Development of biopredictive dissolution methods

Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives

Raimar Loebenberg University of Alberta
August 29-31, 2023

Dissolution and absorption processes

Examples:

Permeability controlled absorption

Dissolution controlled absorption

Lysosomal trapping

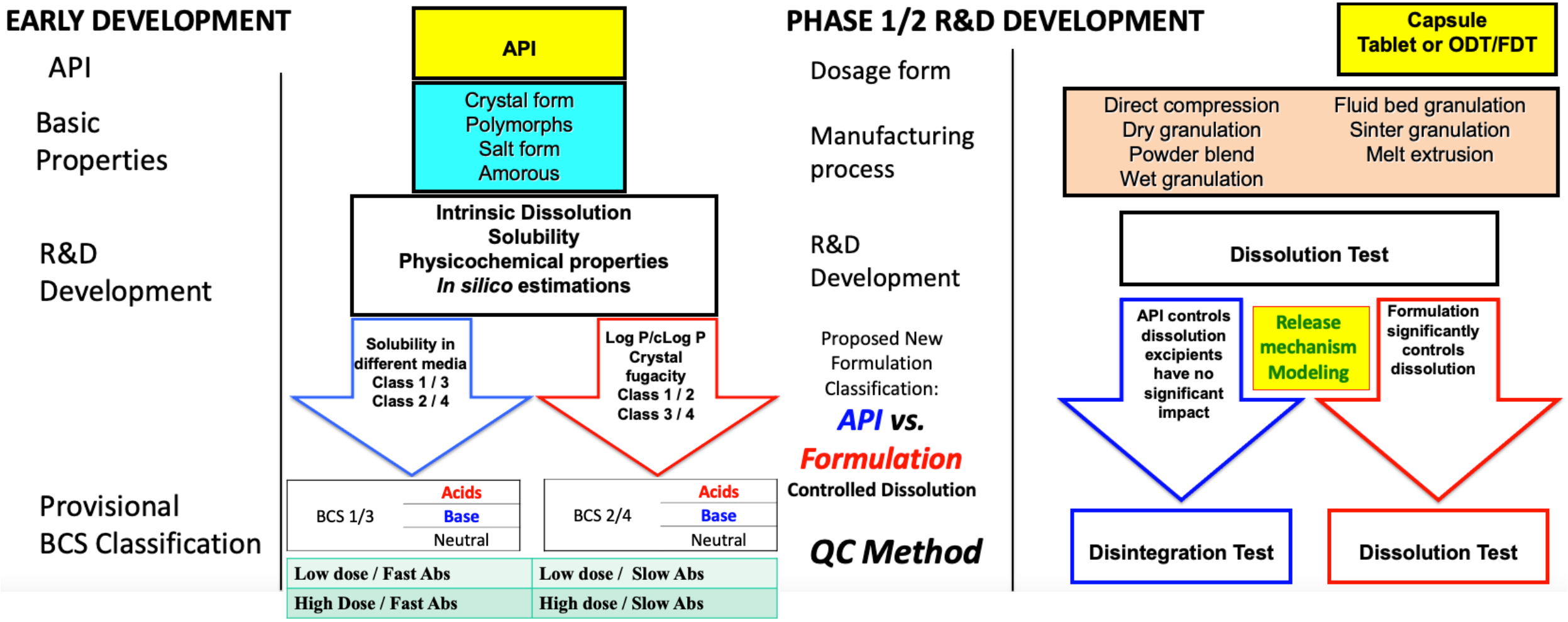
Enteric coated formulations

Biphasic dissolution

Lipid dissolution

Conclusions

Drug Development and QC Method Development Sequences



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ScienceDirect
International Journal of Pharmaceutics 328 (2007) 12–21
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Review

Current perspectives in dissolution testing of conventional and novel dosage forms

In most cases the goals of QC versus R&D approaches make it necessary to **design two different dissolution protocols**. An over-discriminatory test might be suitable for QC purposes to detect even small production deviations. However, such a test is not desirable for the prediction of the *in vivo* performance of drug product. Here dissolution testing should be a sensitive and a reliable predictor of bioavailability

Dissolution testing is used here as a predictive tool for the *in vivo* performance of a drug product. This requires that the *in vitro* and *in vivo* dissolution behavior of a dosage form

be either similar or have a scalable relationship to each other.

Pharmaceutical Research, Vol. 15, No. 5, 1998

Research Paper

Evaluation of Various Dissolution Media for Predicting *In Vivo* Performance of Class I and II Drugs

E. Galia,[1] E. Nicolaides,[2] D. Hörter,[1] R. Löbenberg,[1] C. Reppas,[2] and J. B. Dressman[1,3]

INTRODUCTION

The use of high throughput techniques for screening new compounds for pharmacological activity is becoming increasingly important (1). As a result, drugs being developed today exhibit an ever wider range of physicochemical characteristics. To assess whether these compounds possess not only the desired pharmacological activity but also the properties necessary for adequate bioavailability following oral administration, additional tests are required. Especially sought after are *in vitro* tests that are capable of predicting *in vivo* performance.

As predicted, dissolution of class II drugs proved to be in general much more dependent on the medium than class I drugs. With the array of compendial and physiological media available, **it should be possible to design a suitable set of tests to predict the in vivo dissolution of both class I and II drugs from immediate release formulations**.

minutes. The dissolution rate of metoprolol was shown to be dependent

class I compound (3).

Review Article

Evolution of Choice of Solubility and Dissolution Media After Two Decades of Biopharmaceutical Classification System

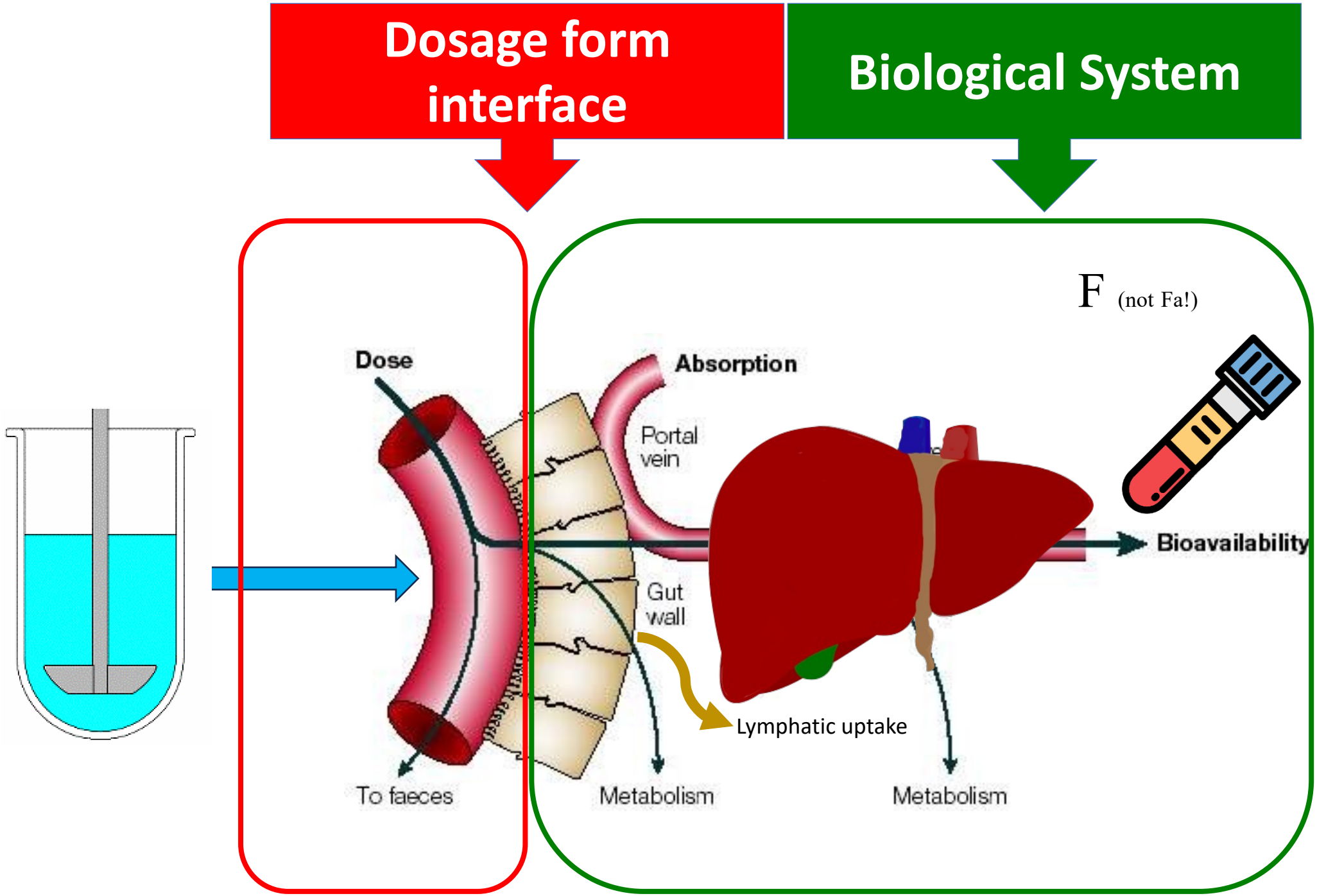
Nadia Bou-Chacra,[1] Katherine Jasmine Curo Melo,[1] Ivan Andrés Cordova Morales,[1] Erika S. Stippler,[2] Filippos Kesisoglou,[3] Mehran Yazdanian,[4] and Raimar Löbenberg[5,6]

Received 14 December 2016; accepted 11 April 2017

Abstract. The introduction of the biopharmaceutics drug classification system (Biopharmaceutics Classification System (BCS)), in 1995, provided a simple way to describe the biopharmaceutics behavior of a drug. Solubility and permeability are among the major

At this time point, **there is no universal medium available which can be used to predict every drug substance's solubility or a drug product's in vivo dissolution behavior**

KEY WORDS: BCS; dissolution; IVIVC; solubility.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Biological System
F (not Fa!)
Dose
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Portal vein
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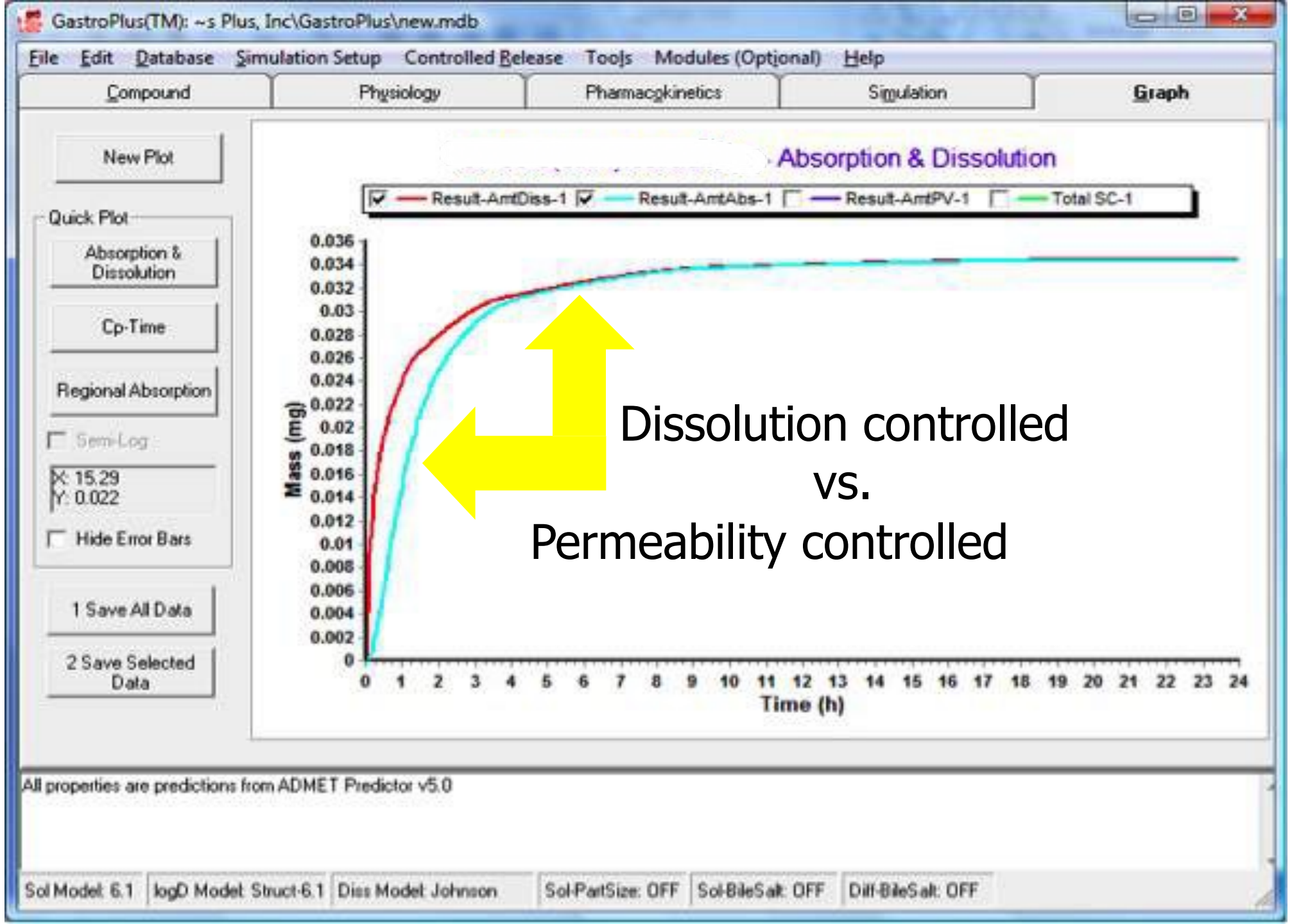
Metabolism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Absorption & Dissolution
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X: 15.29
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Hide Error Bars
1 Save All Data
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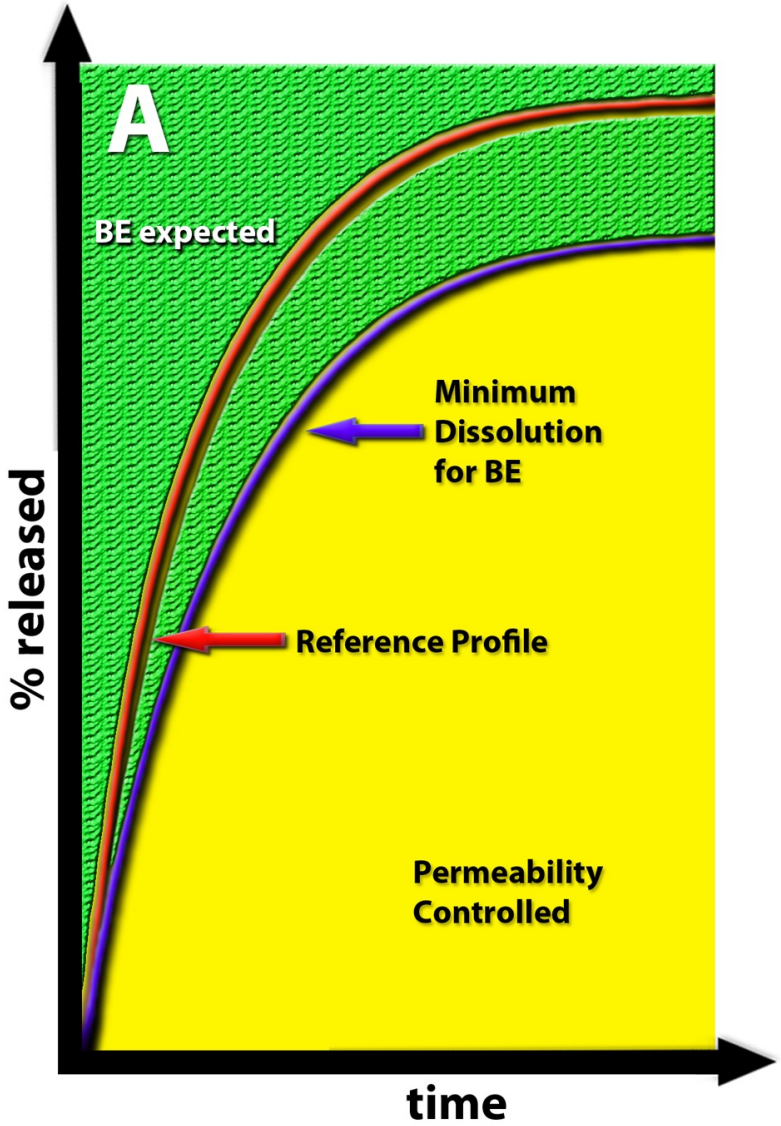
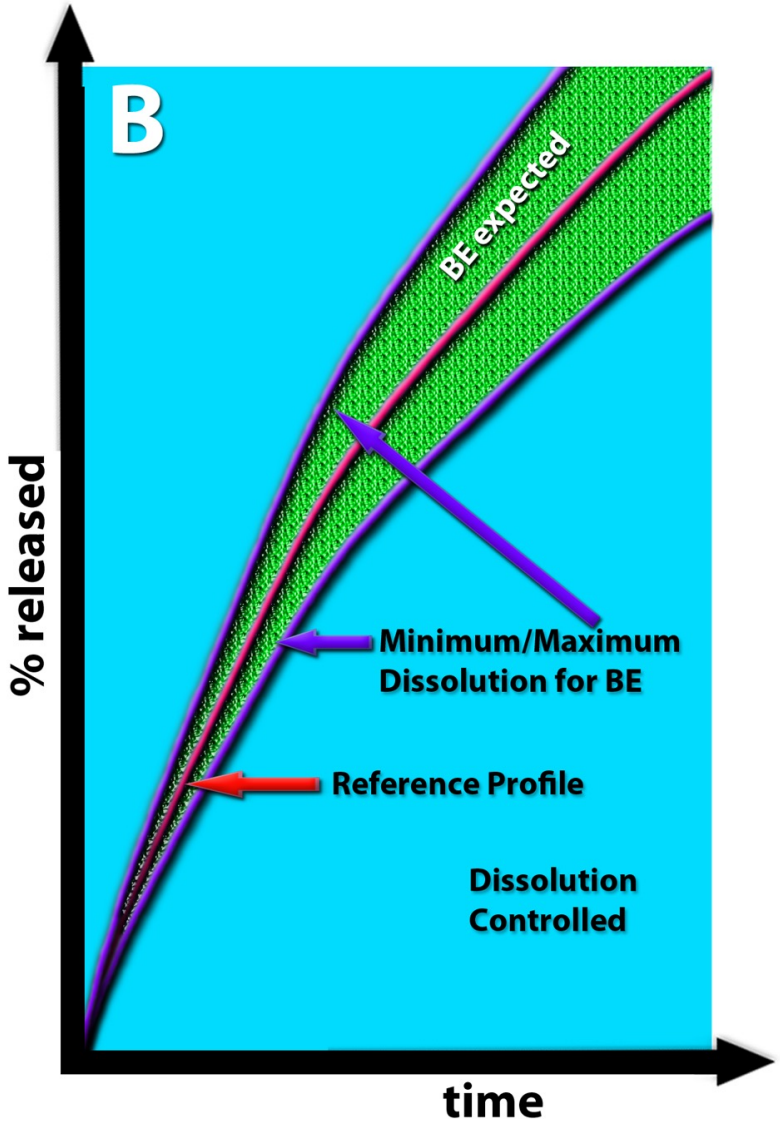
Absorption & Dissolution
Result-AmtDiss-1
Result-AmtAbs-1
Result-AmtPV-1
Total SC-1
Mass (mg)
Time (h)
Dissolution controlled
vs.
Permeability controlled
All properties are predictions from ADMET Predictor v5.0
Sol Model: 6.1
logD Model: Struct-6.1
Diss Model: Johnson
Sol-PartSize: OFF
Sol-BileSalt: OFF
Diff-BileSalt: OFF

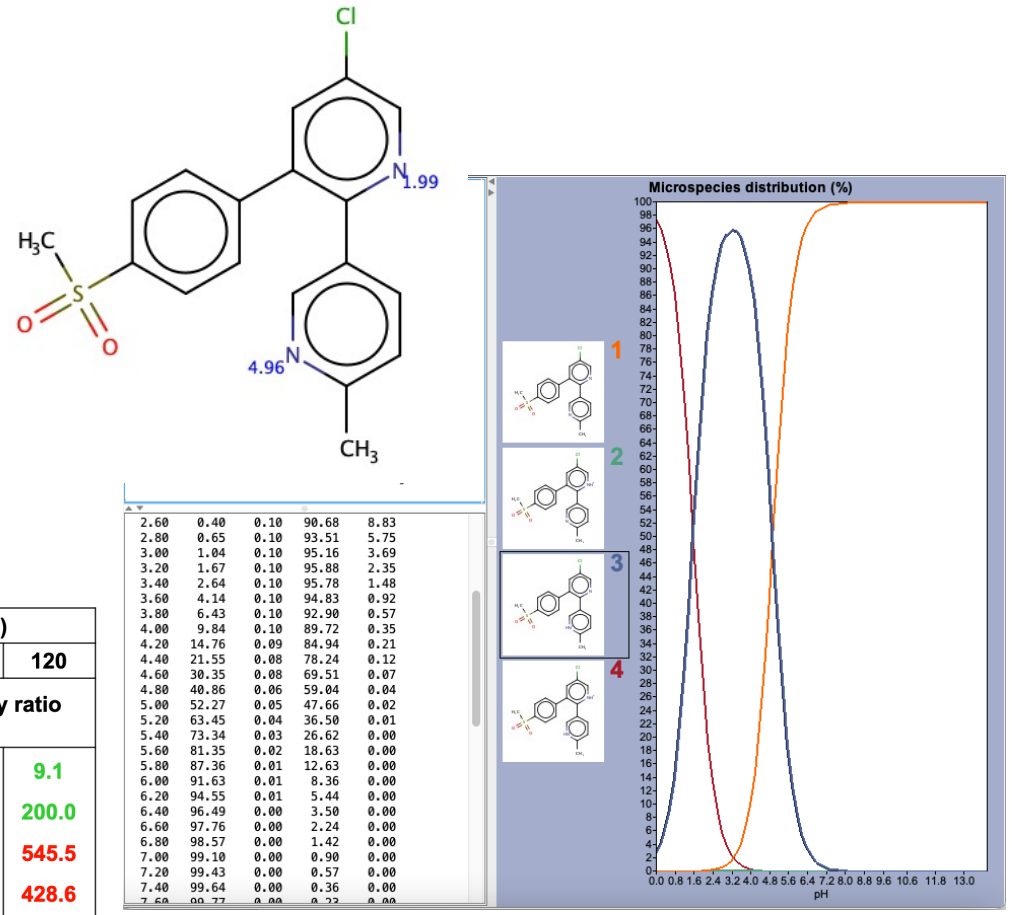
Permeability vs Dissolution Controlled Absorption





Example: Permeability controlled Absorption Dynamic Dissolution of a Weak Base: Etoricoxib

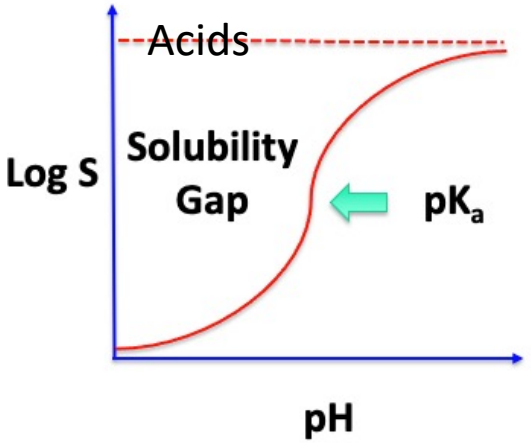
- pKa = 1.99, 4.96
- logP = 3.1
- Oral bioavailability is 100% (Agrawal et al, 2003)

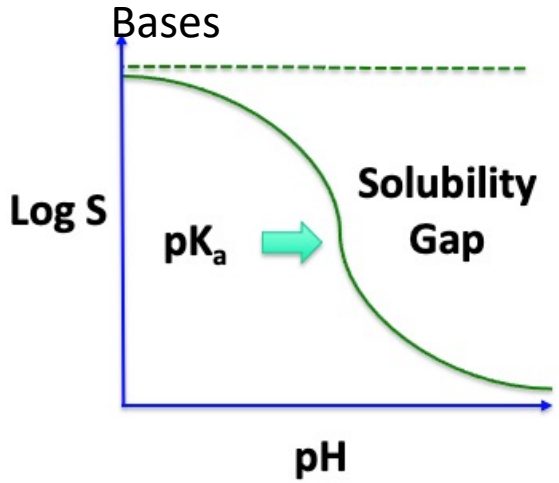


			Dose(mg)		
			60	90	120
	pH	Solubility (mg/mL)	Dose/solubility ratio (mL)		
SGF (Without enzymes)	1.2	13.21 ±1.39	4.5	6.8	9.1
Acetate Buffer	4.1	0.60 ± 0.12	100.0	150.0	200.0
Blank FeSSIF	5.0	0.22 ± 0.04	272.7	409.1	545.5
FeSSIF (with bile salts and lecithin)	5.0	0.28 ± 0.03	214.3	321.4	428.6
Blank FaSSIF	6.5	0.16 ± 0.04	375.0	562.5	750.0
FaSSIF (with bile salts and lecithin)	6.5	0.14 ± 0.03	428.6	642.9	857.1
SIF pH 6.8	6.8	0.14 ± 0.02	428.6	642.9	857.1

Gastrointestinal transit

dosage form ⇨ disintegration ⇨ dissolution ⇨ absorption

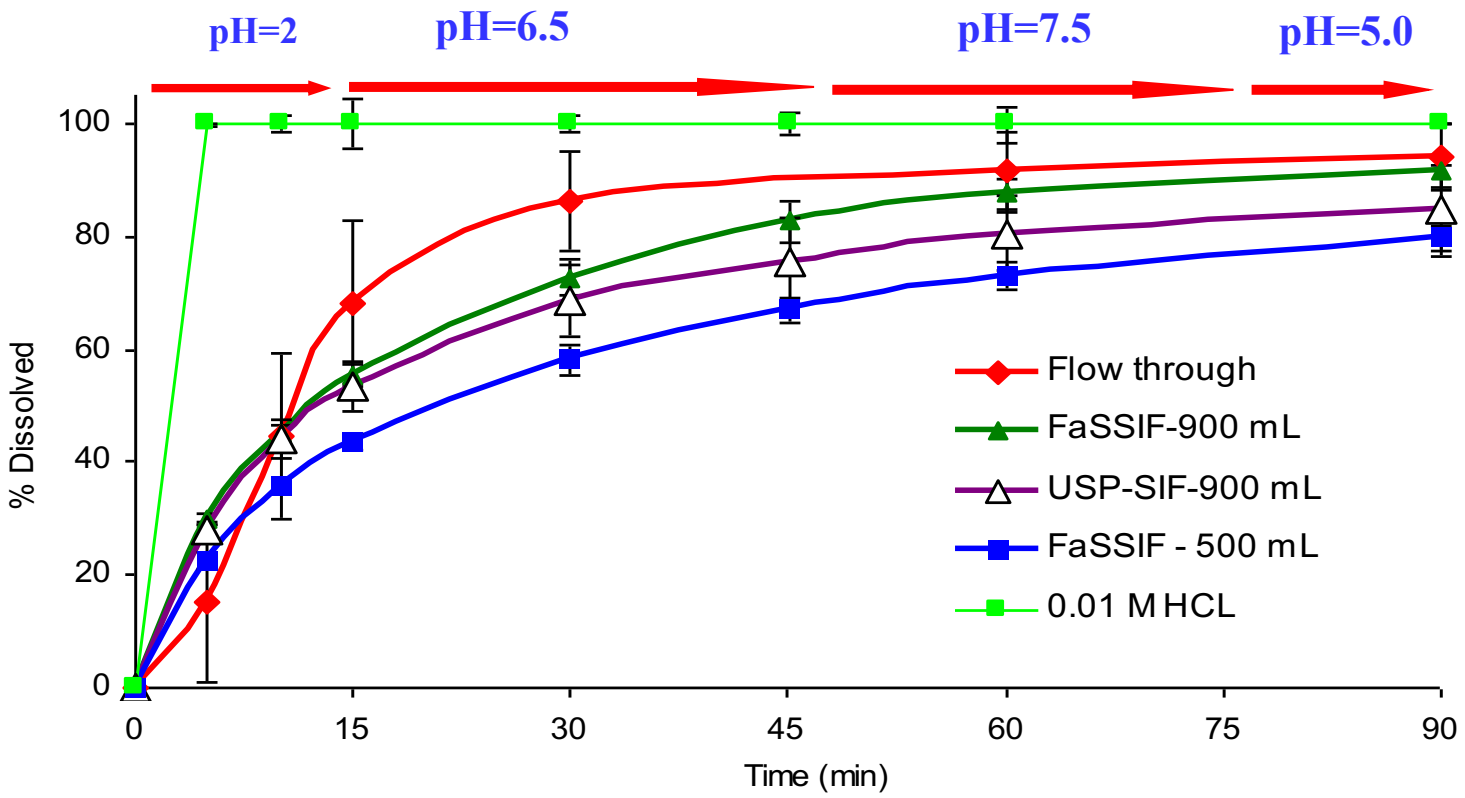


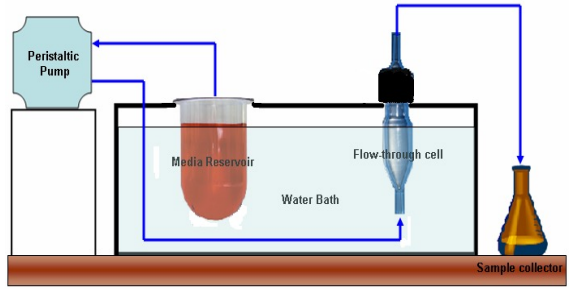


Missing in a compendial dissolution test

motility	permeability	enzymes	
gastric emptying	pH	bacteria	viscosity
pH 1-2	pH 6 -7.5		pH 5

Summary: Dissolution Profiles





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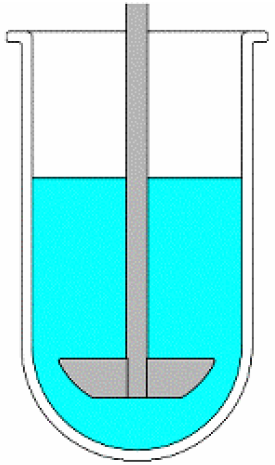
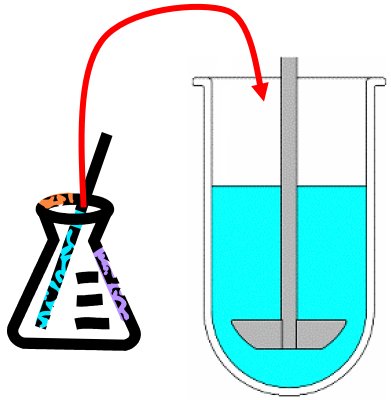
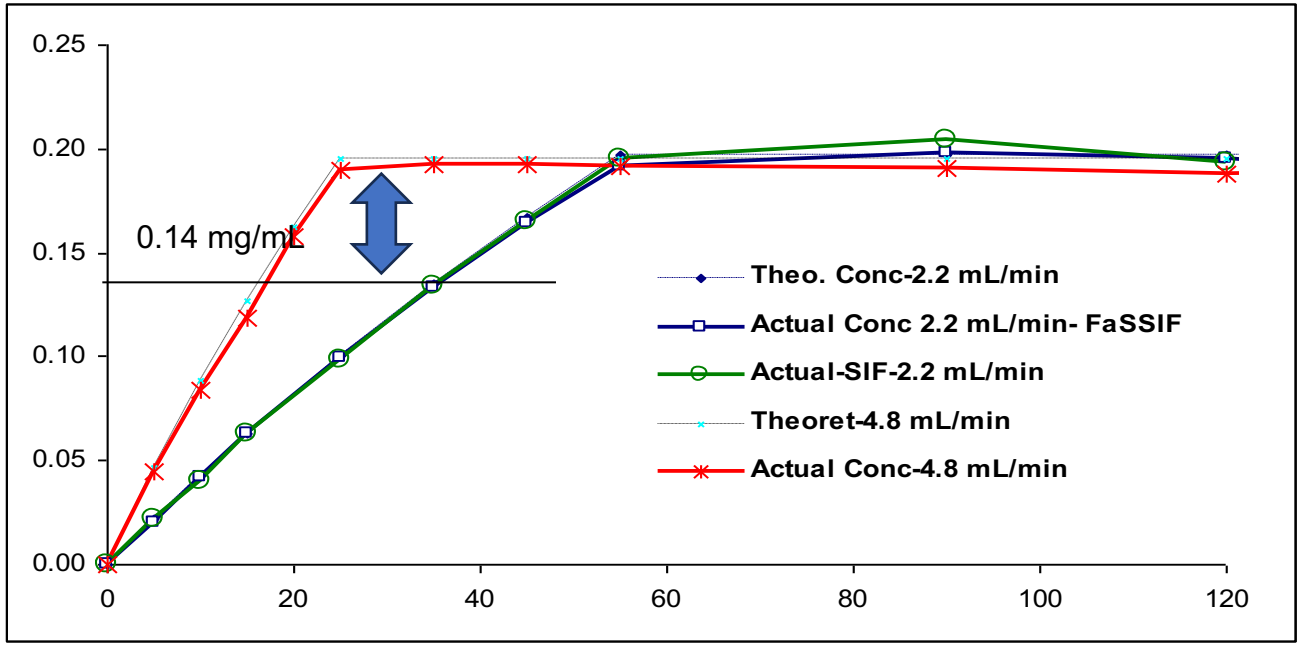


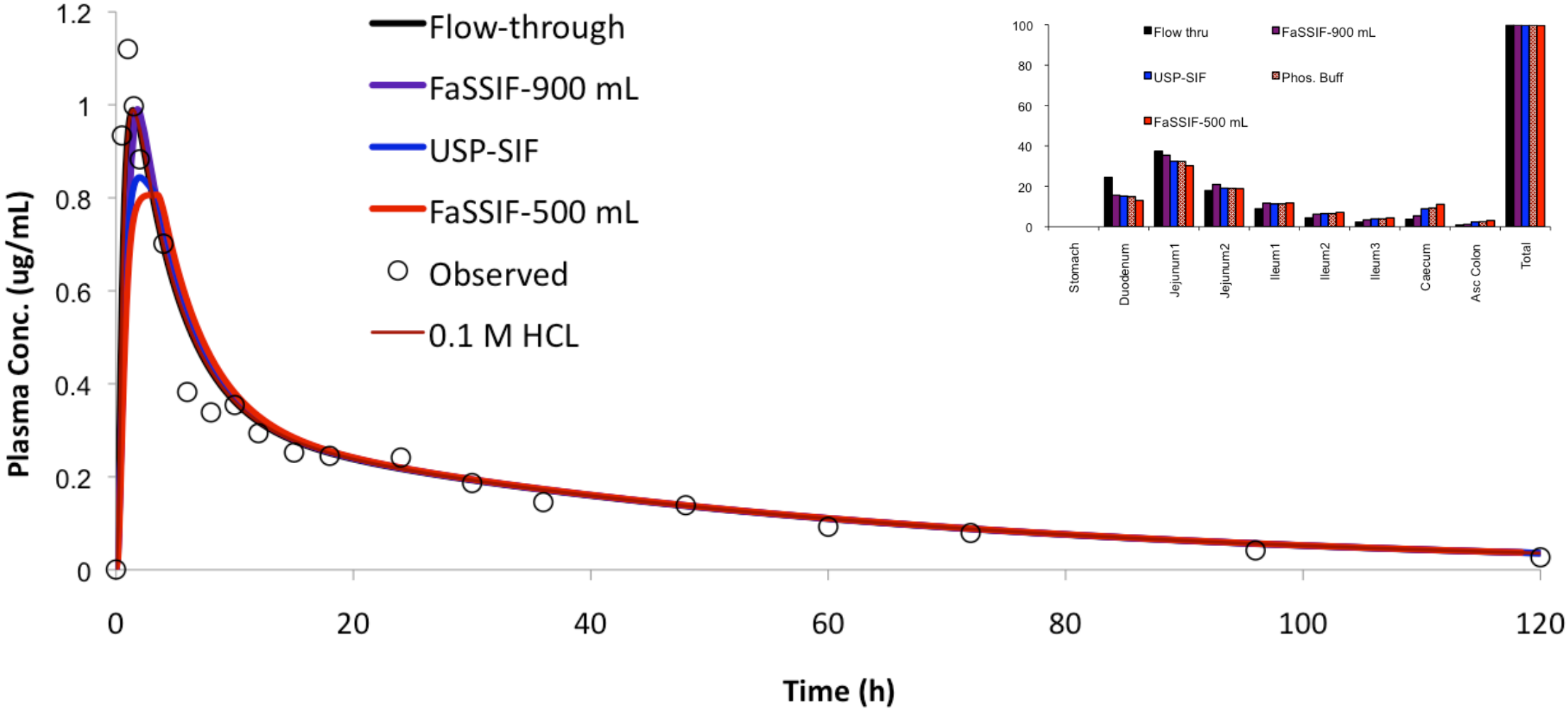
Investigating possible *in vivo* precipitation using a transfer model



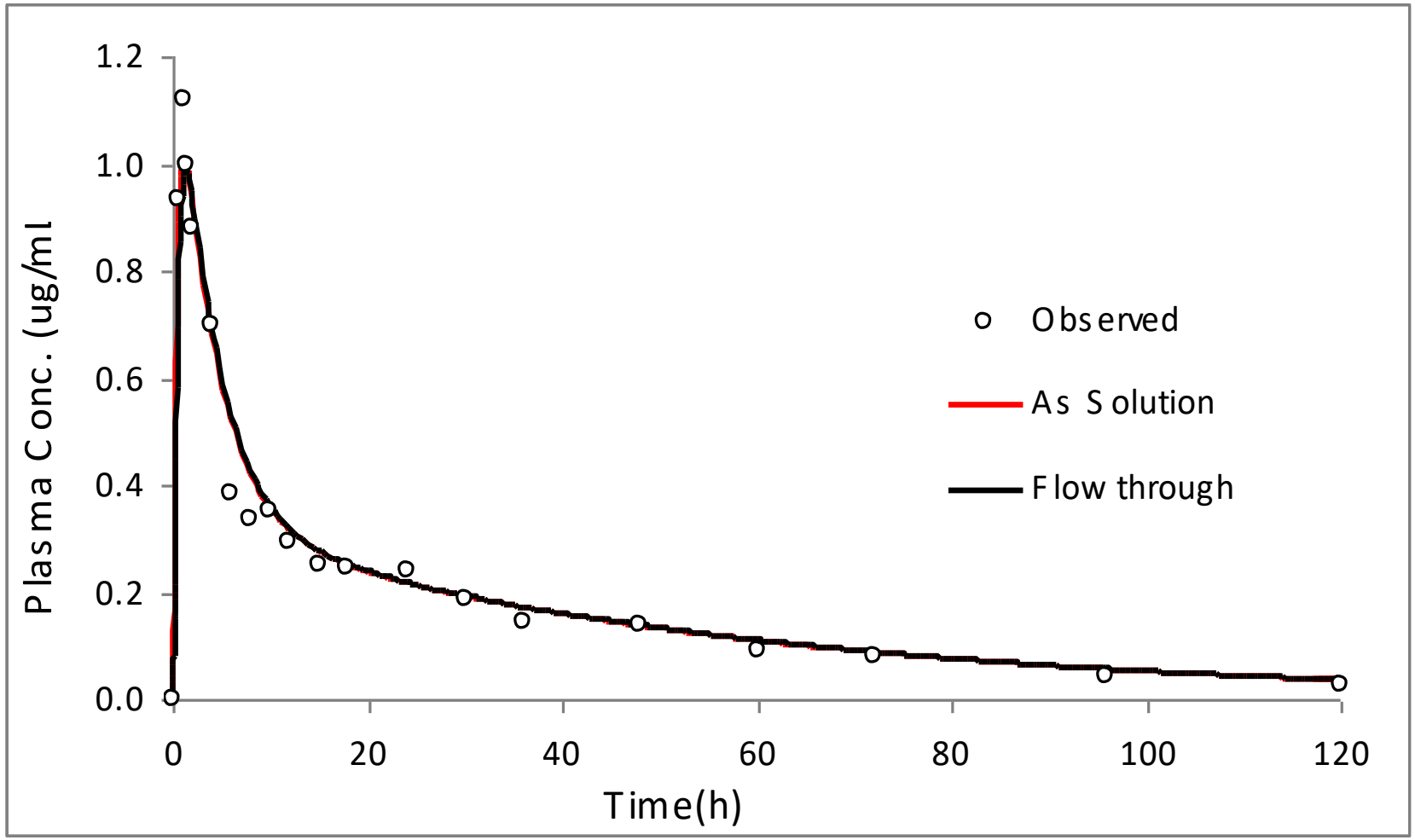


The transfer model showed a higher drug concentration compared to the shake flask method(Back line)

Simulations results



Simulations as a solution compared with flow through cell showed not significant differences



The profiles are superimposable

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journal homepage: www.elsevier.com/locate/ejpb

Research paper

Computer simulations using GastroPlus™ to justify a biowaiver for etoricoxib solid oral drug products

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[b] Merck Frosst Canada Inc., Kirkland, Que., Canada

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Keywords:
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Bioequivalence
IVIVC
In-silico
Permeability
Etoricoxib

In vitro results combined with *in silico* simulations using GastroPlus support scientifically that a biowaiver for immediate release etoricoxib solid oral dosage forms is justified.

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combined with *in silico* simulations using GastroPlus support scientifically that a biowaiver for immediate release etoricoxib solid oral dosage forms is justified.

ASD- Model

Relative Bioavailability Estimation of Carbamazepine Crystal Forms using an Artificial Stomach-Duodenum Model

STEPHEN R. CARINO, DAVID C. SPERRY, MICHAEL HAWLEY

Pfizer Corporation, Michigan Pharmaceutical Sciences, 7000 Portage Road, Kalamazoo, Michigan 49001

Received 4 May 2005; revised 17 August 2005; accepted 23 August 2005

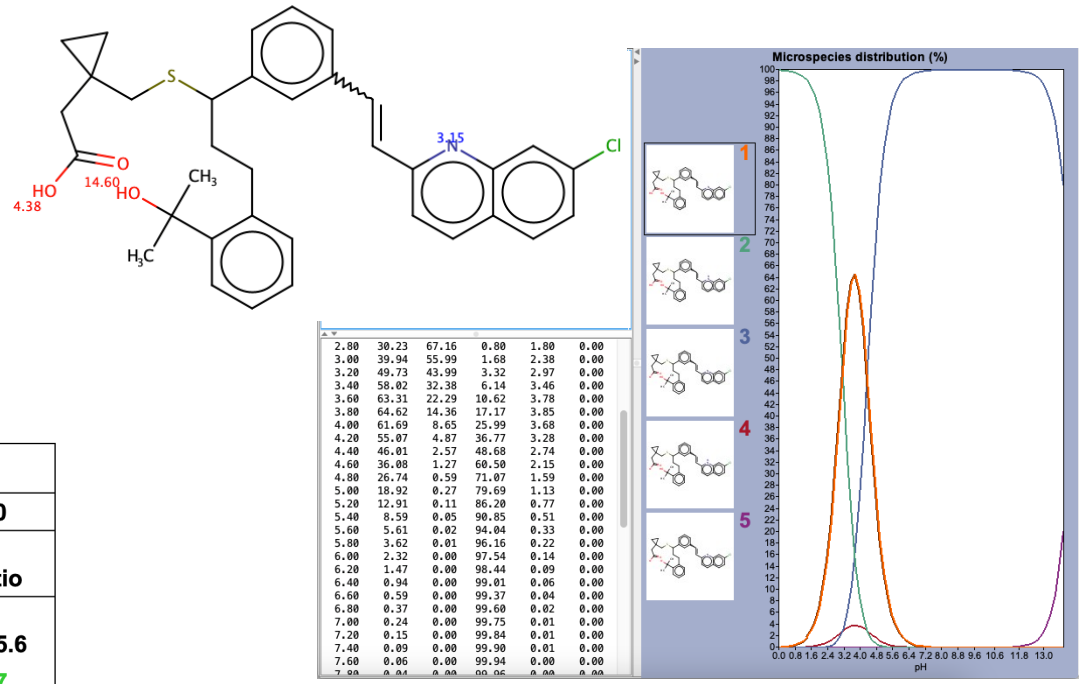
Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20495

ABSTRACT: The *in vitro* dissolution of carbamazepine (CBZ) was investigated using an automated artificial stomach-duodenum (ASD) model. Successful simulation of the dog physiology in the fasted state showed that the rank order of the ASD estimated bioavailabilities is as follows: Form III > Form I > dihydrate. This result is in excellent agreement with those found in literature. Additional simulations comparing different gastric transit times during fasted and fed states are also discussed. J Pharm Sci 95:116–125, 2006

Keywords: carbamazepine; solid forms; dissolution; bioavailability; *in vitro* models; solubility; solid state; thermodynamics; preformulation; polymorphs

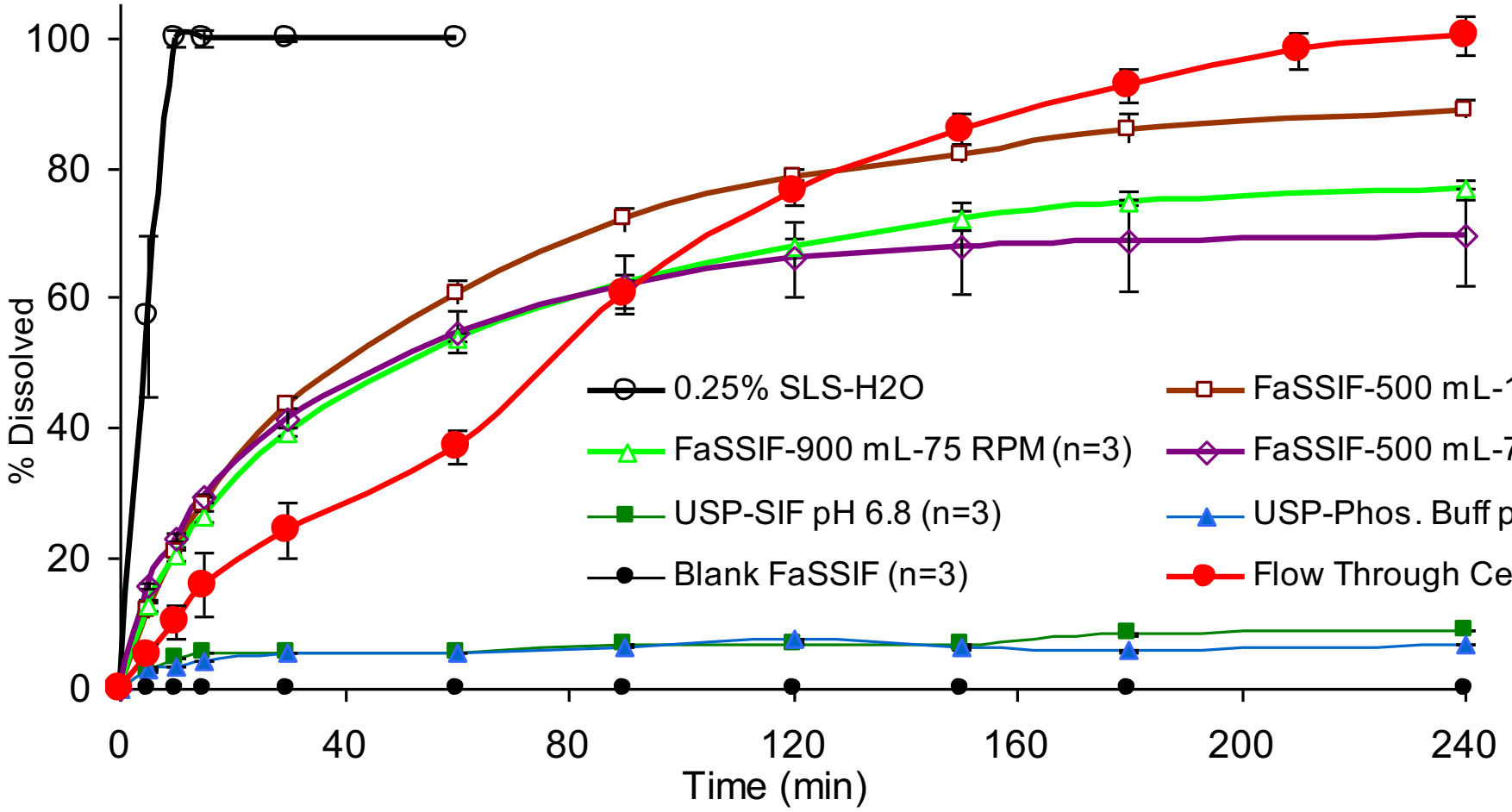
Example: Dissolution controlled Absorption Dynamic Dissolution of Montelukast Sodium

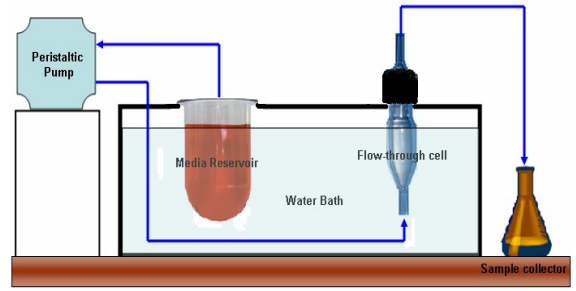
- pKa = 3.1 and 5.7 Basic and Acetic
- logP = 7.01, highly lipophilic
- >99% bound to plasma proteins
- Oral bioavailability variable 58-70% (Cheng, et al 1996)



			Dose (mg)	
			4	10
	pH	Solubility (mg/mL)	Dose/solubility ratio	
SGF (without enzymes)	1.2	0.00018	27777.8	55555.6
SGF-0.25% SLS	2.0	0.240	16.7	41.7
Acetate Buffer	4.1	0.002	2500.0	5000.0
LQ-FeSSIF	5.0	0.030	133.3	333.3
HQ-FeSSIF	5.0	0.015	266.7	666.7
LQ-FaSSIF	6.5	0.020	200.0	500.0
HQ-FaSSIF	6.5	0.205	19.5	48.8
LQ-FaSSIF	7.5	3.370	1.2	3.0
HQ-FaSSIF	7.5	4.690	0.9	2.1

Dissolution Profiles





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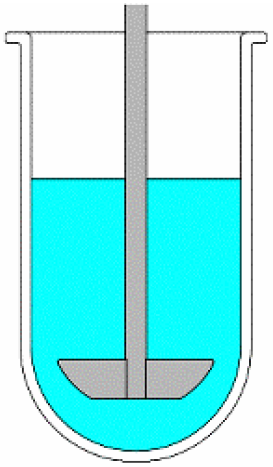
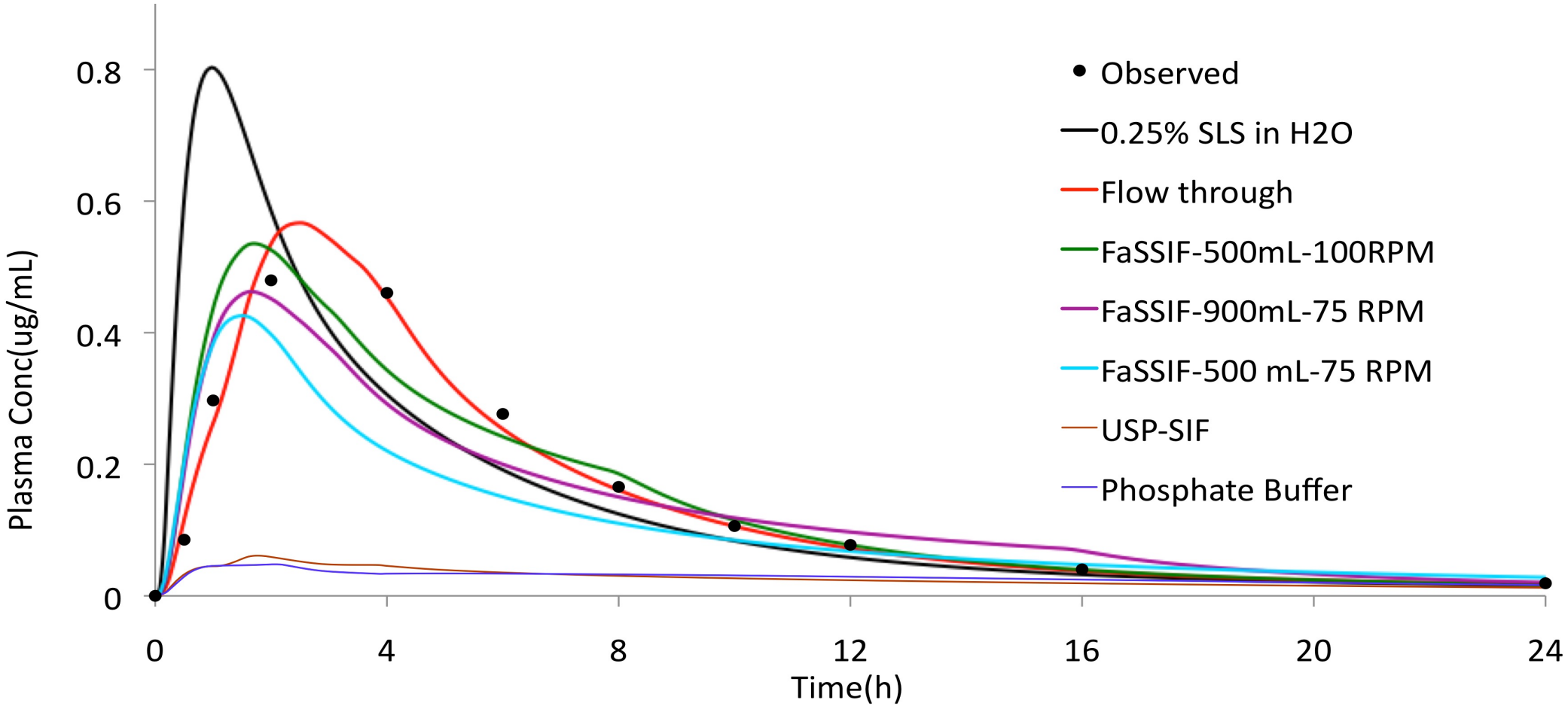


Simulations Results



Dynamic Dissolution Testing To Establish *In Vitro*/*In Vivo* Correlations for Montelukast Sodium, a Poorly Soluble Drug

Arthur Okumu,[1] Marie DiMaso,[2] and Raimar Löbenberg[1,3]

Pharmaceutical Research, Vol. 25, No. 12,
DOI: 10.1007/s11095-008-9642-z

Received April 15, 2008; accepted May 28, 2008; published online June 17, 2008

Purpose. The objectives of the study was to develop a dissolution test method that can be used to predict the oral absorption of montelukast sodium, and to establish an *in vitro*/*in vivo* correlation (IVIVC) using computer simulations.

Methods. Drug solubility was measured in different media. The dissolution behaviour of montelukast sodium 10 mg film coated tablets was studied using the flow-through cell dissolution method following a

Dynamic dissolution testing using the flow through cell seems to be a powerful tool to establish in vitro/in vivo correlations for poorly soluble drugs as input function into GastroPlus.

Open Access Article

An In Vivo Predictive Dissolution Methodology (iPD Methodology) with a BCS Class IIb Drug Can Predict the In Vivo Bioequivalence Results: Etoricoxib Products

by Isabel Gonzalez-Alvarez [1,2], Marival Bermejo [1,2,*], Yasuhiro Tsume [1], Alejandro Ruiz-Picazo [2], Marta Gonzalez-Alvarez [2], Bart Hens [1], Alfredo Garcia-Arieta [3,†], Greg E. Amidon [1] and Gordon L. Amidon [1]

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[2] Department Engineering Pharmacy Section, Miguel Hernandez University, San Juan de Alicante, 03550 Alicante, Spain

[3] División de Farmacología y Evaluación Clínica, Departamento de Medicamentos de Uso Humano, Agencia Española de Medicamentos y Productos Sanitarios, 28022 Madrid, Spain

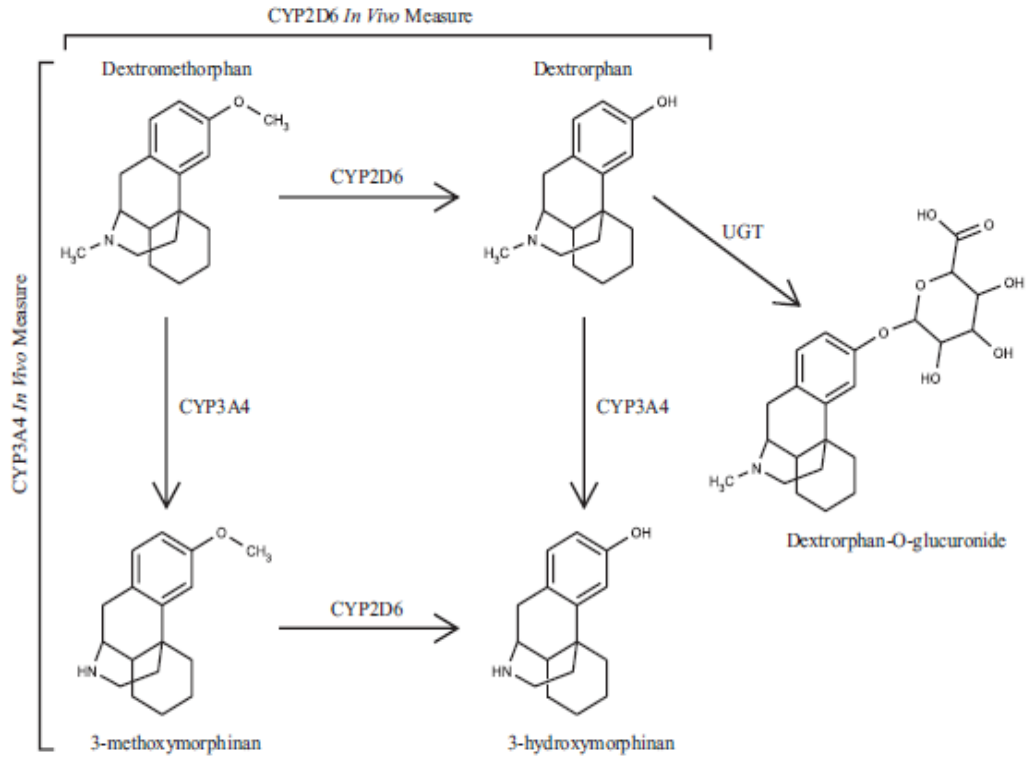
[*] Author to whom correspondence should be addressed.

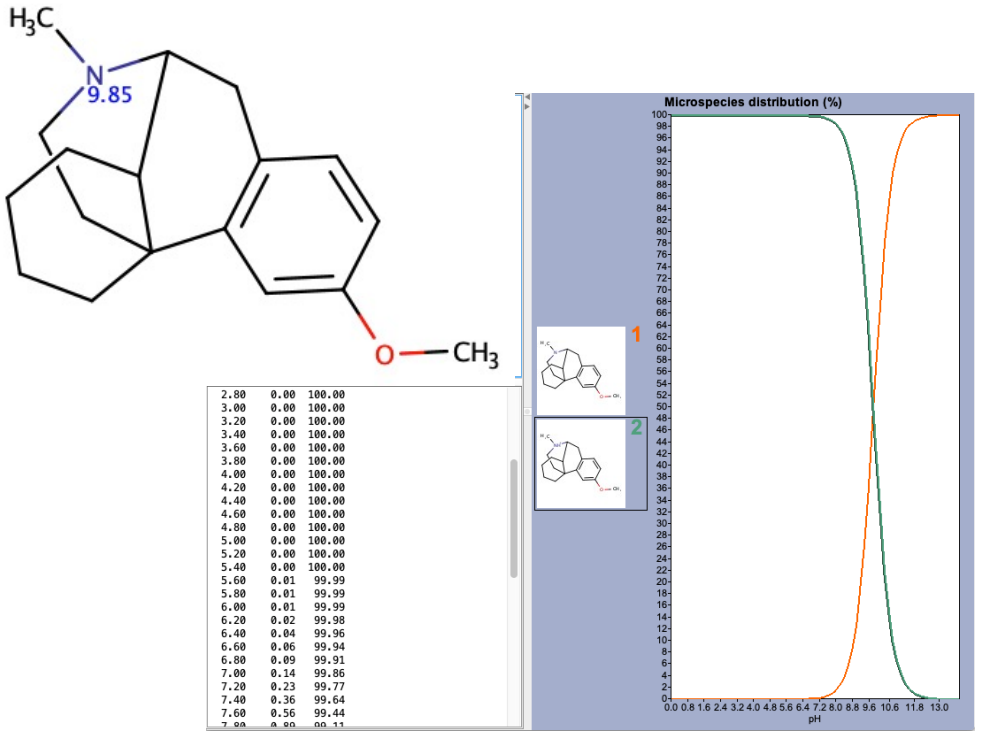
[†] This manuscript represents the personal opinion of the author and does not necessarily represent the views or policy of the Spanish Agency for Medicines and Health Care Products.

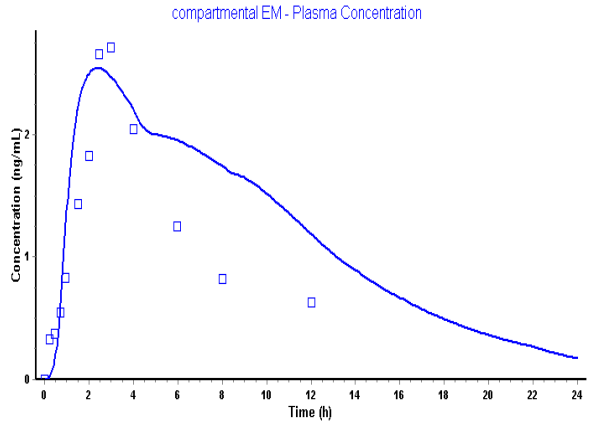
Pharmaceutics **2021**, *13*(4), 507; **https://doi.org/10.3390/pharmaceutics13040507**

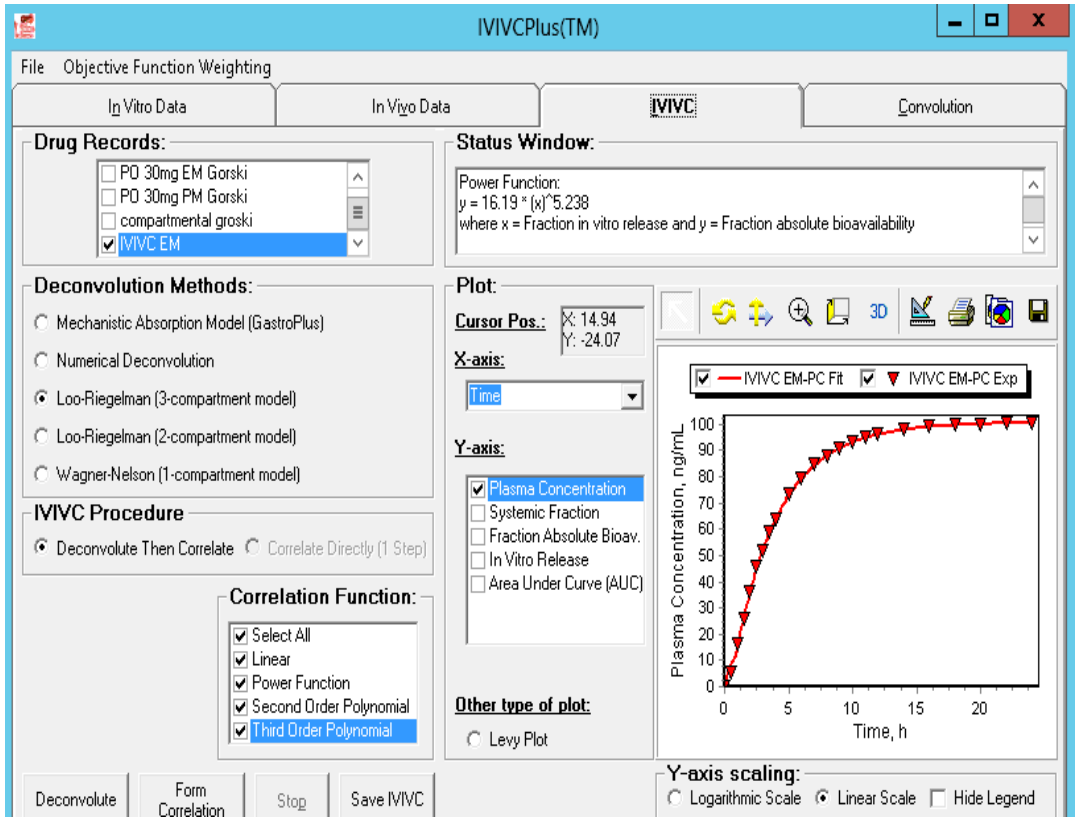
Example: Lysosomal trapping of Dextromethorphan

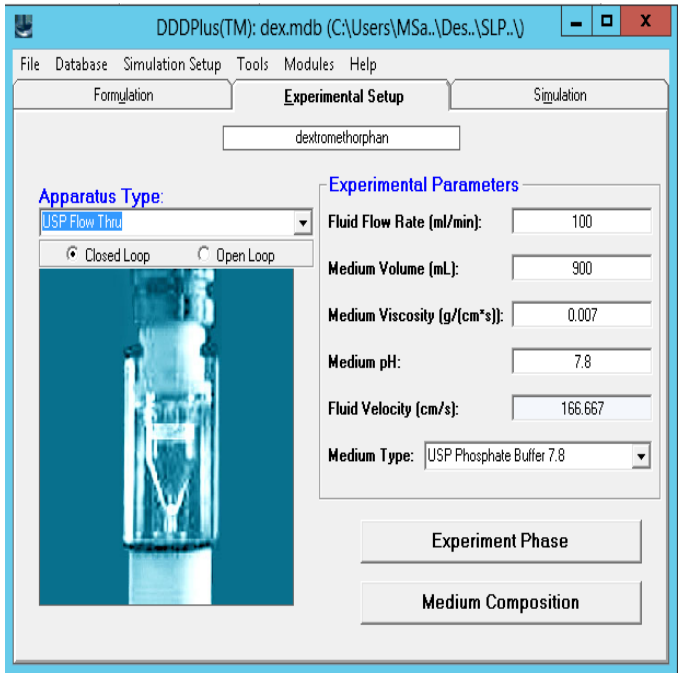
- Weak bases with high pKa
- Pharmacokinetic differences EM/PM






compartmental EM - Plasma Concentration
Concentration (ng/mL)
Time (h)


IVIVCPlus(TM)
File
Objective Function Weighting
In Vitro Data
In Vivo Data
IVIVC
Convolution
Drug Records:
PO 30mg EM Gorski
PO 30mg PM Gorski
compartmental groski
IVIVC EM
Status Window:
Power Function:
y = 16.19 * (x)^5.238
where x = Fraction in vitro release and y = Fraction absolute bioavailability
Deconvolution Methods:
Mechanistic Absorption Model (GastroPlus)
Numerical Deconvolution
Loo-Riegelman (3-compartment model)
Loo-Riegelman (2-compartment model)
Wagner-Nelson (1-compartment model)
IVIVC Procedure
Deconvolute Then Correlate
Correlate Directly (1 Step)
Correlation Function:
Select All
Linear
Power Function
Second Order Polynomial
Third Order Polynomial
Plot:
Cursor Pos.:
X: 14.94
Y: -24.07
X-axis:
Time
Y-axis:
Plasma Concentration
Systemic Fraction
Fraction Absolute Bioav.
In Vitro Release
Area Under Curve (AUC)
Other type of plot:
Levy Plot
IVIVC EM-PC Fit
IVIVC EM-PC Exp
Plasma Concentration, ng/mL
Time, h
Y-axis scaling:
Logarithmic Scale
Linear Scale
Hide Legend
Deconvolute
Form Correlation
Stop
Save IVIVC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File
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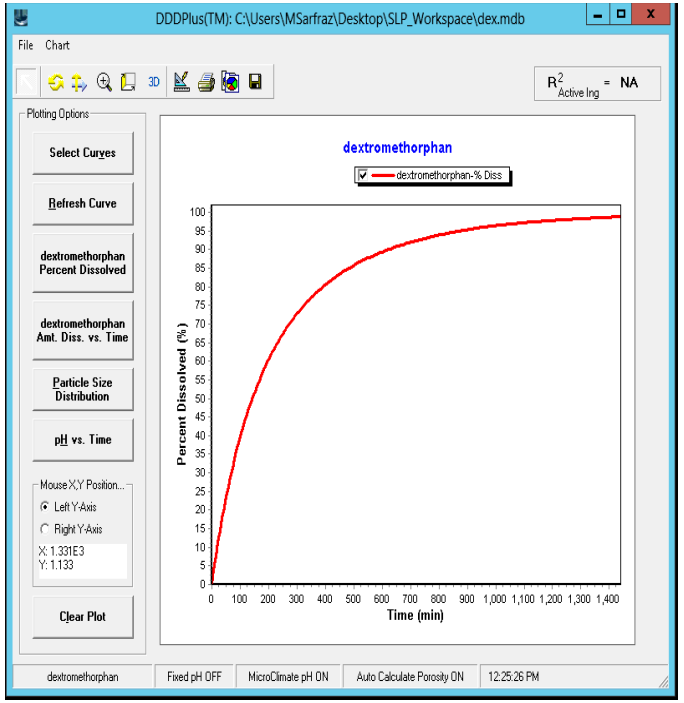
Simulation Setup
Tools
Modules
Help
Formulation
Experimental Setup
Simulation
dextromethorphan
Apparatus Type:
USP Flow Thru
Closed Loop
Open Loop
Experimental Parameters
Fluid Flow Rate (ml/min): 100
Medium Volume (mL): 900
Medium Viscosity (g/(cm*s)): 0.007
Medium pH: 7.8
Fluid Velocity (cm/s): 166.667
Medium Type: USP Phosphate Buffer 7.8
Experiment Phase
Medium Composition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File
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Plotting Options
Select Curves
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dextromethorphan Percent Dissolved
dextromethorphan Amt. Diss. vs. Time
Particle Size Distribution
pH vs. Time
Mouse X,Y Position...
Left Y-Axis
Right Y-Axis
X: 1.331E3
Y: 1.133
Clear Plot
dextromethorphan
dextromethorphan-% Diss
Percent Dissolved (%)
Time (min)
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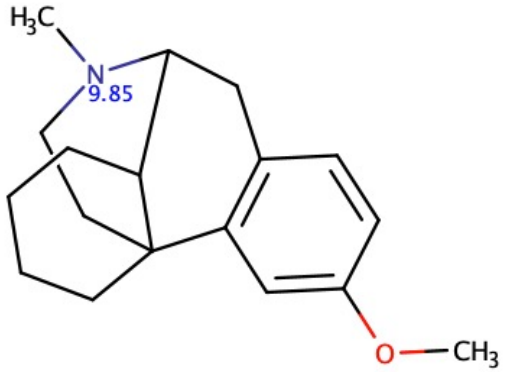
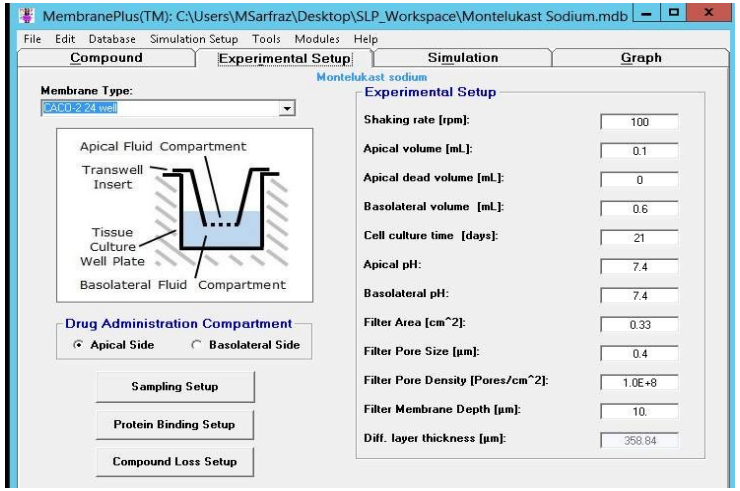
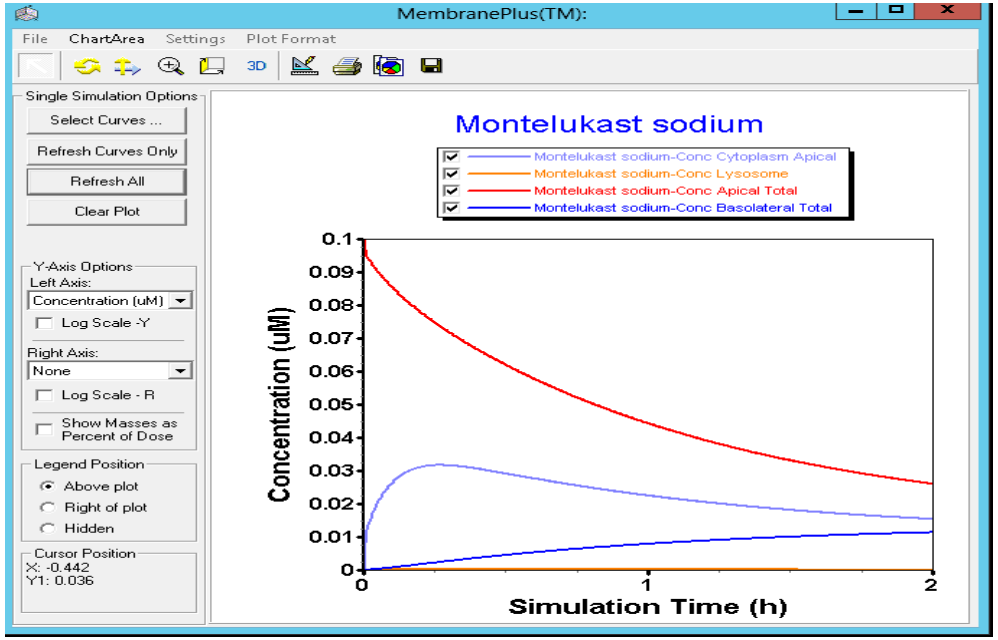
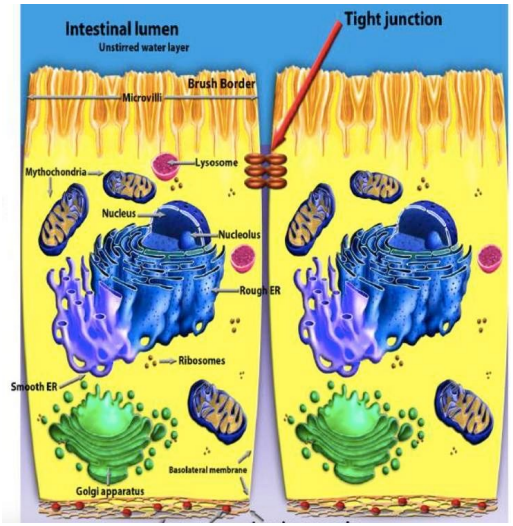
MicroClimate pH ON
Auto Calculate Porosity ON
12:25:26 PM

Membrane Plus simulations







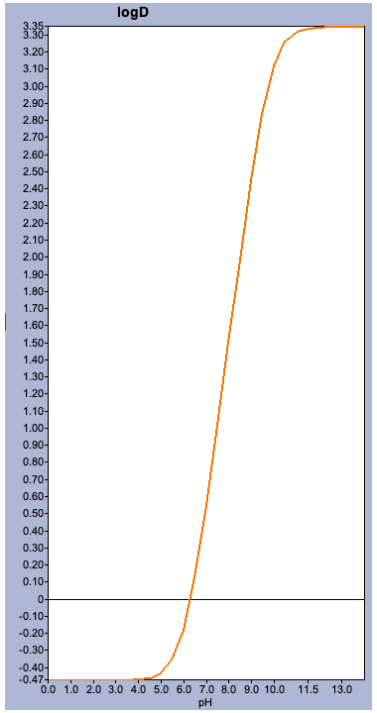


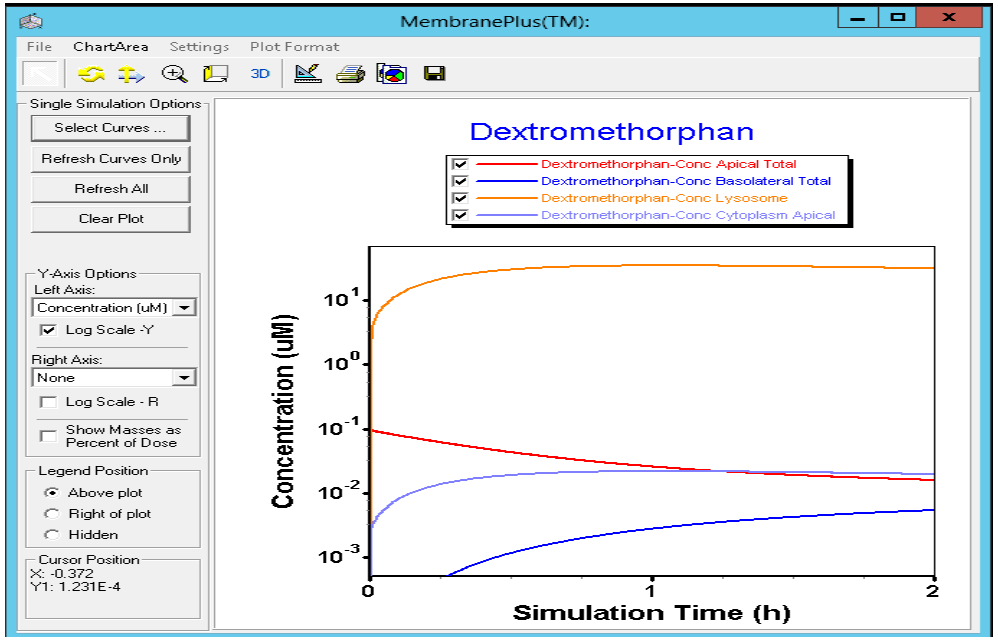
Gut: pH 5.5 -7.0

Cytoplasm pH 7

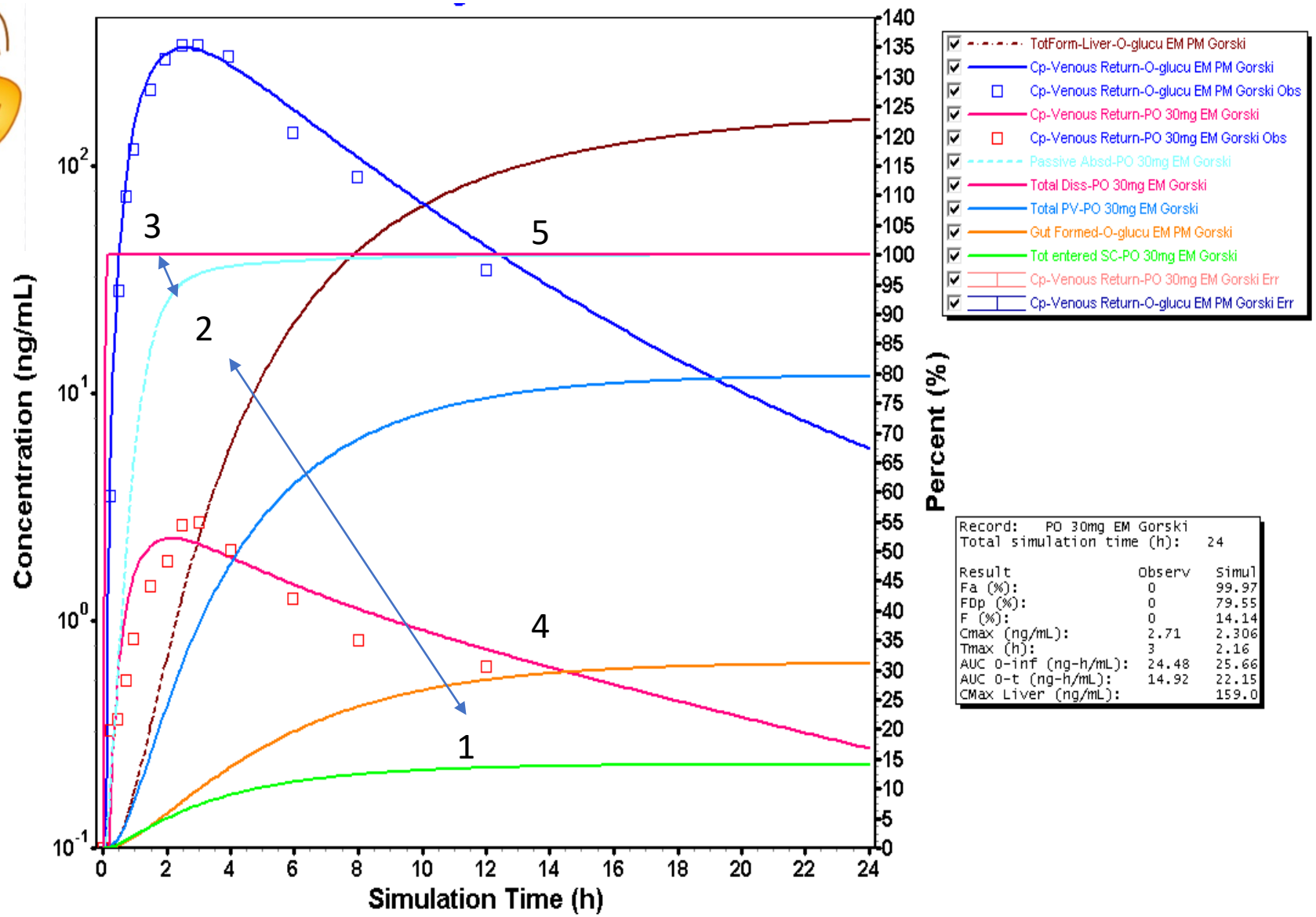
Lysosome: pH 4.5 -5.5

Blood 7.4





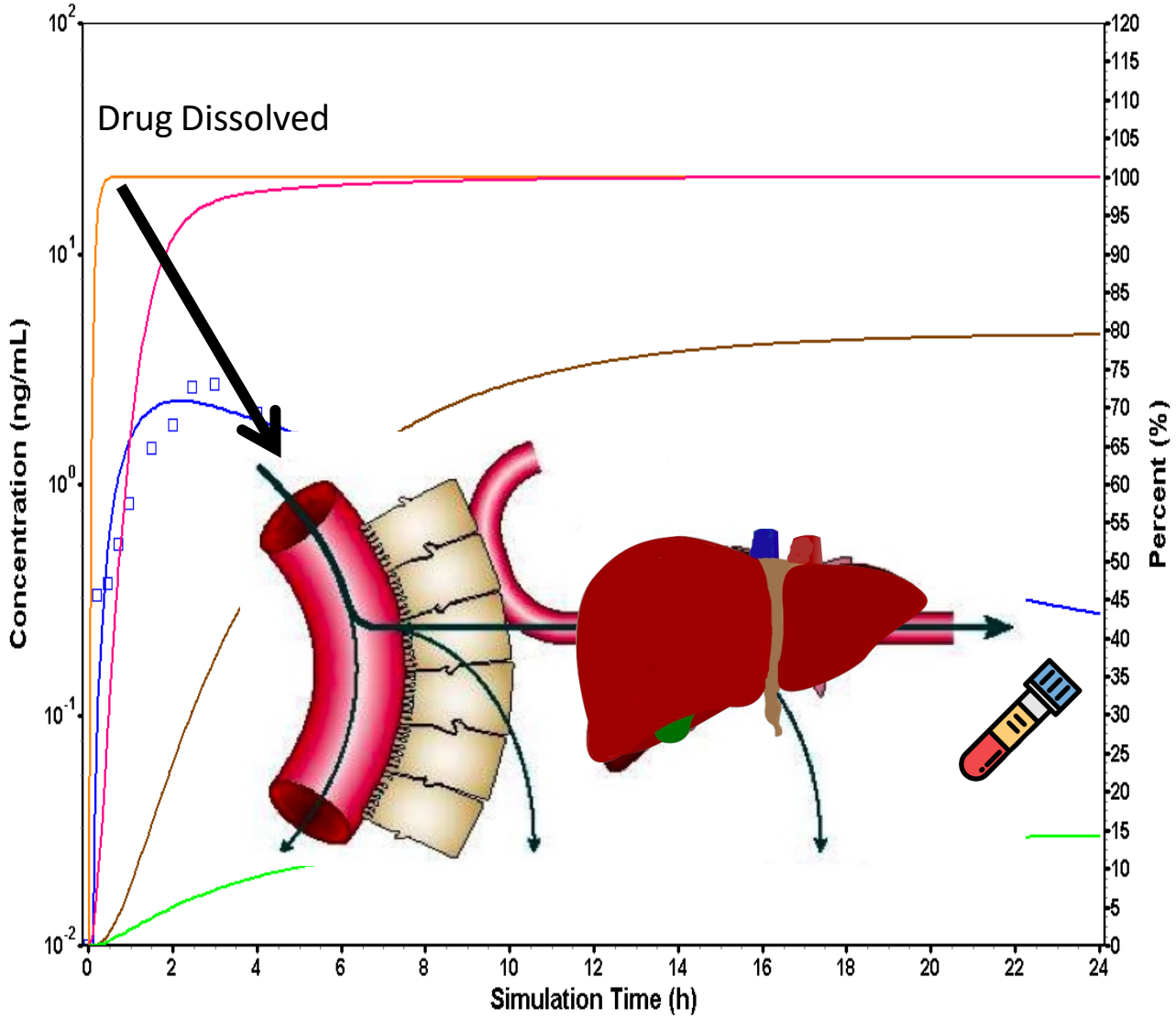
Simulation of PO 30mg EM Gorski study



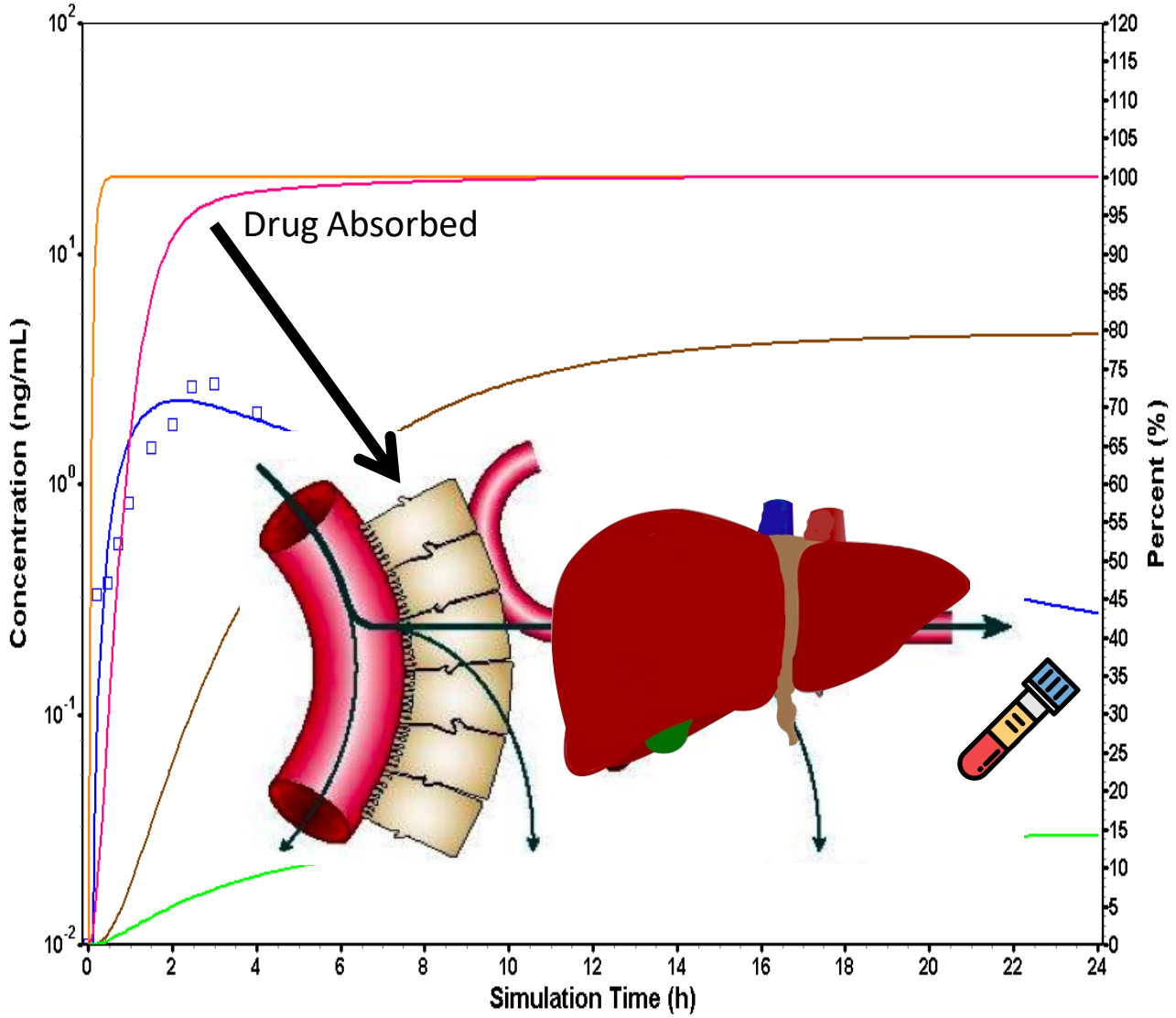
Record: PO 30mg EM Gorski
Total simulation time (h): 24

Result	Observ	Simul
Fa (%):	0	99.97
FDp (%):	0	79.55
F (%):	0	14.14
Cmax (ng/mL):	2.71	2.306
Tmax (h):	3	2.16
AUC 0-inf (ng-h/mL):	24.48	25.66
AUC 0-t (ng-h/mL):	14.92	22.15
CMax Liver (ng/mL):		159.0

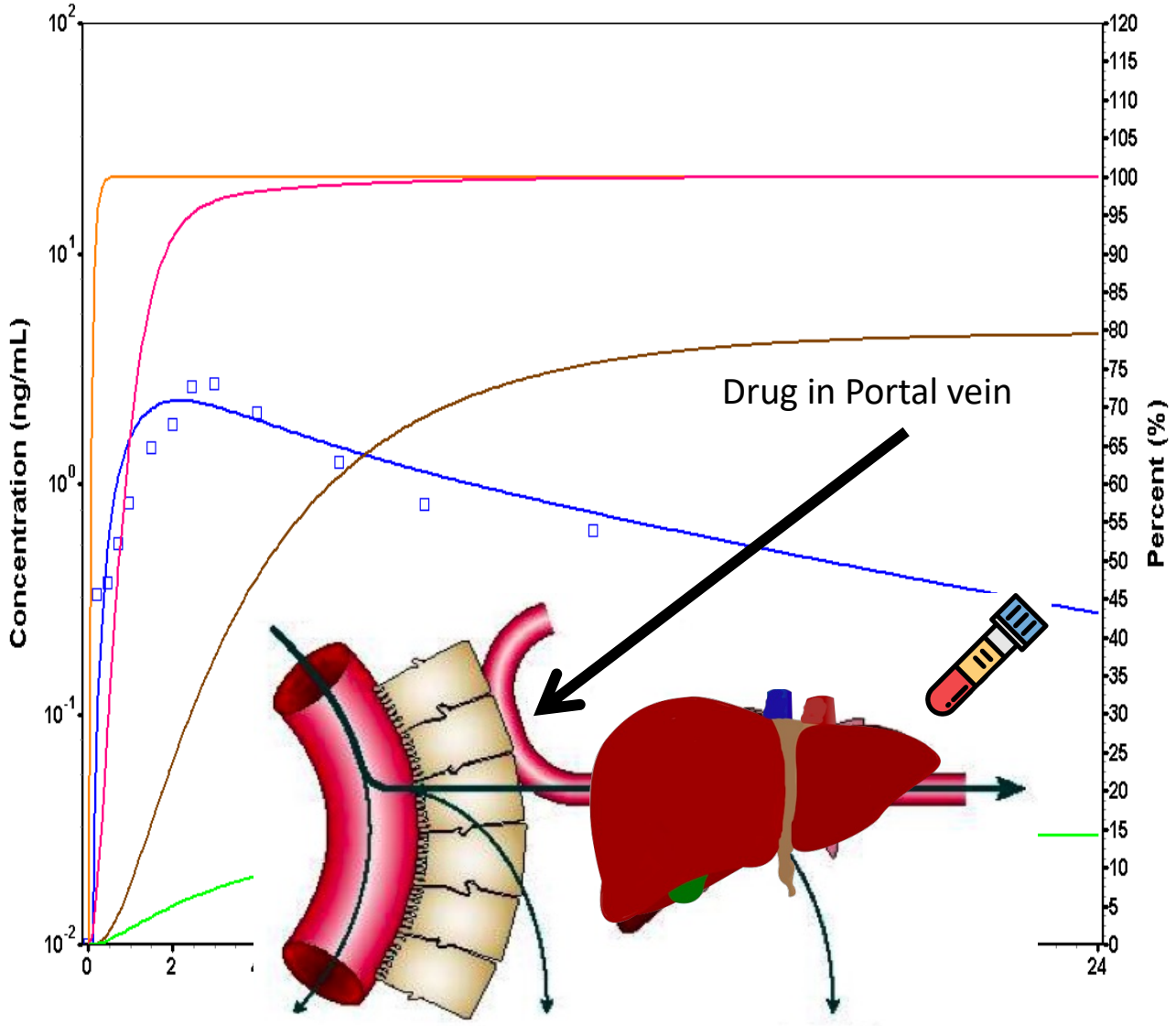
Dextromethorphan
in Extensive metabolizers



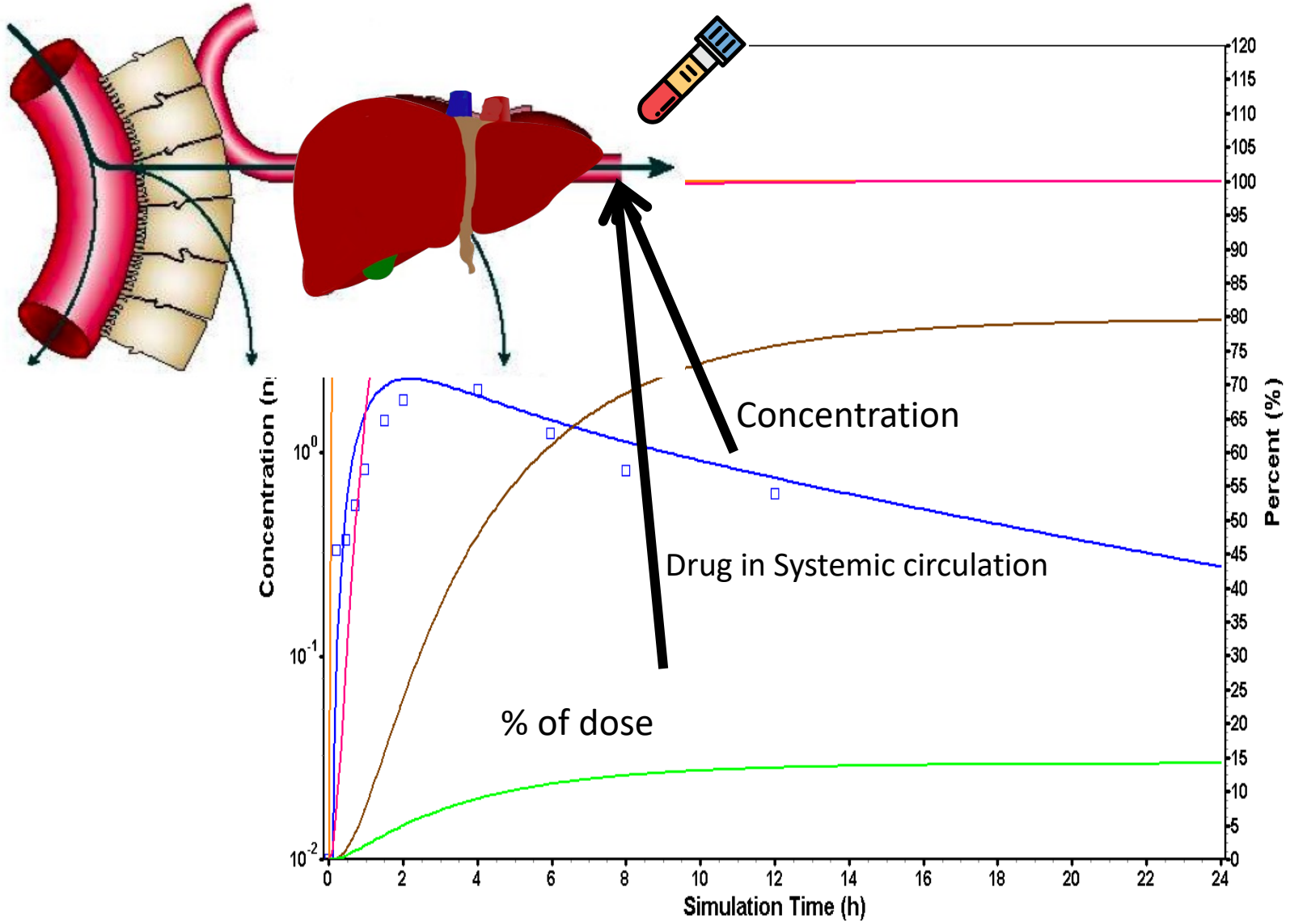
Dextromethorphan in Extensive metabolizers



Dextromethorphan
in Extensive metabolizers



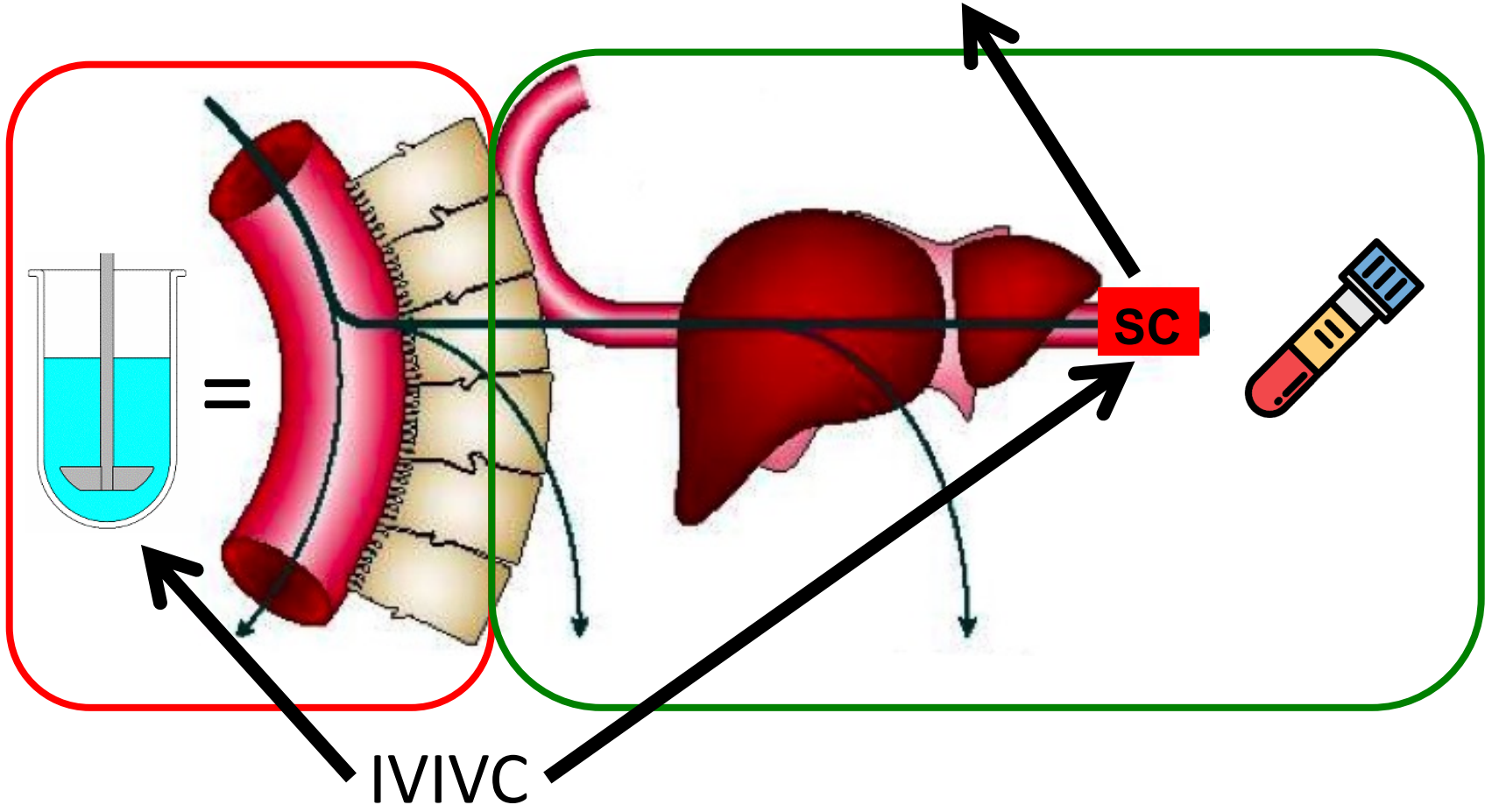
Dextromethorphan in Extensive metabolizers



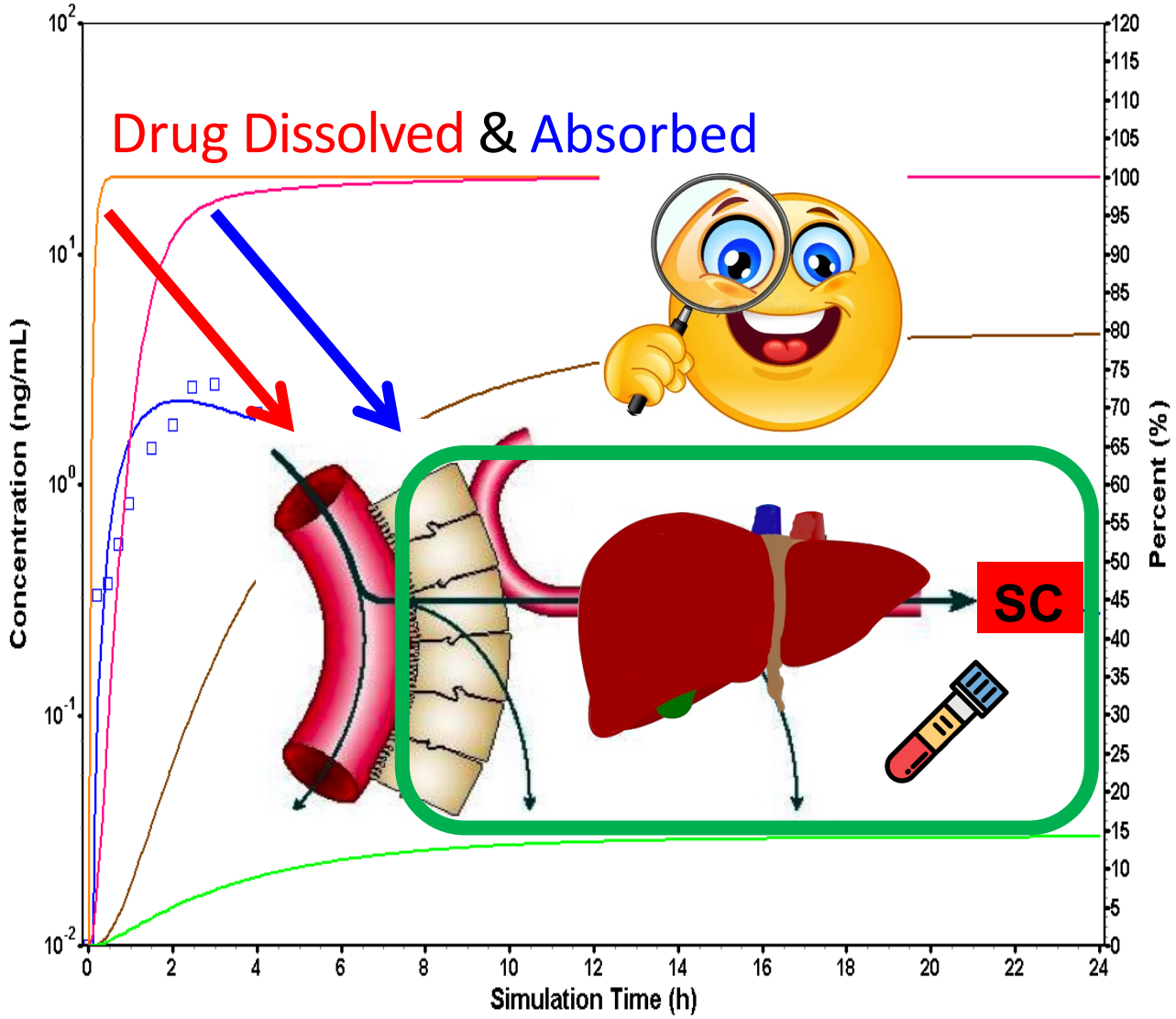
Classical PK model

Wagner Nelson: $D_0 = D_{body} + D_{urine} + D_{not\ Abs}$

$\%\ D_{Abs} = D_{body} + D_{urine}$



Dosage form impact is limited to the gut lumen / enterocyte interface!!!



Journal of Pharmaceutical Sciences 108 (2019) 268-278

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

The Irrelevance of *In Vitro* Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping

Michael B. Bolger [1,2], Joyce S. Macwan [1], Muhammad Sarfraz [3,4], May Almukainzi [5], Raimar Löbenberg [3,*]

[1] Simulations Plus, Inc., Lancaster, California 93534
[2] USC School of Pharmacy, Pharmacology and Pharmaceutical Sciences, Los Angeles, California 90089
[3] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, T6G 2E1 Canada
[4] College of Pharmacy, Al Ain University of Science and Technology, Al Ain, United Arab Emirates
[5] College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia

For this class of drug, the rate of in vitro and in vivo dissolution is not a sensitive factor in determining bioequivalence.

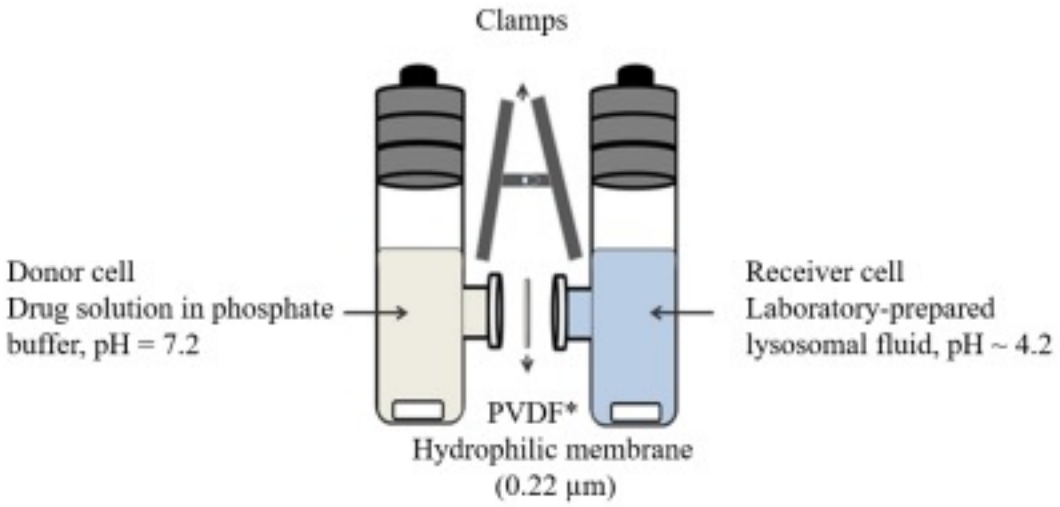
This study shows that dissolution and the rate of absorption into the enterocytes are clinically irrelevant for the performance of DEX immediate release product. **An understanding of the entire underlying mechanistic processes of drug disposition is needed to define clinically relevant product specifications for DEX.**

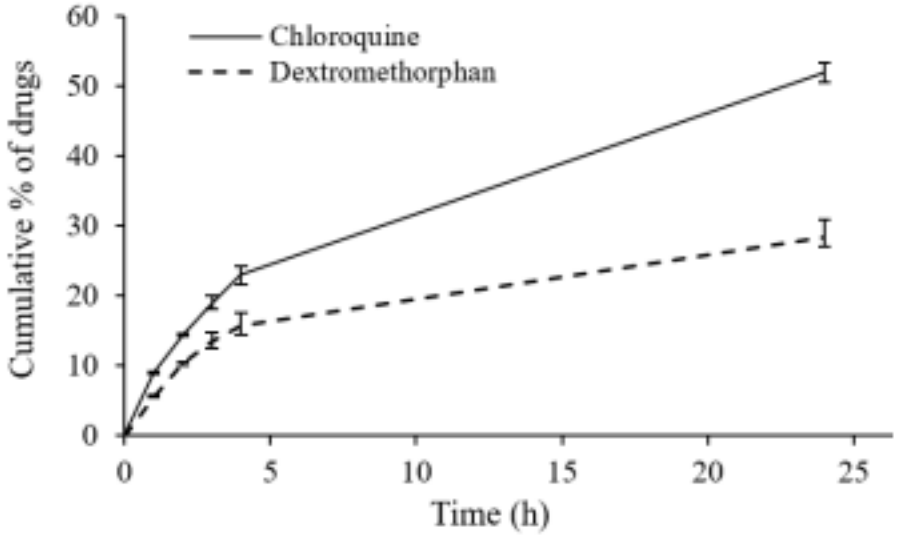
Sub-cellular sequestration of alkaline drugs in lysosomes: new insights for pharmaceutical development of lysosomal fluid

Malaz Yousef[1,2], Tyson S. Le[1], Jieyu Zuo[1], Chulhun Park[3], Nadia Bou Chacra[4], Neal M. Davies[1,*], and Raimar Löbenberg[1,*]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada.
[2]Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.
[3]College of Pharmacy, Jeju National University, Jeju 63243, South Korea.
[4]Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, Brazil.

The obtained result helps fill the void with a lysosomal fluid that can be used to examine various factors related to pharmaceutical product performance including dissolution, solubility, and disposition which are relevant and necessary parts of drug and product development.





Enteric Coated Dosage Forms

European Journal of Pharmaceutics and Biopharmaceutics 142 (2019) 8–19

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Simulated, biorelevant, clinically relevant or physiologically relevant dissolution media: The hidden role of bicarbonate buffer

Daniela Amaral Silva[a], Jozef Al-Gousous[b], Neal M. Davies[a], Nadia Bou Chacra[c], Gregory K. Webster[d], Elke Lipka[e], Gordon Amidon[b], Raimar Löbenberg[a,*]

Considerable discrepancies between phosphate and bicarbonate buffer dissolution results have been reported for certain dosage forms, e.g. enteric coated formulations.
The role and need of bicarbonate-based buffers in quality control testing requires scientific analysis.

buffer systems has evolved. However, there are inherent difficulties associated with these buffers, such as

1946

Canadian Medical Association
Journal
Volume 55, Issue 5,
1946, Pages 445-447

THE ABSORPTION OF ENTERIC-COATED AMMONIUM CHLORIDE

By Frances L. Selye, M.D.

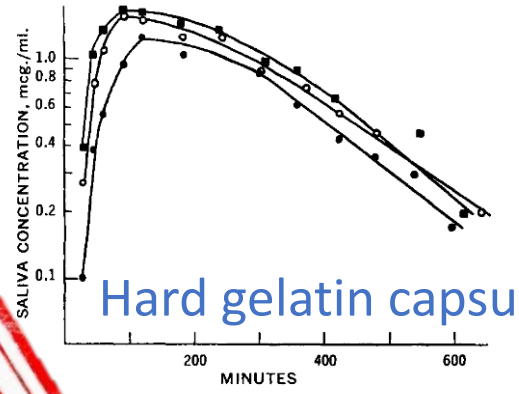
Conclusions

1. In a small percentage of cases enteric-coated ammonium chloride tablets pass unchanged through the gastro-intestinal tract.
2. In a larger percentage of cases, and i both healthy young adults tested, prolong administration of such tablets results in n acidosis although the tablets are destroyed before excretion, presumably at a level too low in the intestinal tract to allow effective absorption.
3. Ammonium chloride when administered in a gelatin-coated tablet is invariably absorbed and only rarely not well tolerated.

FAILURE

1972

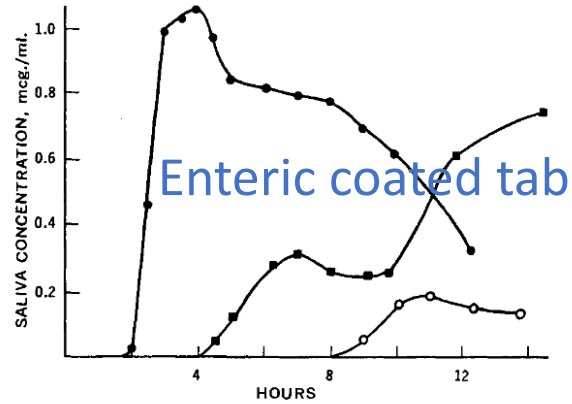
Concentration of salicylic acid in saliva



Hard gelatin capsules

b

Concentrations of salicylic acid in saliva following the ...tion of 650 mg. aspirin in hard gelatin capsules on three ...nt occasions. Blood samples were also taken in one experi-...nt (●). Key: a, Subject 1; and b, Subject 2.



Enteric coated tablets

Figure 4—*Concentrations of salicylic acid in saliva of three subjects following the administration of 650 mg. aspirin in enteric-coated tablets.*

European Journal of Pharmaceutics and Biopharmaceutics 139 (2019) 47–58

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

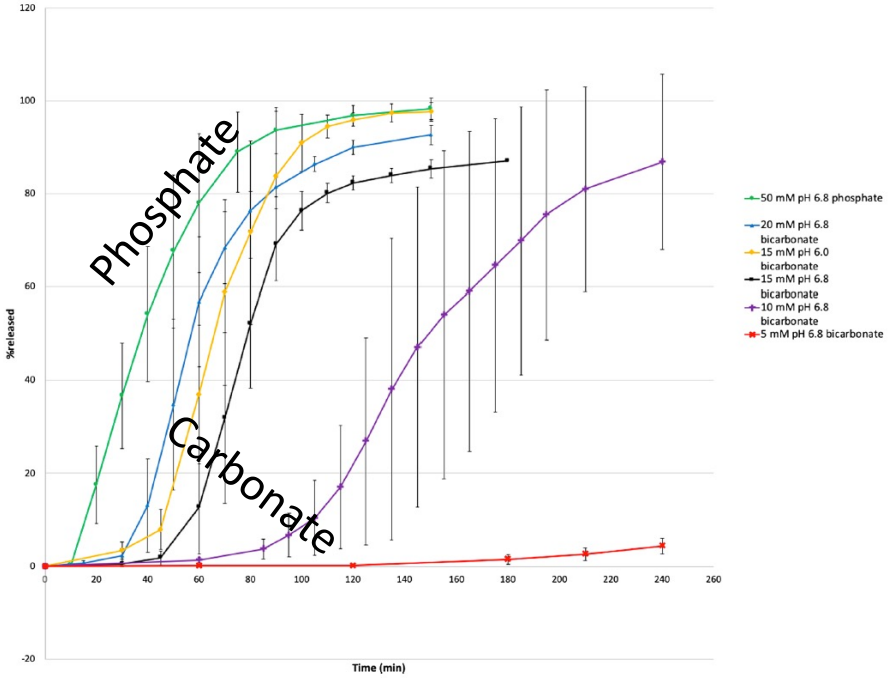
journal homepage: www.elsevier.com/locate/ejpb

Research paper

Mechanistic analysis and experimental verification of bicarbonate-controlled enteric coat dissolution: Potential *in vivo* implications

J. Al-Gousous[a,*,1], H. Ruan[a,b,1], J.A. Blechar[c], K.X. Sun[a], N. Salehi[d], P. Langguth[c], N.M. Job[a], E. Lipka[e], R. Loebenberg[f], M. Bermejo[g], G.E. Amidon[a], G.L. Amidon[a]

[a] College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109, USA
[b] Department of Chemical Drug, Zhejiang Institute for Food and Drug Control, Hangzhou, Zhejiang 310052, China
[c] Institute of Pharmacy and Biochemistry, Johannes Gutenberg Universität Mainz, Staudingerweg 5, 55128 Mainz, Germany
[d] Department of Chemical Engineering, University of Michigan, 300 Hayward St, Ann Arbor, MI 48109, USA
[e] TSRL Inc., 540 Avis Drive, Ann Arbor, MI 48108, USA
[f] Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2H7, Canada
[g] Department of Engineering, Pharmacy Section, Miguel Hernandez University , San Juan de Alicante, 03550 Alicante, Spain



These results demonstrate the importance of thoroughly investigating the intestinal bicarbonate concentrations and using bicarbonate buffers or properly designed surrogates (if possible) when evaluating enteric drug products during product development and quality control.

rapid to reach equilibrium in the diffusion layer surrounding a dissolving ionizable solid. This results in the effective pKa of bicarbonate in the diffusion layer being lower than that determined potentiometrically at

Journal of Controlled Release 325 (2020) 323–334

Contents lists available at ScienceDirect

Journal of Controlled Release

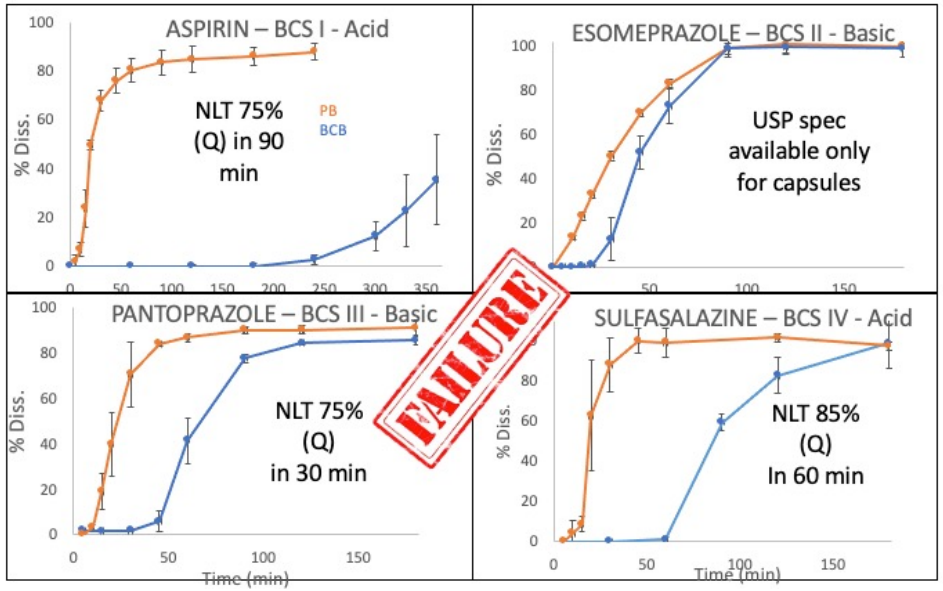
journal homepage: www.elsevier.com/locate/jconrel

Mechanistic understanding of underperforming enteric coated products: Opportunities to add clinical relevance to the dissolution test

Table 4
USP tolerance specification for drug release in the buffer stage and percent released in PB and BCB.

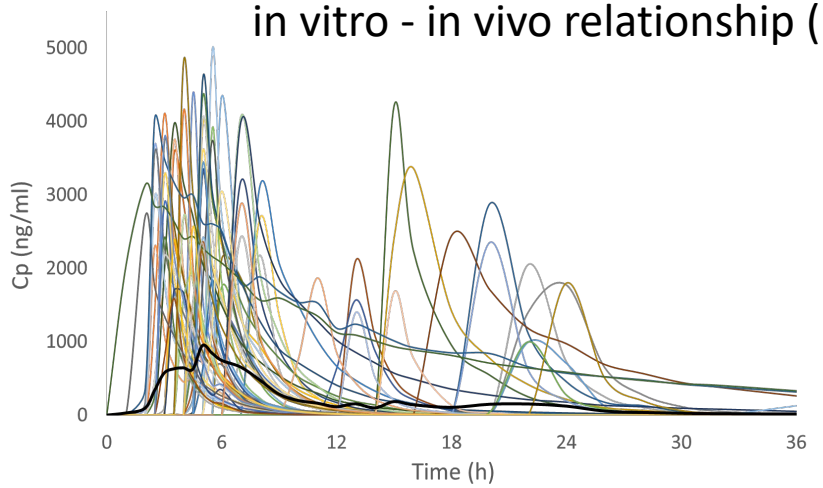
Drug	USP tolerance specification	Q (%) at the specified time	
		PB	BCB
Aspirin	NLT 75% in 90 minutes	83.4%	0.0%
Pantoprazole sodium	NLT 75% in 30 minutes	78.6%	1.80%
Sulfasalazine	NLT 85% in 60 minutes	99.3%	1.10%
Diclofenac sodium	NLT 75% in 45 minutes	90.4%	0.40%
Esomeprazole magnesium*	N/A	N/A	N/A

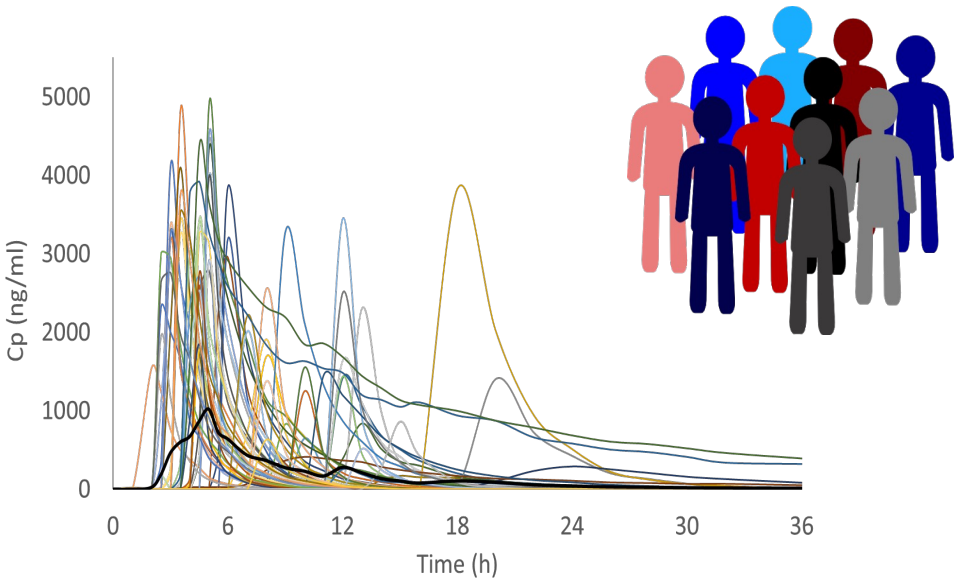
All formulations displayed a fast release in phosphate buffer and complied with the compendial performance specifications.
On the other hand, they all had a much slower drug release in bicarbonate buffer and failed the USP acceptance criteria. Also, the nature of the drug (acid vs base) impacted the dissolution behavior in BCB.
This pilot study indicates that **compendial dissolution test for enteric coated tablets lacks physiological relevance** and it needs to be re-evaluated.
Thus, an in vivo relevant performance method for EC products is needed.

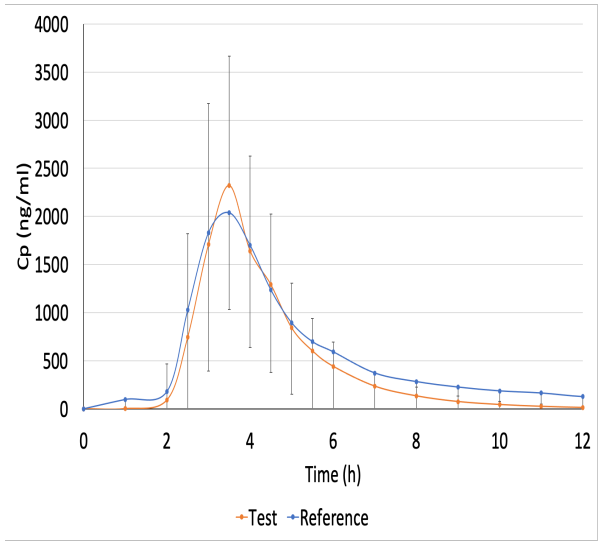


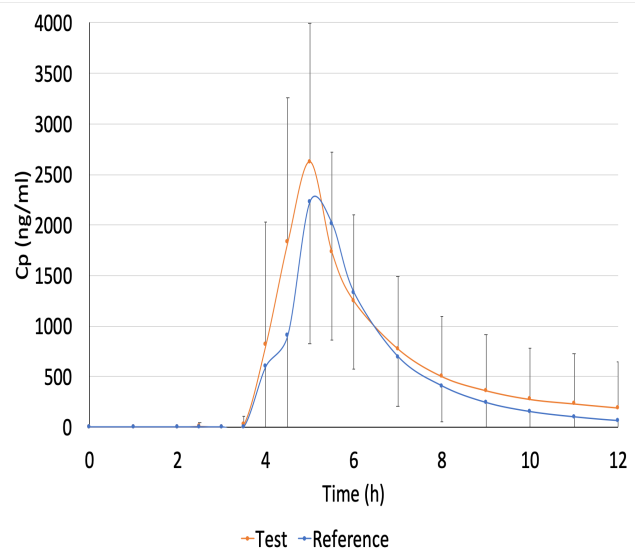
Analysis of a failed in vivo BE study of Pantoprazole

In this study we investigated the use of in vitro biopredictive dissolution conditions together with alternative in vitro - in vivo relationship (IVIVR) approaches to support the development of EC formulations.





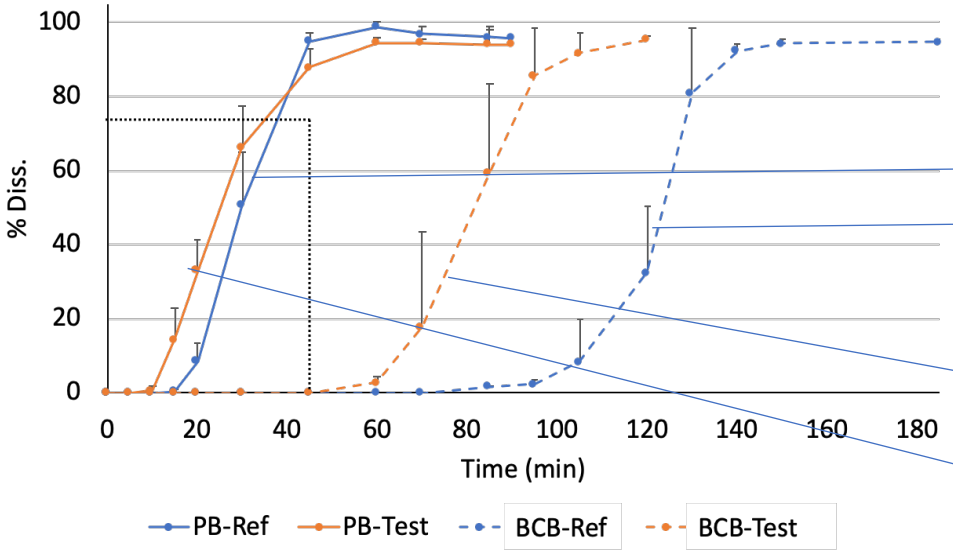


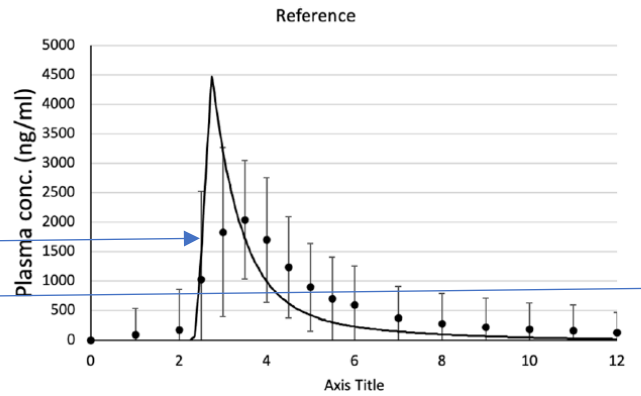


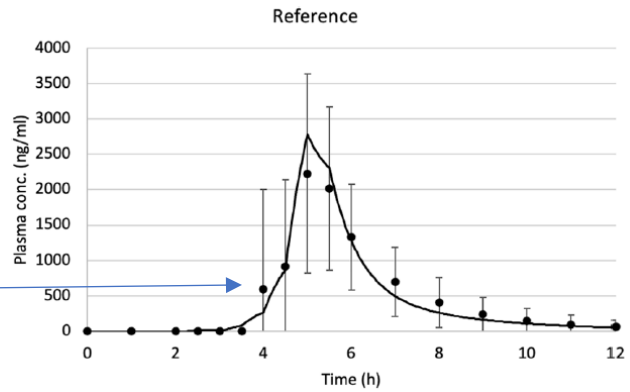
Number of subjects per Tmax cohort for test and reference fo

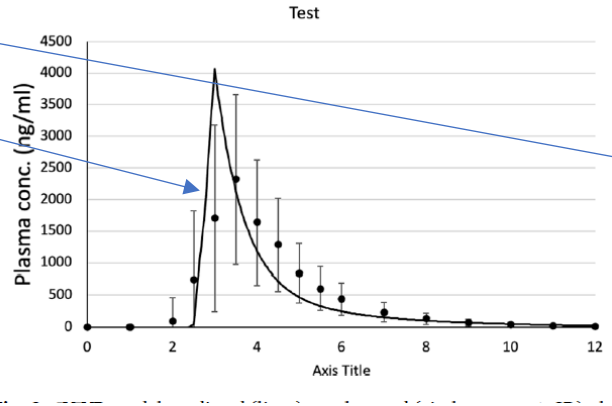
Tmax cohort	Number of subjects	
	Reference	Test
Cohort 1 (2.0-3.5h)	21	17
Cohort 2 (4.0-5.5h)	22	22
Cohort 3 (After 6.0)	27	31
Total	70	70

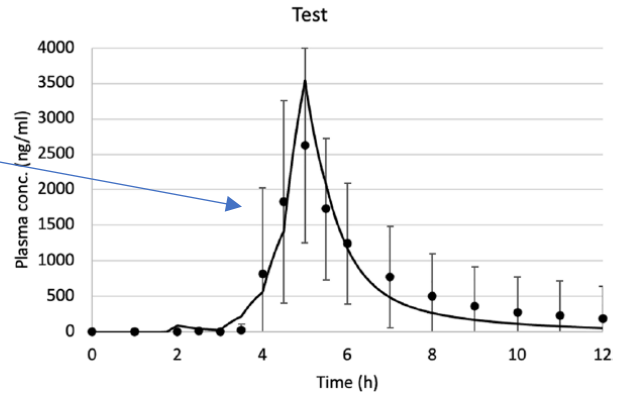
Analysis of a failed in vivo BE study of Pantoprazole











Convolution validation statistics for Test and Reference.

	Cmax (ng/mL)		% Pred error	AUC (ng/mL*h)		% Pred error	Rsq	SEP	MAE	AIC
	Obs.	Pred.		Obs.	Pred.					
Reference Cohort 1 (PB)	2037	4472	119.5	6668	5165	22.5	0.766	467.8	341	259.2
Test Cohort 1 (PB)	2321	4064	75.1	5388	4900	9.05	0.723	636.2	314.2	269.7
Reference Cohort 2 (BCB)	2227	2774	24.5	5435	5176	4.7	0.952	183.6	109.9	227.4
Test Cohort 2 (BCB)	2624	3538	34.8	6546	5940	9.2	0.909	294.1	204.8	243.4

BCB: Bicarbonate buffer; PB: Phosphate buffer.

International Journal of Pharmaceutics 605 (2021) 120857

Contents lists available at ScienceDirect

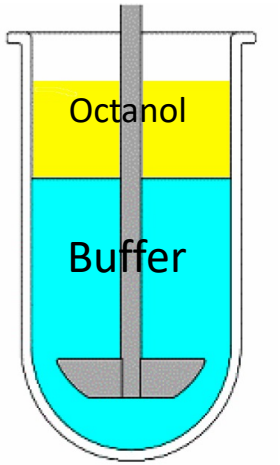
International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

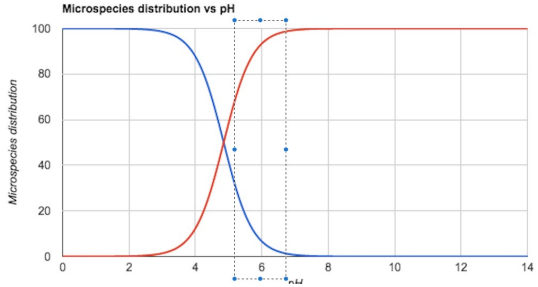
Physiologically relevant dissolution conditions towards improved in vitro - in vivo relationship – A case study with enteric coated pantoprazole tablets

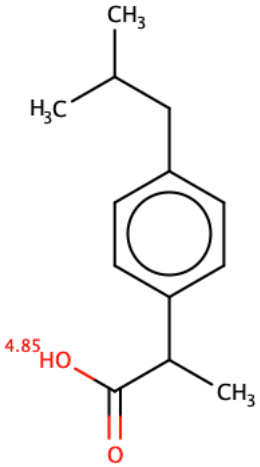
Daniela Amaral Silva [a,1], Marcelo Gomes Davanço [b,1], Neal M. Davies [a], Johannes Krämer [c], Patricia de Oliveira Carvalho [b], Raimar Löbenberg [a,*]

Incorporating physiological aspects into the in vitro dissolution method can give a better mechanistic understanding of a formulation's in vivo performance. Using physiologically relevant in vitro data in combination with compendial results might be a powerful approach to develop a formulation that can have an optimized performance in different population groups, increasing the likelihood for a successful BE study and for a robust formulation development process.



BIPHASIC – Dissolution Ibuprofen





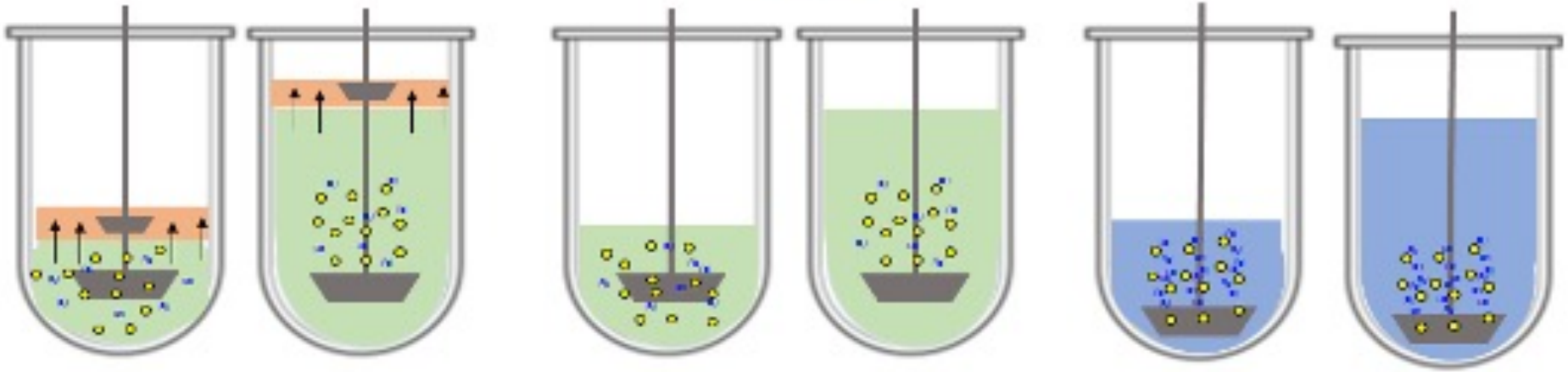
Ibuprofen 400mg

Wet granulation

Direct compression

MCC | Dextrose | $CaHPO_4$ | $CaSO_4`

MCC | Dextrose | $CaHPO_4$ | $CaSO_4`



200mL 900mL

BIPHASIC DISSOLUTION

Phosphate buffer 5mM + Octanol

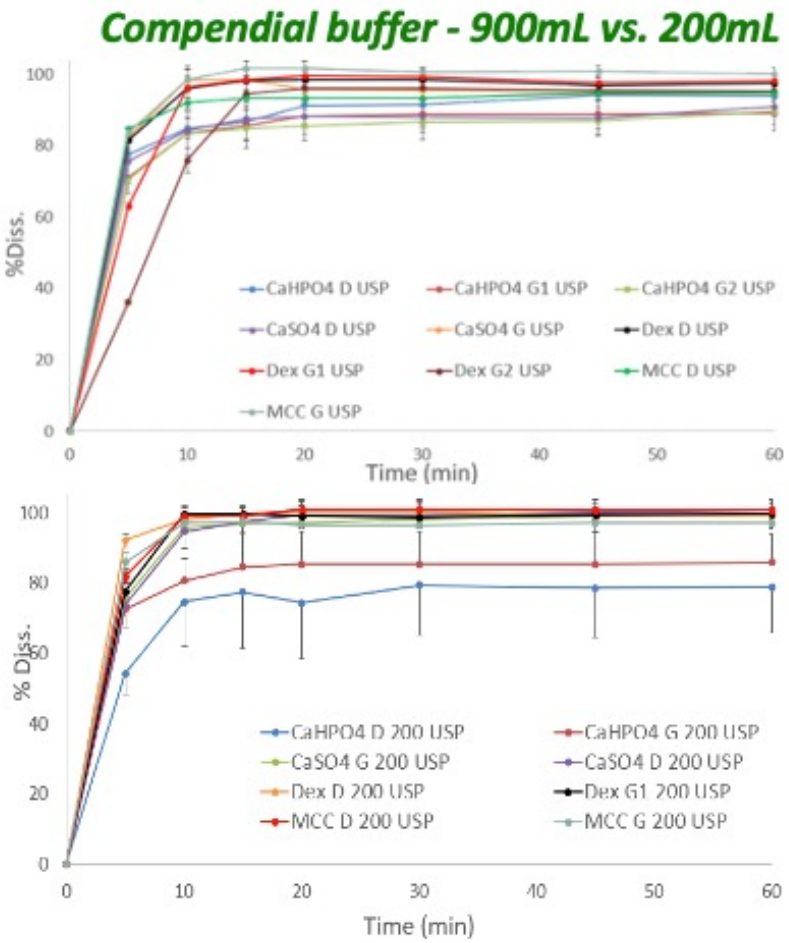
200mL 900mL

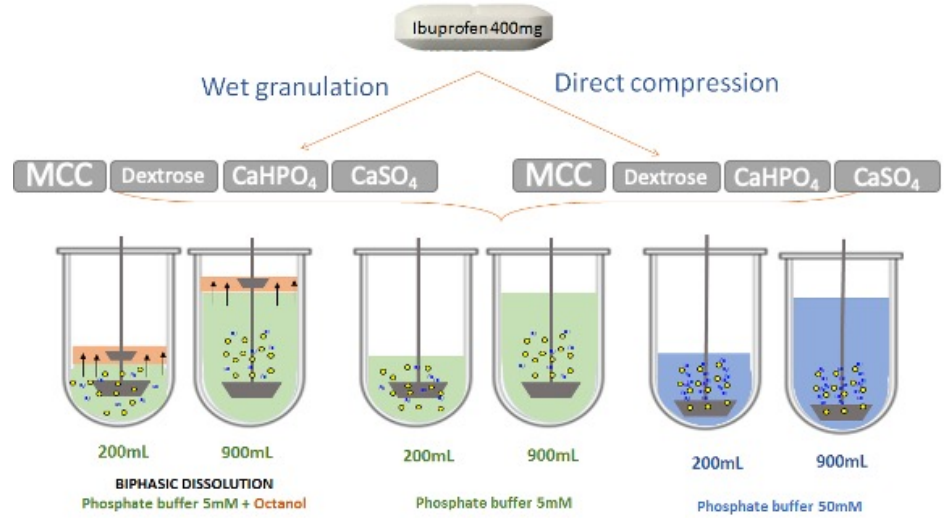
Phosphate buffer 5mM

200mL 900mL

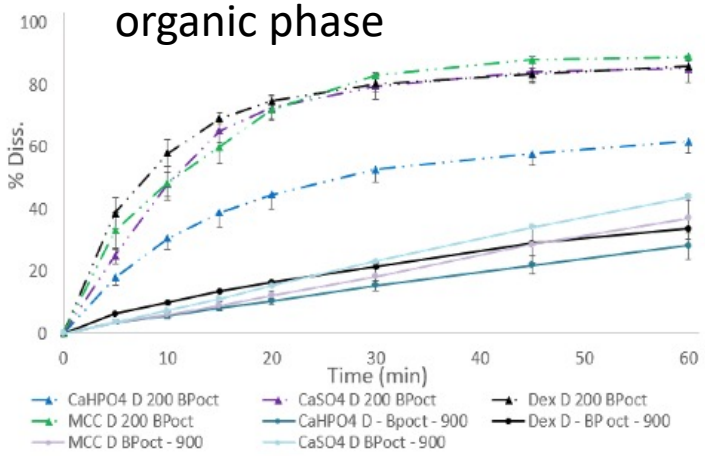
Phosphate buffer 50mM

BIPHASIC – Dissolution Ibuprofen

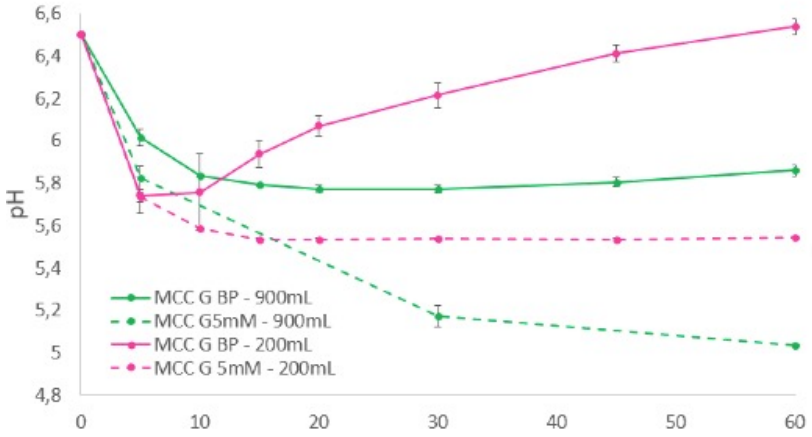




Effect of volume: 200 / 900 ml on the uptake into the organic phase



Effect of volume: 200 / 900 ml on the uptake into the pH



pharmaceutics

MDPI

Article

Biphasic Dissolution as an Exploratory Method During Early Drug Product Development

Daniela Amaral Silva [1], Jozef Al-Gousous [2], Neal M. Davies [1], Nadia Bou Chacra [3], Gregory K. Webster [4], Elke Lipka [5], Gordon L. Amidon [2] and Raimar Löbenberg [1,*]

[1] Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2E1, Canada; amaralsi@ualberta.ca (D.A.S.); ndavies@ualberta.ca (N.M.D.)

[2] College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA; jalgouso@umich.edu (J.A.-G.); glamidon@med.umich.edu (G.L.A.)

This study revisited the rationale of using **lower buffer capacity media to increase the physiological relevance of in vitro testing**. This system was demonstrated to have a superior discriminatory power regarding the manufacturing method and excipient effects. The use of an absorptive phase added a sink to the low buffer capacity media, which **decreased pH shifts** while the test was performed.

power, whereas low buffer capacity media discriminated between manufacturing methods. The use

Lipid Dissolution

Certain oral drugs (lymphotropics, log P> 5, triglyceride solubility > 50 mg/ml) follow the same path and packaged into ‘’chylomicrons” within intestinal cells before being **transported through the lymphatic system instead of the portal** pathway.[2]

Standard dissolution tests do not provide any information on the drug's absorption pathway, whether it is through the portal or lymphatic circulation.

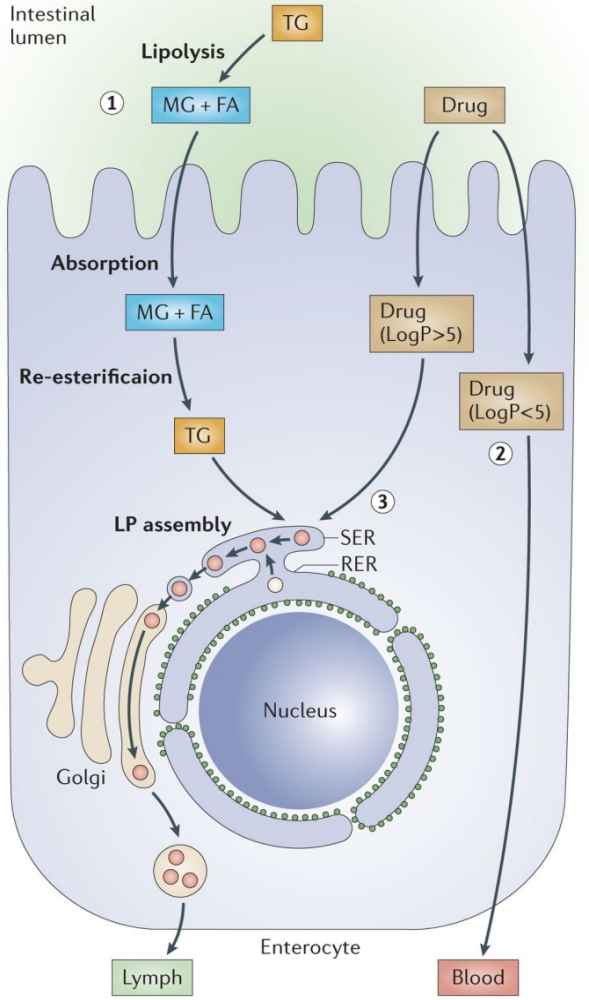


Fig 5. Pathways of drug absorption from the intestinal cells*

*Used under OA license from Nature Reviews Drug Discovery. 2015; 14: 781–803.

Simulated Lymphatic Fluid for In-Vitro Assessment in Pharmaceutical Development

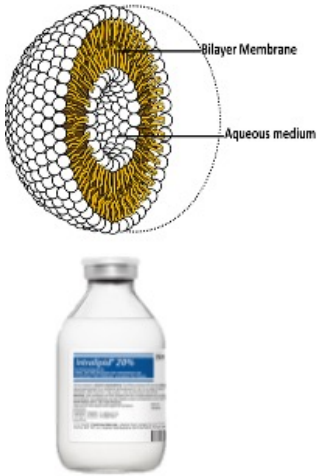
Malaz Yousef[1,2*], Chulhun Park[1], Tyson S. Le[1], Nadia Bou Chacra[3], Neal M. Davies[1], and Raimar Löbenberg[1]

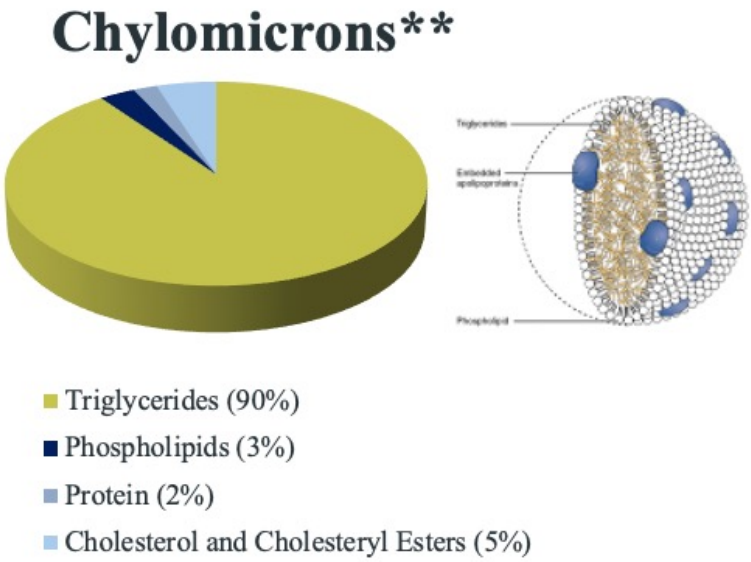
[1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada.
[2]Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.
[3]Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo, Brazil.

e-mail: malaz@ualberta.ca

ABSTRACT

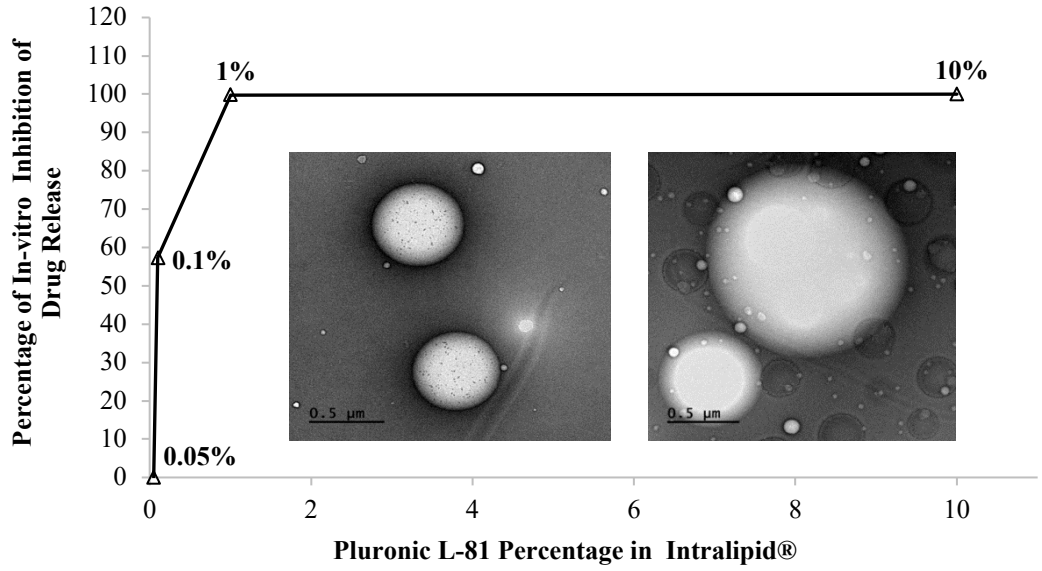
In addition to removing excess extracellular fluid and mobilizing immune cells throughc fluid provides a means for drug transport. Lymphatic drug delivery can impart higher eff especially following oral administration. Currently, there is no standardized composition for s Standardization of a simulated lymphatic fluid media would be an important and novel contı

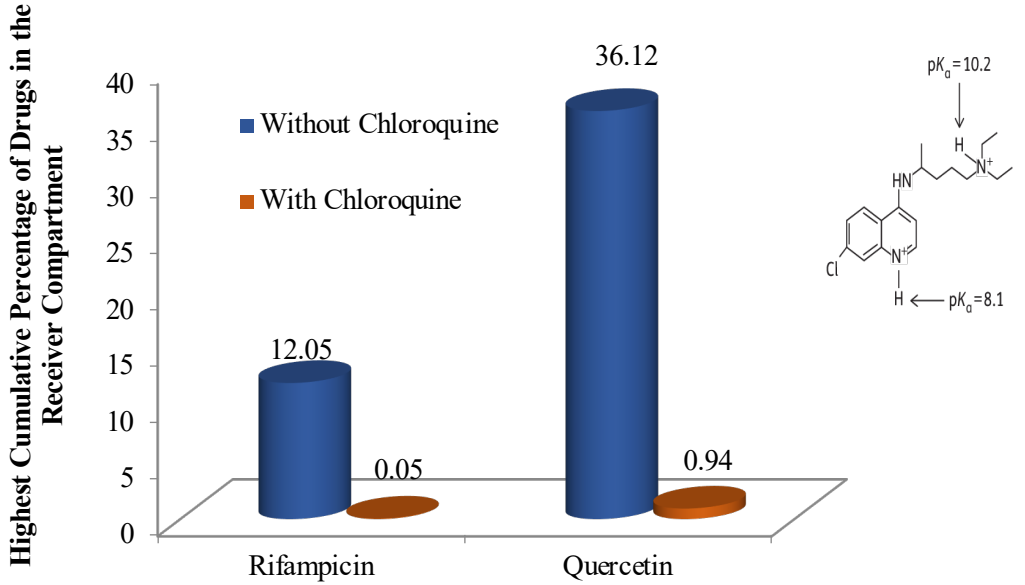




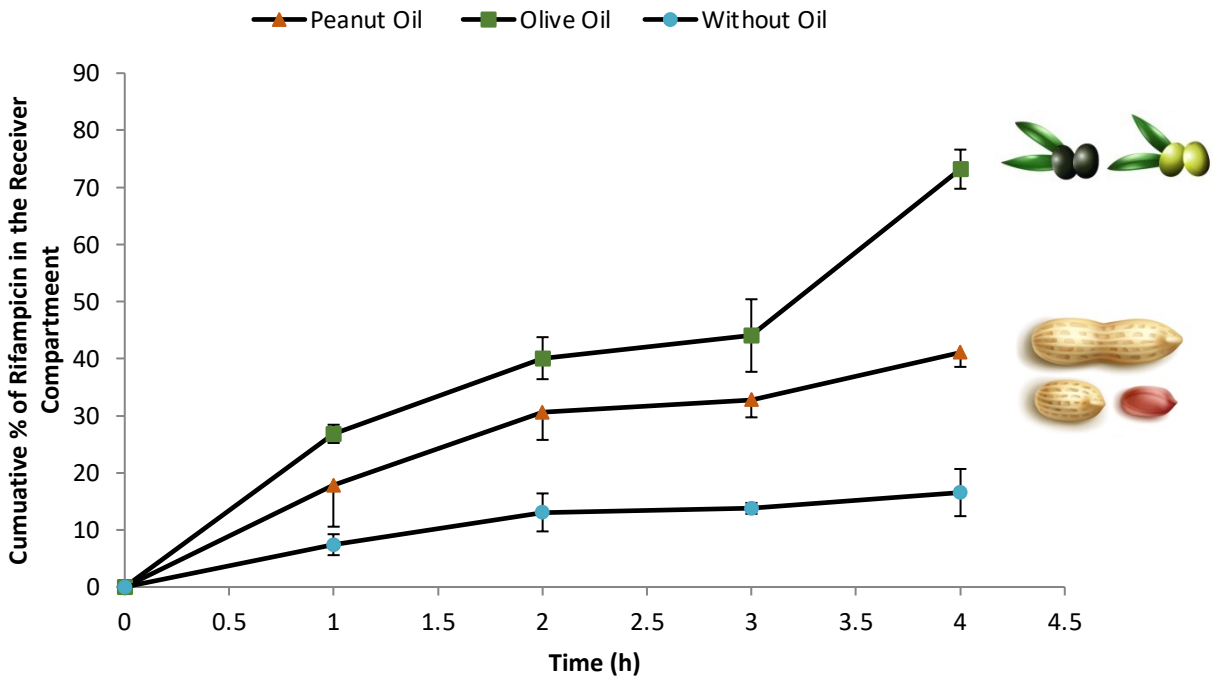
Reagent	CAS number	Amount for 1 L of Simulated Lymphatic Fluid
Sodium chloride	7647-14-5	8.035 g
Sodium bicarbonate	144-55-8	0.355 g
Potassium chloride	7447-40-7	0.225 g
Potassium phosphate dibasic	7758-11-4	0.231 g
Magnesium chloride hexahydrate	7791-18-6	0.311 g
1 M Hydrochloric acid	7647-01-0	39 mL
Calcium chloride dihydrate	10035-04-8	0.292 g
Sodium sulfate	7757-82-6	0.072 g
Tri(hydroxymethyl) aminomethane	7283-04-7	6.118 g
Protein (human serum albumin)	70024-90-7	40 g
Intralipids	68890-65-3	100 mL

Uptake Inhibition

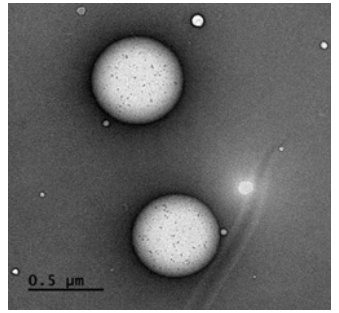


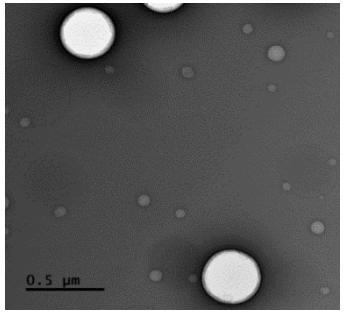


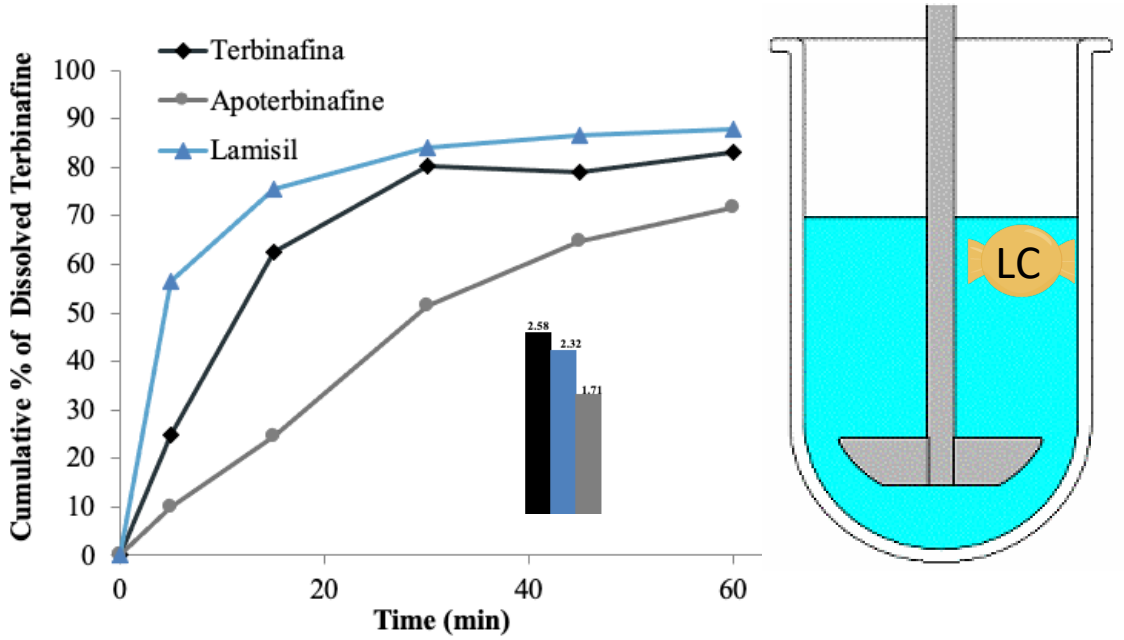
Uptake Enhancement

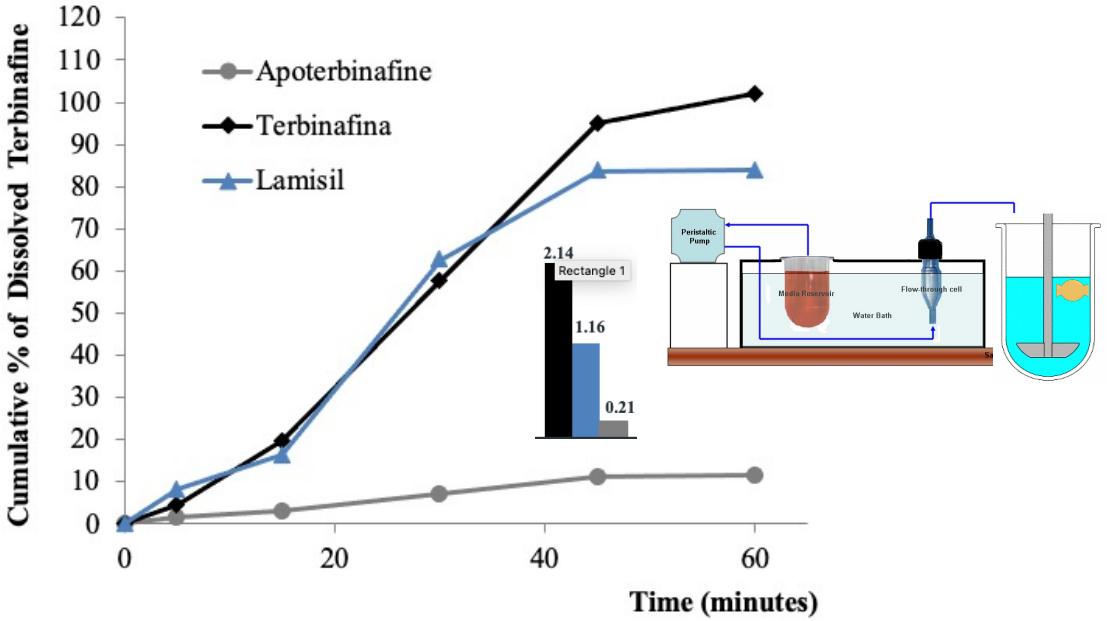


Fatty Acid	Olive Oil	Peanut Oil
Palmitic Acid	7.5-20	11-14
Stearic Acid	0.5-5	
Oleic Acid	55-83	45-53
Linoleic Acid	3.5-21	27-32









Lipid Dissolution

Terbinafina*	Lamisil**	Apo-Terbinafine***
Hydroxypropylcellulose	Hydroxypropyl methylcellulose	Methylcellulose
Microcrystalline cellulose	Microcrystalline cellulose	Colloidal anhydrous silica
Colloidal silicon dioxide	Colloidal silicon dioxide	Croscarmellose sodium
Sodium starch glycolate	Sodium starch glycolate	Magnesium stearate
Magnesium stearate	Magnesium stearate	

The **first lymphatic-focused dissolution model** was developed.

The model can be useful for **formulation and manufacturing assessment** and contribute to *in-vitro* **bioequivalence guidelines** of lymphotropic formulations

- Flow-through cells and transfer-models are useful for dynamic dissolution protocols.
- Small volumes and low buffer concentrations should be considered to mimic the physiologic environments in the GI-tract.
- The dosage form impact ends at the gut lumen / enterocyte interface.
- Enteric coated formulations should be developed using carbonate buffers or surrogate buffers.
- Biphasic dissolution is an important tool to mimic the GI-environment with dissolution and absorption occurring in parallel.
- Lipid dissolution is a promising approach to assess excipient effects for lymphotropic drugs.