynch, C., Haidar, S., Polli, J.E., and Wang, H. (2010): Effects of Commonly Used Excipients on the Expression of CYP3A4 in Colon and Liver Cells. DOI 10.1007/s11095-010-0170-2. *Pharm. Res*. 27:1703–1712.

Effects of Commonly Used Excipients

- 19 excipients, including hydroxypropyl methylcellulose, pregelatinized starch, croscarmellose sodium, crospovidone, and polysorbate-80
- Human PXR activation assays; CYP3A4 expression in immortalized human liver cells (HepG2 and Fa2N4), human primary hepatocytes (HPH), and the intestinal LS174T cell models
- Pregnane X receptor (PXR) is a promiscuous nuclear receptor known to bind a variety of structurally-diverse compounds and regulate a number of metabolically-important genes (e.g. CYP3A4, CYP2B6, MDR1).

Effects of selected excipients on the expression of CYP3A4 and MDR1

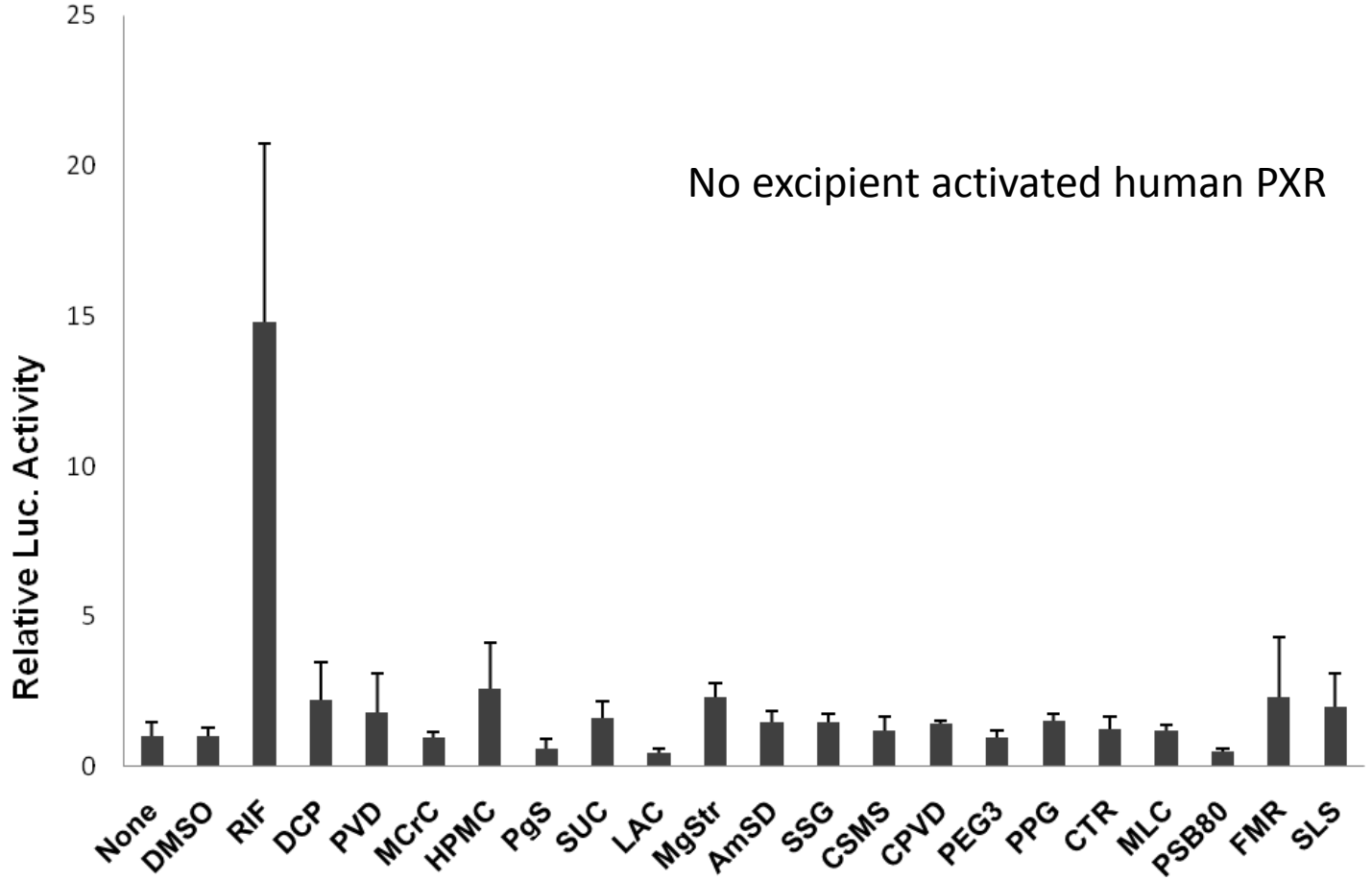
	Fa2N4		HPH		LS174T	
Excipient	mRNA	Protein	mRNA	Protein	CYP3A4	MDR1
HPMC	↑	↓	=	X	↓	↓[a]
PgS	=	=	↓	X	↓	↓
CCS	↑	=	↑	X	↓[a]	↓[a]
X-PVP	↑[a]	↓	=	X	↓	↓[a]
PS-80	↑/↓[b]	↓	↓	↓	=	=

[a] Change was not statistically significant.

[b] At low dose, PS-80 increased CYP3A4 expression 3.02-fold, but high dose PSB80 decreased expression to 0.37-fold.

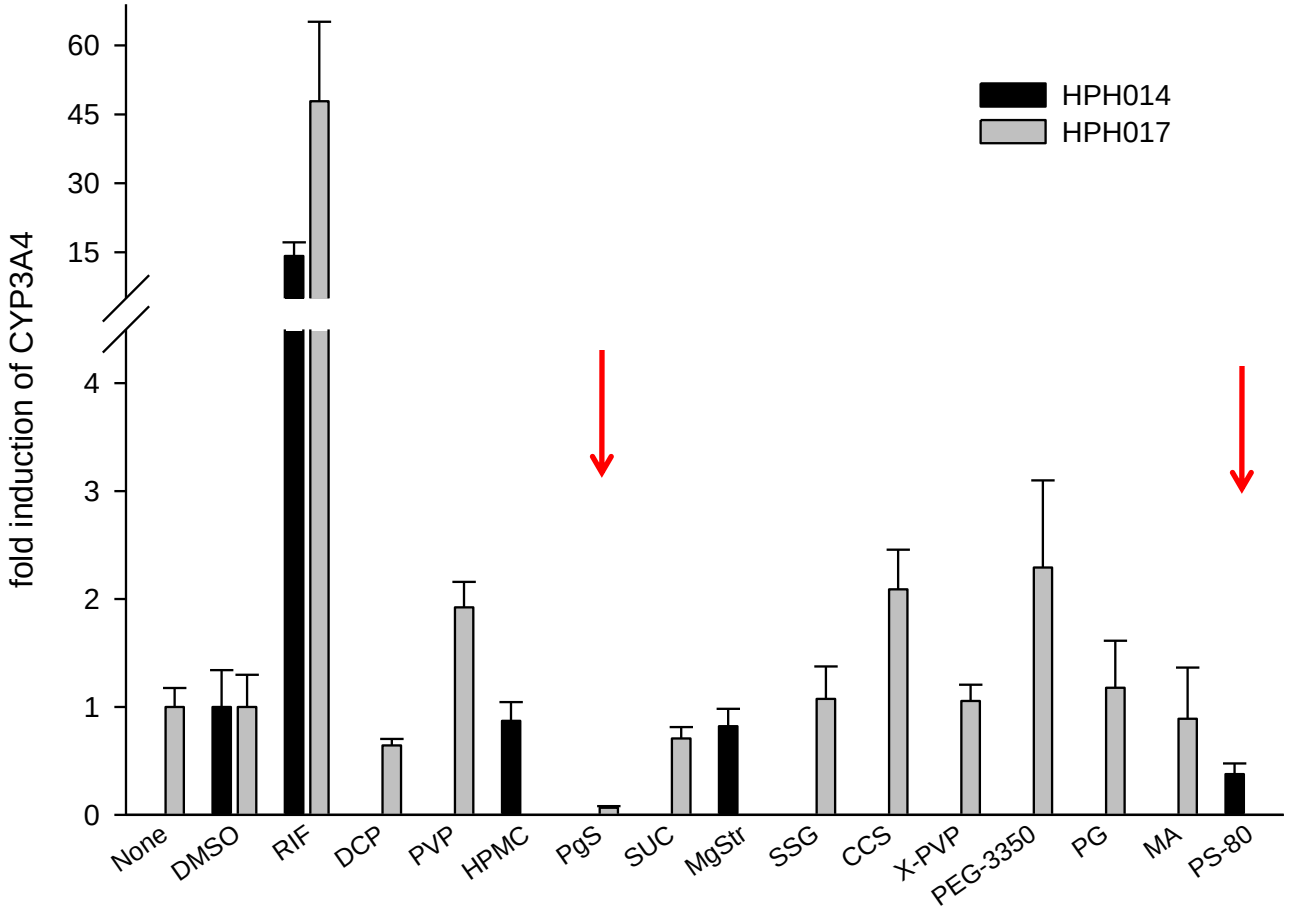
HPMC, pregelatinized starch, and polysorbate 80 – some tendency to repress

PXR reporter assay in HepG2 cells

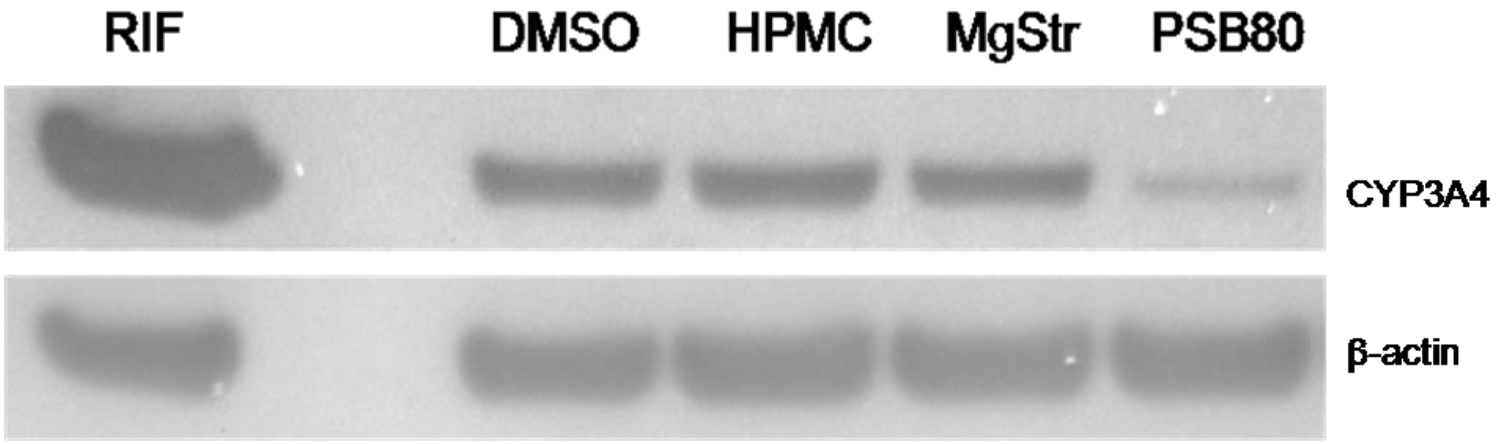


Excipient effect on CYP3A4 expression in human primary hepatocytes

No excipient practically induced CYP3A4



Excipient effect on CYP3A4 expression in human primary hepatocytes



Excipient Effect on Drug Permeability

Excipient	Quantity in IR dosage form	Concentration used in Caco-2 study
Lactose	500 mg	2 mg/ml
Sodium lauryl sulfate	10 mg	0.04 mg/ml
Tween 80	450 mg	1.8 mg/ml
HPMC	30 mg	0.12 mg/ml
Docusate sodium	5 mg	0.02 mg/ml
EDTA	15 mg	0.06 mg/ml
Propylene glycol	3.75 ml	1.5 %v/v
PEG 400	3.75 ml	1.5 %v/v
Anhydrous cherry flavor	0.15 ml	0.006 %v/v

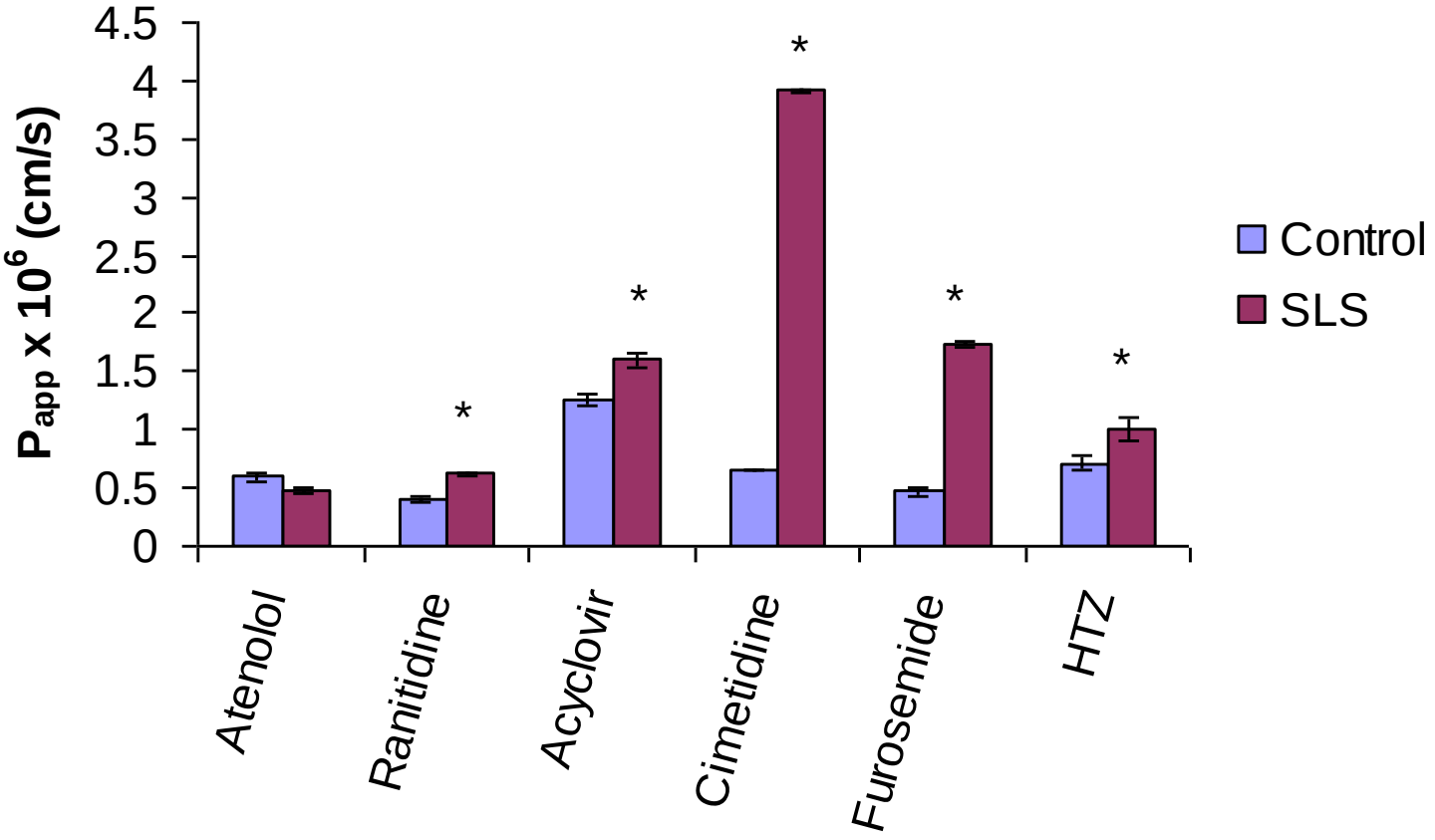
- Concentration calculated assuming a unit dose weight of 500 mg of solid formulation and 15 ml for liquid formulation
- Rege, B.D., Yu, L.X., Hussain, A.S., and Polli, J.E. (2001). Effect of common excipients on Caco-2 transport of low permeability drugs. *J. Pharm. Sci*. 90:1776-1786.

HPMC

Drug	Papp (SEM) x 10^6 [cm/sec]	
	Control	HPMC
Atenolol	0.592 (0.041)	0.506 (0.009)
Ranitidine	0.405 (0.031)	0.484 (0.025)
Acyclovir	1.26 (0.05)	1.31 (0.04)
Cimetidine	0.650 (0.007)	0.898 (0.065)*
Furosemide	0.466 (0.029)	0.428 (0.048)
HCTZ	0.710 (0.063)	0.790 (0.027)

* p = 0.035

Sodium Lauryl Sulfate



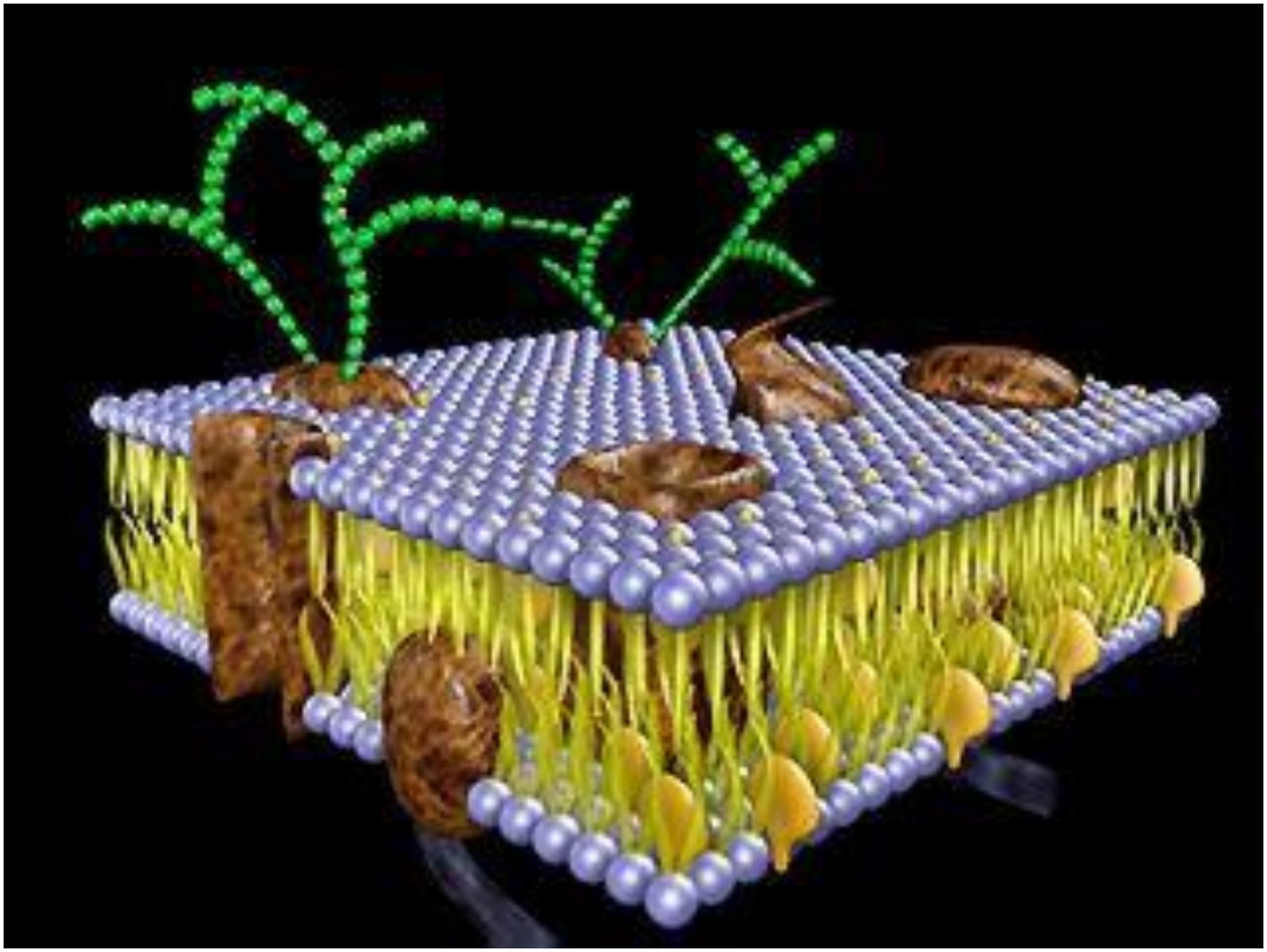
* $p < 0.05$

Tween 80

Drug	Papp (SEM) x 10^6 [cm/sec]	
	Control	Tween 80
Atenolol	0.592 (0.041)	0.649 (0.036)
Ranitidine	0.405 (0.031)	0.713 (0.039)*
Acyclovir	1.26 (0.05)	1.27 (0.02)
Cimetidine	0.650 (0.007)	1.52 (0.06)*
Furosemide	0.466 (0.029)	3.49 (0.35)*
HCTZ	0.710 (0.063)	1.81 (0.06)*

* $p < 0.05$

Singer-Nicolson Fluid Mosaic Model



Influence of Excipients on Anisotropy

Fluidity Modulator or Nonionic Surfactant	**Steady state anisotropy as % of control**	
	DPH	TMA-DPH
Cholesterol	186.6 ± 2.4	98.5 ± 0.5
Benzyl Alcohol	90.4 ± 1.1	87.1 ± 1.6
Tween 80		
0.025 mM	65.2 ± 1.8	97.9 ± 1.4
1 mM	50.9 ± 2.6	100.0 ± 0.5
Cremophor EL		
0.025 mM	64.0 ± 0.9	99.3 ± 0.7
1 mM	63.1 ± 0.9	99.9 ± 0.8
Vitamin E TPGS		
0.025 mM	105.8 ± 0.6	101.2 ± 1.6
1 mM	128.7 ± 3.5	102.8 ± 1.1
N-octyl glucoside	97.0 ± 1.3	99.2 ± 0.9

Rege, B.D., Kao, J.P.Y., and Polli, J.E. (2002): Effects of nonionic surfactants on membrane transporters in Caco-2 cell monolayers. *Eur. J. Pharm Sci*. **16**:237-246.

Effect of Nonionic Surfactant on Permeability

- Tween 80
  - R123 and gly-sar
- Cremophor EL
  - R123 and (mildly) benzoic aid
- Vitamin E TPGS
  - R123

Consideration in the Use of In Vitro Studies

- Biological relevance of the model
- Consumer risk versus producer risk
- Resolution of assay versus bioequivalence requirements

Outline

- Background
  - Prior human in vivo studies
- Recent series of in vivo human studies of 14 common excipients
- Potential transporter (or enzyme or nuclear receptor) x excipient interaction concern
- Conclusions