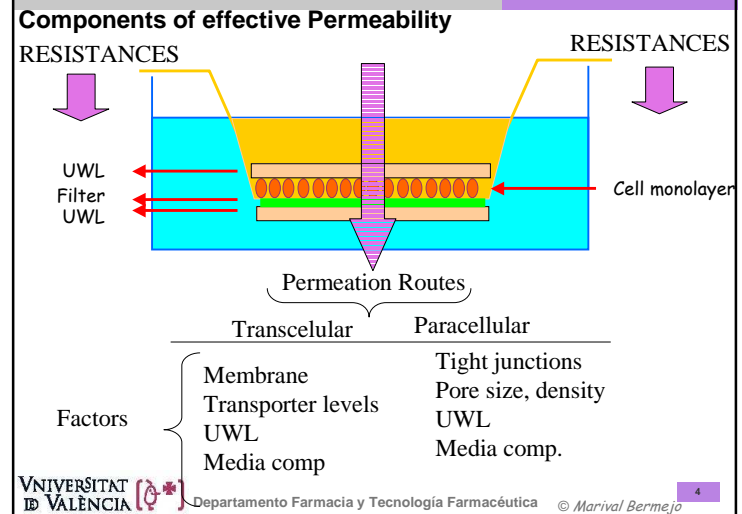
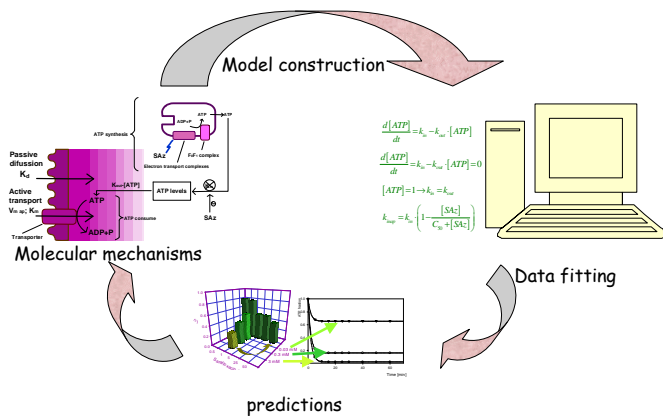
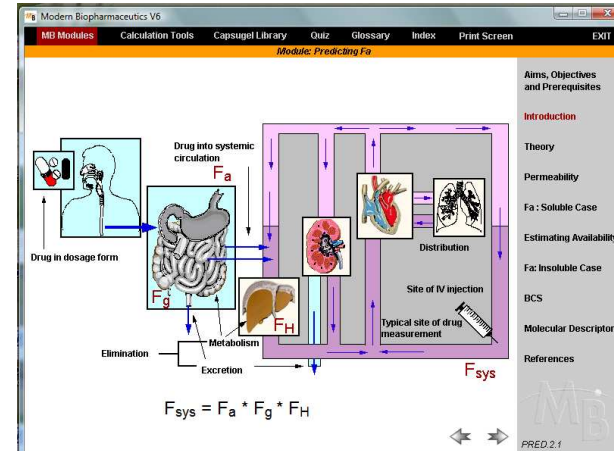


Compartmental modeling of data in permeability assays

Marival Bermejo, Isabel González-Álvarez,
 Depto. Farmacia y Tecnología Farmacéutica
 Facultad de Farmacia. Universidad de Valencia
 España



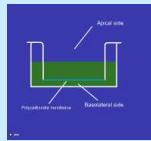
Experimental Conditions affecting Permeability

- Pre - experimental factors



SOP's
Plasticware
Media-serum...

- Experimental conditions



Media pH
Stirring rate
Sink vs nonSink

- Post-experimental factors:
Calculations



$$\frac{d[ATP]}{dt} = k_a - k_r [ATP] = 0$$

$$\frac{d[ATP]}{dt} = k_a - k_r [ATP]$$

Post- Experimental factors

- Calculation of effective permeability
- Estimation of transport components

Post- Experimental factors

Sink conditions and single barrier model

$$J = A \cdot P_{eff} (C_D - C_R)$$

sink conditions $C_R \approx 0$

C_D constant

$$P_{eff} = \frac{dM/dt}{A \cdot C_D}$$

Post- Experimental factors

Sink conditions and single barrier model

- Correction for donor concentration change
- Calculation of effective permeability (under non-sink conditions)

$$\frac{M_R}{M_{D(0)}} = \left(\frac{V_R}{V_R + V_D} \right) \cdot (1 - e^{-\alpha \beta t})$$

$$\alpha = A \cdot P_{app} / V_D$$

$$\beta = \frac{V_R + V_D}{V_R}$$

Post- Experimental factors

- Calculation of effective permeability

Methods to Calculate Permeability

Method	Equation	Donor Concentration Adjustment
A	Transport approach	Yes
B	Transport approach	No
C	Slope approach	Yes
D	Slope approach	No

$$P = \frac{dM_R^{SS}}{dt} \cdot \frac{1}{A \cdot C_D}$$

$$P = \frac{slope}{A \cdot C_D}$$

Pharmacopeial forum vol 28(1) 2002

Post- Experimental factors

- Calculation of effective permeability

Table 2. Influence of Calculation Method on Apparent Permeability²

Method	$P_{drug} \times 10^6$ (cm/sec)
A	44.6 (± 0.6) ³
B	36.7 (± 0.1)
C	45.0 (± 0.4) ³
D	36.1 (± 0.3)

² mean permeability (± SEM)

³ Donor adjustment resulted in significantly higher permeability.

Pharmacopeial forum vol 28(1) 2002

	A	B	C	D	E	F	G	H
47	Concentraciones acumuladas							
48	Insert Surface (cm ²)							1.131
49	Receiver(ml)	1.2						
50	take(ml)	0.6	dilu(ml)	0.6				
51	Time	area	con(µM)	accu(µM)	Accu(µM)	Accu (nmol)		
52	10	22.1	22.10	22.10	22.10	26.52		
53	20	26.7	26.70	37.75	37.75	45.3		
54	30	28.6	28.60	53.00	53.00	63.6		
55	40	27.2	27.20	65.90	65.90	79.08		
56	50	25.3	25.30	77.60	77.60	93.12		
57	60	23.5	23.50	88.45	88.45	106.14		
59	B(nmol/min)	1.5915						
60	A(nmol)	13.2560						
61	R2	0.9943						
63	P (cm/sec)	4.72E-05						
64	P (cm/sec)10 ⁶	47.23						

$$\frac{dM_R(t)}{dt} = P \times A \times C_{D0} \Rightarrow \frac{dM_R(t)}{dt} \times \frac{1}{A \times C_{D0}} = P$$

Integrating gives (57):

$$\frac{M_R(t)}{C_{D0}} = P \times A \times t + const$$

	A	B	C	D	E	F	G
13	C79						
14	Compound	Day 1	Day 2	Direction	Concentration		
15	Cellprolol	Day 1	BA		21 uM		
16	concentrations and fitted curve						
17	Cellprolol	Day 2	BA				
18	A (cm ²)	1.131					
19	Vd (cm ³)	0.400					
20	Vr (cm ³)	1.200					
21	Vs (cm ³)	0.600					
22	t	0.500					
23	C40 (uM)	496.600					
24	Cr0 (uM)	0.000					
30	Insert 3						
31	start	1	Non-linear curve-fit				
32	stop	6	t (s)	Cr exp (uM)	Cr theor (uM)	diff ² Cr	Mtot (nmol)
33			0	0	0.000	0.000	
34			600	22.1	20.328	3.140	198.640
35	Patart	1.26E-07	1200	26.7	27.580	0.774	186.443
36	P (cm/s)	7.91E-05	1800	28.6	28.918	0.101	169.895
37			2400	27.2	27.702	0.252	152.544
38			3000	25.3	25.493	0.037	135.923
39	SSR	4.55E+00	3600	23.5	23.004	0.246	120.627
40							
41							
42							
43	Cr0 recal	0.0000					

$$M_R = \left(\frac{V_R}{V_R + V_D} \right) \cdot (1 - e^{-\alpha \beta t})$$

$$M_{D(0)} = \left(\frac{V_R}{V_R + V_D} \right) \cdot (1 - e^{-\alpha \beta t})$$

$$\alpha = A \cdot P_{app} / V_D$$

$$\beta = \frac{V_R + V_D}{V_R}$$

	t (s)	Cr exp (uM)	Crel	Cumulative fraction	theor	(exp-theor) ²	Cd (uM)
70	0	0	0	0	0	0.003	6.94545E-06
71	600	22.1	0.05135952	0.0506	0.047	1.26307E-05	430.3
72	1200	26.7	0.06964915	0.0914	0.091	1.30826E-09	383.35
73	1800	28.6	0.08471564	0.1363	0.136	1.9751E-07	337.6
74	2400	27.2	0.09100033	0.1793	0.180	9.10422E-07	298.9
75	3000	25.3	0.09590599	0.2234	0.225	1.5316E-06	263.8
76	3600	23.5	0.10162162	0.2699	0.269	7.4812E-07	231.25
77							266.5
78							
79	P	7.40E-05					
80	ordenada	0.002635421					
81	SSE	2.29651E-05					
82							
83							
84							

The analysis is easily improved by considering the change of C_D . The donor concentration $[C_D(t_i)]$ can be calculated at each sample occasion (i) from the donor concentration at the previous occasion $[C_D(t_{i-1})]$ and the amount that has entered the receiver chamber during that time interval.

$$C_D(t) = C_D(t_{i-1}) - \frac{[C_R(t) - f \times C_R(t_{i-1})] \times V_R}{V_D} \quad [\text{Eq. 6}]$$

Post- Experimental factors

- Estimation of Transport Components:
 - P versus C data fitting: UWL and filter resistance correction
 - C versus t data fitting : donor and acceptor sampling.

Classical approaches

- Initial velocity approach
 - Single Barrier (two compartment model)
 - Need for sink conditions
 - Absence of mass balance problems
 - Negligible UWL and filter effects

Molecular based transport models

Tran TT, Mittal A, Aldinger T, Polli JW, Ayrton A, Ellens H, Bentz J. 2005. The elementary mass action rate constants of P-gp transport for a confluent monolayer of MDCKII-hMDR1 cells. *Biophysics Journal* 88:715-738.

Tran TT, Mittal A, Gales T, Maleeff B, Aldinger T, Polli JW, Ayrton A, Ellens H, Bentz J. 2004. Exact kinetic analysis of passive transport across a polarized confluent MDCK cell monolayer modeled as a single barrier. *Journal of Pharmacology Science* 93:2108-2123.

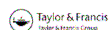
Post- Experimental factors

- Estimation of Transport Components:
 - C/Q versus t data fitting : donor and acceptor sampling. (first example)
 - P versus C data fitting: UWL and filter resistance correction (second example)

Post- Experimental factors

- Estimation of Transport Components:
 - Q versus t data fitting

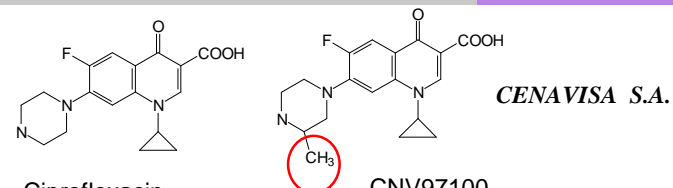
Xenobiotica, December 2005; 35(12): 1067–1088



Kinetic modelling of passive transport and active efflux of a fluoroquinolone across Caco-2 cells using a compartmental approach in NONMEM

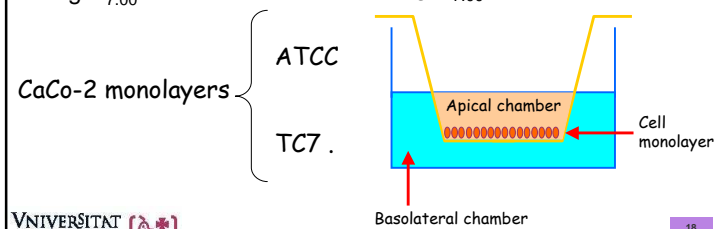
I. GONZÁLEZ-ALVAREZ¹, C. FERNÁNDEZ-TERUEL²,
T. M. GARRIGUES¹, V. G. CASABO¹, A. RUIZ-GARCÍA*, & M. BERGEJO¹

¹Dipartimento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Valencia, Valencia, Spain and ²Intervale Biokinetics S.L., Valencia, Spain



Ciprofloxacin
MW: 331 g/mol
Log $D_{7.00} = -1.12$

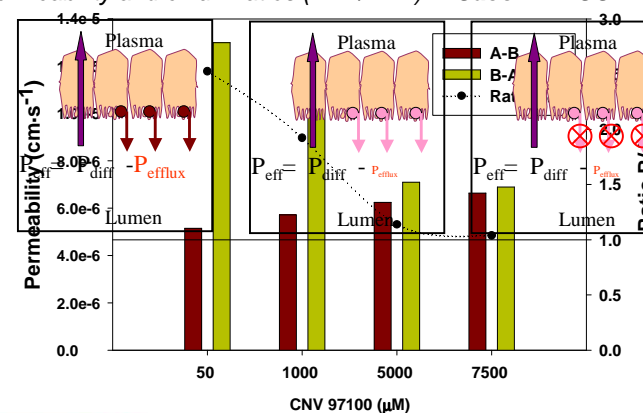
CNV97100
MW: 345 g/mol
Log $D_{7.00} = -0.65$

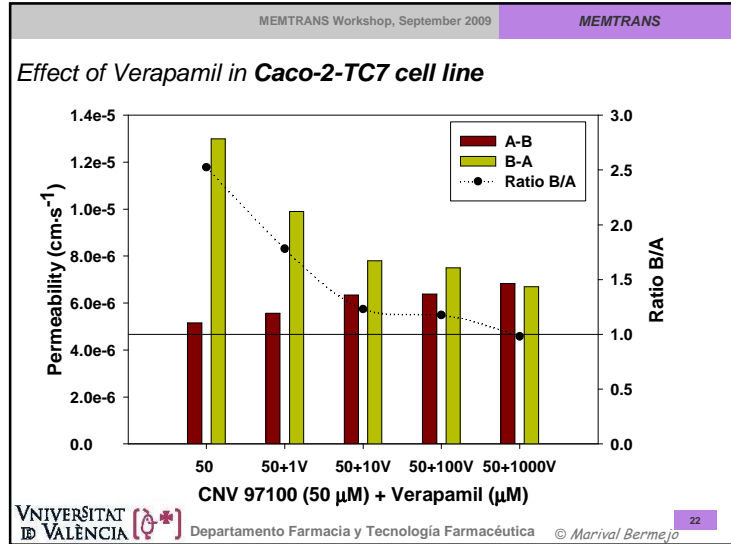
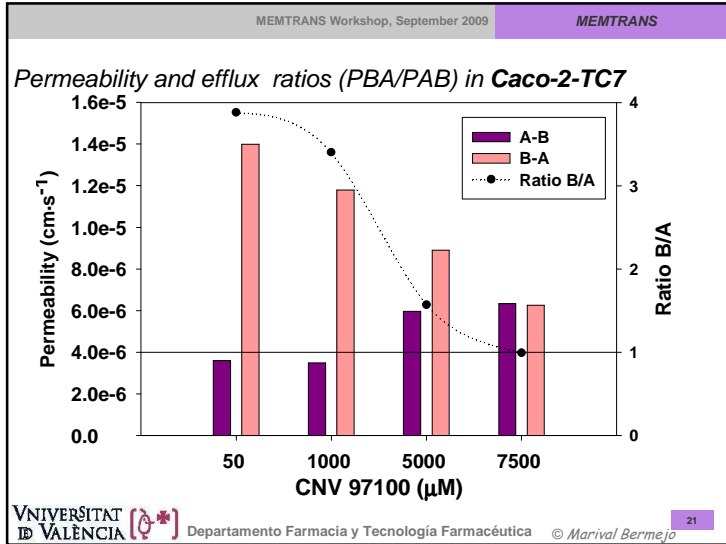


Experimental design

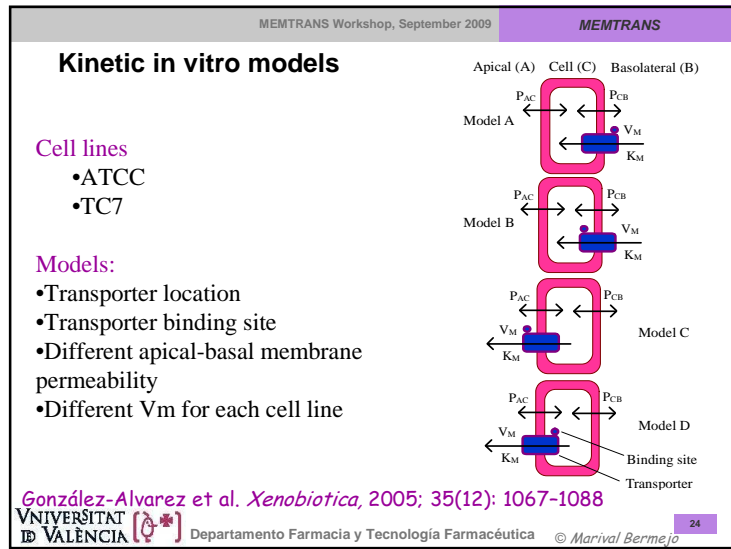
- ATCC and TC7 cell lines
- Donor concentration from 50 μM to 7500 μM .
- A to B and B to A transport experiments
- Transport experiments: CNV97100 (50 μM) in presence of Verapamil (1;10;100 and 1000 μM)
- Sampling from donor (2) and receiver (4)

Permeability and efflux ratios (PBA/PAB) in Caco-2-ATCC





- MEMTRANS Workshop, September 2009 MEMTRANS
- ### NONMEM Model construction
- Three compartment system
 - Parameters with physiological and mechanistic meaning.
 - Assumptions:
 - Passive diffusion and Michaelis menten transport component
 - Negligible paracellular permeability****
 - Negligible filter resistance***
 - UWL not is a limiting step****
 - Competitive inhibition mechanism for verapamil
 - *** the model could accomodate these three components
- VNIVERSITAT ID VALÈNCIA (Q*) Departamento Farmacia y Tecnología Farmacéutica © Marival Bermejo 23



Pharmacostatistic model.

- Inter-individual variability of the kinetic parameters

$$\theta_i = \theta_p \cdot e^{\eta} \quad (\eta = N(0, \omega^2))$$

- Residual variability

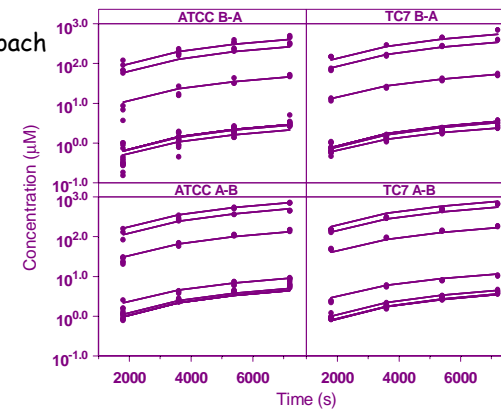
$$y_i = y_p \cdot e^{\varepsilon} \quad (\varepsilon = N(0, \sigma^2))$$

NONMEM V level 1.1
first order method (FO)
ADVAN6 subroutine

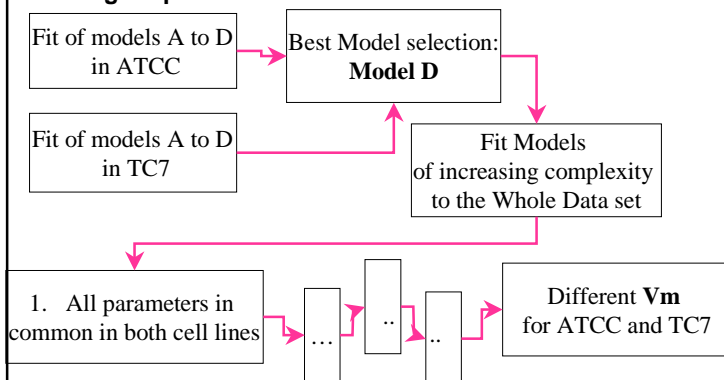
Classical approach
Peff versus C



Q versus t



Modeling Steps



Criteria for model selection

- Experimental versus predicted values plot
- R²
- Randomness of residuals
- Minimum objective function. (MOF)
 - Snedecor's F test p<0.05
- Parameter's Standard Error of estimation.

MEMTRANS Workshop, September 2009 MEMTRANS

Differential equations: Model D

- Model Apical transporter
- Intracellular*** binding site
- Different Apical and Basolateral resistances

Model D

$$\frac{dQ_A}{dt} = Cl_{AC} \cdot \left(\frac{Q_C}{V_C} - \frac{Q_A}{V_A} \right) + \frac{V_M \cdot \frac{Q_C}{V_C}}{K_M + \frac{Q_C}{V_C}}$$

$$\frac{dQ_C}{dt} = -Cl_{CB} \cdot \left(\frac{Q_C}{V_C} - \frac{Q_B}{V_B} \right) - Cl_{AC} \cdot \left(\frac{Q_C}{V_C} - \frac{Q_A}{V_A} \right) - \frac{V_M \cdot \frac{Q_C}{V_C}}{K_M + \frac{Q_C}{V_C}}$$

$$\frac{dQ_B}{dt} = Cl_{CB} \cdot \left(\frac{Q_C}{V_C} - \frac{Q_B}{V_B} \right)$$

$P = \frac{Cl}{S}$ NONMEM V level 1.1 first order method (FO) ADVAN6 subroutine

González-Alvarez et al. *Xenobiotica*, 2005; 35(12): 1067-1088

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnología Farmacéutica © Marival Bermejo 29

MEMTRANS Workshop, September 2009 MEMTRANS

In vitro fitting parameters ATCC and TC7.

Parameters	Values (CV%)	
	ATCC	TC7
Cellular volume (mL)	7.38·10 ⁻² (22.2)	
K _M (μM)	3.76·10 ² (37.5)	
P _{AC} (cm·s ⁻¹)	8.40·10 ⁻⁶ (7.5)	
P _{CB} (cm·s ⁻¹)	3.45·10 ⁻⁵ (28.8)	
V _M (nmol·s ⁻¹ ·cm ²)	6.17·10 ⁻³ (24.6)	1.27·10 ⁻² (22.4)

$\frac{Cl}{A} = P$ $R = \frac{1}{P}$

Gonzalez-Alvarez I et al. *Xenobiotica*, 2005; 35(12)

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnología Farmacéutica © Marival Bermejo 30

MEMTRANS Workshop, September 2009 MEMTRANS

- Basolateral to Apical transport is more sensitive to pump inhibition than the Apical to Basolateral one due to the different barrier properties of apical and basolateral membranes
- The slight differences in P-gp expression have a kinetic relevance that was possible to detect by means of curve fitting and model selection.

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnología Farmacéutica © Marival Bermejo 31

MEMTRANS Workshop, September 2009 MEMTRANS

Table III. Parameters of the two-compartment fit.

Parameter	Value	CV (%)
P _{dir} (cm s ⁻¹)	7.08 × 10 ⁻⁶	2.96
V _m (nmol s ⁻¹ cm ²)	6.14 × 10 ⁻³	41.70
*ΔV _m (nmol s ⁻¹ cm ²)	2.13 × 10 ⁻³	76.08
K _m (μM)	1483.5	46.31
K _i (μM)	0.80	53.22
f _{max} (cm s ⁻¹) ATCC	4.14 × 10 ⁻⁶	18.36
f _{max} (cm s ⁻¹) TC7	5.57 × 10 ⁻⁶	14.84

*Corresponds to the increase in V_m in the TC7 cell line due to higher transporter expression.

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnología Farmacéutica © Marival Bermejo 32

Post- Experimental factors

- Estimation of Transport Components:
 - C versus t data fitting : donor and acceptor sampling. (first example)
 - P versus C data fitting: UWL and filter resistance correction (second example)

Post- Experimental factors

P versus C data fitting: UWL correction

0022-3959/07/2011-133-144\$20.00
 The Journal of Pharmacology and Experimental Therapeutics
 Copyright © 2007 by The American Society for Pharmacology and Experimental Therapeutics
 JPEP 2011-133-144, 2007

Vol. 320, No. 1
 107433636224
 Printed in U.S.A.

Bias in Estimation of Transporter Kinetic Parameters from Overexpression Systems: Interplay of Transporter Expression Level and Substrate Affinity

Anand Balakrishnan,¹ Naissan Hussainzada, Pablo Gonzalez, Marival Bermejo, Peter W. Swaan, and James E. Polli

Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, Maryland (A.B., N.H., P.G., P.W.S., J.E.P.); and Department of Pharmacy and Technology, University of Valencia, Valencia, Spain (M.B.)

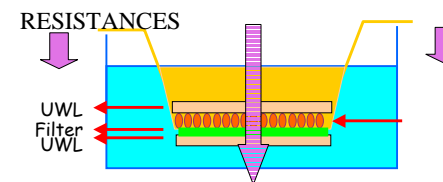
Received May 5, 2006; accepted October 11, 2006

Objective

- To delineate the interplay between transporter expression and substrate affinity and the influence of the UWL on the estimation of transport parameters.
- Transport experiments of Sodium Taurocholate were performed in MDCK-hASBT cells with different expression levels

Post- Experimental factors

P versus C fitting: UWL correction

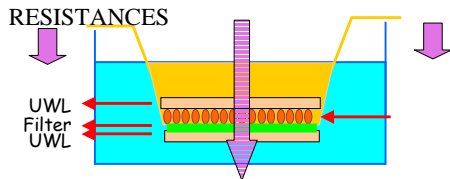


the ABL-absent model is as follows:

$$J = \frac{J_{\max} \times S}{K_t + S} + P_p \times S$$

Post-Experimental factors

P versus C fitting: UWL correction



$$\frac{1}{P_{ap}} = \frac{1}{P_{cell}} + \frac{1}{P_{ABL}}$$

$$P_{ap} = \frac{P_{cell} \cdot P_{ABL}}{P_{cell} + P_{ABL}}$$

Post-Experimental factors

P versus C data fitting: UWL correction

$$P_{app} = \frac{P_{ABL} \times \left(\frac{J_{max}}{K_t + S} + P_p \right)}{P_{ABL} + \frac{J_{max}}{K_t + S} + P_p}$$

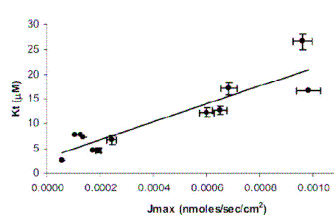
$$\frac{1}{P_{ap}} = \frac{1}{P_{cell}} + \frac{1}{P_{ABL}}$$

$$P_{ap} = \frac{P_{cell} \cdot P_{ABL}}{P_{cell} + P_{ABL}}$$

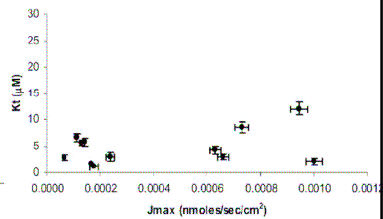
Since $J_{ABL} = P_{app} \times S$,

$$J_{ABL} = \frac{P_{ABL} \times \left(\frac{J_{max}}{K_t + S} + P_p \right) \times S}{P_{ABL} + \frac{J_{max}}{K_t + S} + P_p}$$

134 Balakrishnan et al.



ABL-absent model

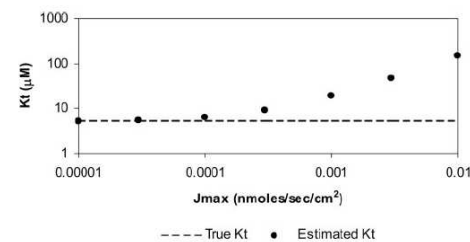


ABL-present model

Error-free simulations

Simulate data with ABL-present model (known K_m , V_{max})

Fit ABL-absent model to J vs C data to estimate K_m , V_{ax}



MEMTRANS Workshop, September 2009 MEMTRANS

Simulations with 15% random error (on J) 15 scenarios, 100 experiments (3 replicates)

Probability of obtaining statistically significant K_t estimate under different scenarios of K_t and J_{max}

K_t	Probability of Successful K_t Estimation		
	J_{max} 0.001 nmol/cm ² /s	J_{max} 0.0003 nmol/cm ² /s	J_{max} 0.0001 nmol/cm ² /s
μM			
1	10 (94)	13 (81)	65 (59)
3	19 (83)	58 (59)	90 (32)
5	43 (74)	79 (46)	91 (15)
10	59 (58)	92 (30)	84 (12)
25	87 (36)	86 (15)	64 (5)

↓

% of Total resistance due to UWL

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnologia Farmacèutica © Marival Bermejo 41

MEMTRANS Workshop, September 2009 MEMTRANS

Scaling up?

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnologia Farmacèutica © Marival Bermejo 42

MEMTRANS Workshop, September 2009 MEMTRANS

Modern Biopharmaceutics V6

MB Modules Calculation Tools Capsugel Library Quiz Glossary Index Print Screen EXIT

Module: GI Tract

Small Intestine: Amplification of Surface Area

Due to amplified surface area, the small intestine is the most efficient place for absorption

Amplification Factor: (relative to cylinder)

Intestine Cylinder (3,300 cm ²)	Folds (10,000 cm ²)	Villi (100,000 cm ²)	Microvilli in Absorptive Cell (2,000,000 cm ²)
1	x 3	x 30	x 600

Aims, Objectives and Prerequisites

Anatomy & Function

- Introduction
- Stomach - Anatomy
- Stomach - Function
- Small Intestine - Anatomy
- Small Intestine - Function
- Large Intestine - Anatomy
- Large Intestine - Function

Secretion

Motility

Absorption

References

GI.2e.2

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnologia Farmacèutica © Marival Bermejo 43

MEMTRANS Workshop, September 2009 MEMTRANS

Scaling-Up results

Effective Permeability= Transcellular + Paracellular

Cell model

A-to-B $P_{eff} = P_{diff} - \frac{V_m}{K_m + C}$

B-to-A $P_{eff} = P_{diff} + \frac{V_m}{K_m + C}$

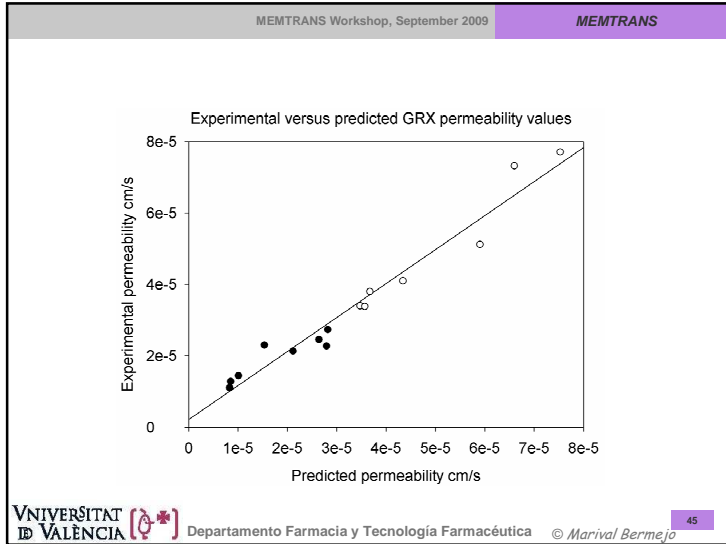
x Area correction
x expression level correction

Paracellular correction

Rat, Human

Rat $P_{eff}^{Rat} = F \cdot (P_{diff} - \frac{V_m}{K_m + C})$

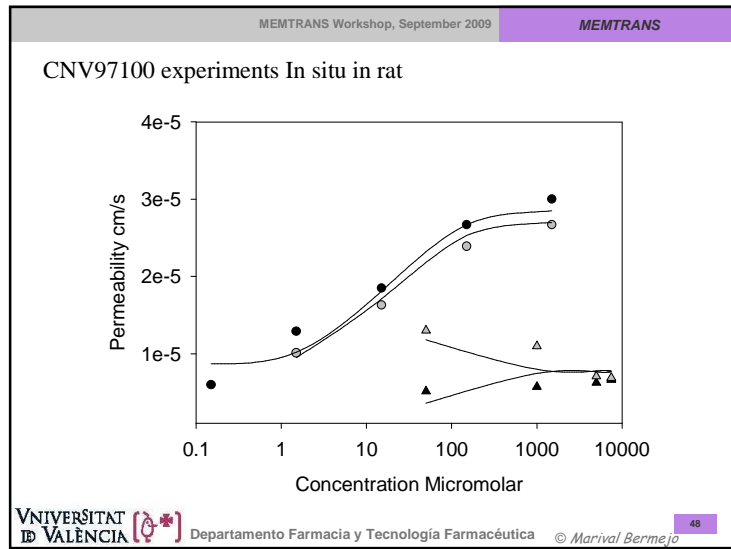
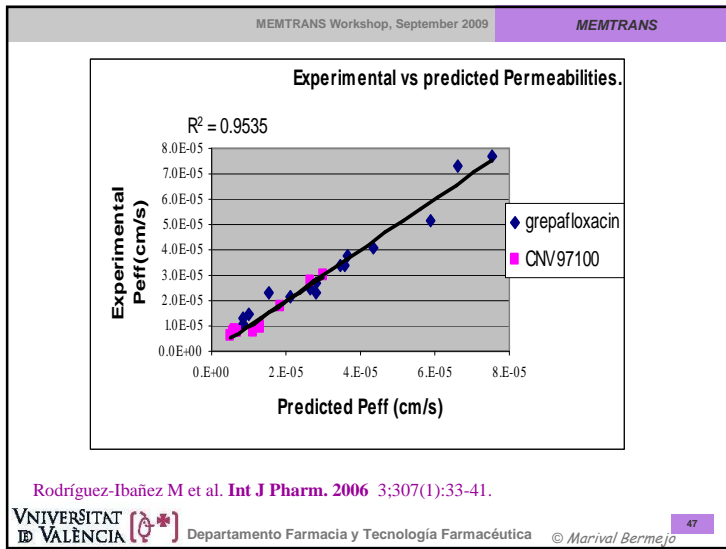
VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnologia Farmacèutica © Marival Bermejo 44



MEMTRANS Workshop, September 2009 MEMTRANS

	Value	CV %
Grepafloracin		
P_{DIFF} cm/s	1.80E-05	8.09
V_M nmol/(cm ² ·s)	1.02E-02	48.02
K_M microM	1000.04	47.27
F	4.30	11.18
CNV97100		
P_{DIFF} cm/s	8.00E-06	9.5
V_M nmol/(cm ² ·s)	1.15E-04	46.14
K_M microM	20.41	47.79
F	3.84	11.35

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmacia y Tecnología Farmacéutica © Marival Bermejo 46



MEMTRANS Workshop, September 2009 MEMTRANS

BDD: 548 pp.1-11 (col.fig.: NIL) PRODTYPE: COM 3B2 ED: MARIAMMA SCAN:XXXXXXXXXX PAGO: SCAN:XXXXXXXXXX

BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. 28: 1-11 (2007)
 Published online in Wiley InterScience
 (www.interscience.wiley.com) DOI: 10.1002/bdd.548

1 3 5 7 9 11 13

In situ Kinetic Modelling of Intestinal Efflux in Rats: Functional Characterization of Segmental Differences and Correlation With In Vitro Results

Isabel González-Alvarez^a, Carlos Fernández-Teruel^b, Vicente G. Casabó-Alós^a, Teresa M. Garrigues^a, James E. Polli^c, Ana Ruiz-García^a and Marival Bermejo^{a*}

^aDepartament Farmàcia i Tecnologia Farmacèutica, Facultat de Farmàcia, Universitat de València, Av. Vicente A. Estellés, S/n Burjassot 46100 València, España
^bIntervale Biokinetics SL, Paterna 46980 València, España
^cDepartment of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD 21201, USA

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmàcia i Tecnologia Farmacèutica © Marival Bermejo 49

MEMTRANS Workshop, September 2009 MEMTRANS

$F_a = 1 - e^{-S_f \cdot k_{a_{cells}} \cdot T}$
 $F_a = 1 - e^{-k_{a_{int}} \cdot T}$

Caco-2 Rat

Parameter	Units	Estimate	StdError	CV%
T	hours	1.314	0.175	13.32
SF	-	5.587	1.118	20.02

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmàcia i Tecnologia Farmacèutica © Marival Bermejo 50

MEMTRANS Workshop, September 2009 MEMTRANS

Transit Dissolution and Absorption in a Tube

Dimensionless differential equations describing total mass balance in the tube model

$$\frac{dr^*}{dt^*} = \frac{Dn(1-C^*)}{2r^*}$$

$$\frac{dC^*}{dt^*} = \frac{3}{2} Do Dnr^* (1-C^*) - 2AnC^*$$

$$t_{obs}^* = \frac{r_0^2 p}{2DC_s} \quad t_{abs}^* = \frac{R}{P_{eff}}$$

$$Dn = \frac{t_{res}}{t_{diss}} \quad An = \frac{t_{res}}{t_{abs}}$$

$$Do = \frac{Dose / V_d}{C_s}$$

These equations are solved numerically to obtain the fraction absorbed as a function of Do , Dn , and An .

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmàcia i Tecnologia Farmacèutica © Marival Bermejo 51

MEMTRANS Workshop, September 2009 MEMTRANS

References

- Gonzalez-Alvarez I, Fernandez-Teruel C, Garrigues TM, Casabo VG, Ruiz-Garcia A, Bermejo M. Kinetic modelling of passive transport and active efflux of a fluoroquinolone across Caco-2 cells using a compartmental approach in NONMEM. *Xenobiotica*. 2005 Dec;35(12):1067-88. PMID: 16418062
- Balakrishnan A, Hussainzada N, Gonzalez P, Bermejo M, Swaan PW, Polli JE. Bias in estimation of transporter kinetic parameters from overexpression systems: Interplay of transporter expression level and substrate affinity. *J Pharmacol Exp Ther*. 2007 Jan;320(1):133-44. Epub 2006 Oct 12. PMID: 17038509
- Bermejo M, Avdeef A, Ruiz A, Nalda R, Ruell JA, Tsinman O, Gonzalez I, Fernandez C, Sanchez G, Garrigues TM, Merino V. PAMPA--a drug absorption in vitro model 7. Comparing rat in situ, Caco-2, and PAMPA permeability of fluoroquinolones. *Eur J Pharm Sci*. 2004 Mar;21(4):429-41. PMID: 14998573
- González-Alvarez I, Fernández-Teruel C, Casabó-Alós V, Garrigues TM, Polli JE, Ruiz-García A, Bermejo M. In situ kinetic modelling of intestinal efflux in rats: functional characterization of segmental differences and correlation with in vitro results. *Biopharm. Drug Dispos.* 28: 229-239 (2007) PMID: 17410527

mbermejo@uv.es

VNIVERSITAT ID VALÈNCIA (Q*) Departament Farmàcia i Tecnologia Farmacèutica © Marival Bermejo 52

Acknowledgements

TEAM:

Isabel González
Vicente Casabó
Carlos Fernández
Gloria P. Sánchez
Amparo Centelles

•Compounds:

Dr. Joan Freixas CENAVISA SA

Cell Lines:

- Prof. Ming Hu Washington State University.
- Professor Monique Rousset, INSERM U178

Funds:

- GV (GV 99-99-1-12)
- MEC (SAF 96 1710)
- EC

mbermejo@umh.es



BioSim
NETWORK OF EXCELLENCE

memtrans

VNIVERSITAT
ID VALÈNCIA

Departamento Farmacia y Tecnología Farmacéutica © Marival Bermejo

53

