The use of Saliva instead of Plasma as a Surrogate in Drug BA/BE and TDM Studies in Humans

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جامعة البترا

Outline

- Introduction
- Objectives
- Design & Methods
- Results & Discussion
- Conclusions
- Acknowledgements

Introduction

- Salivary excretion of some drugs has been reported previously as a good indicator for drug bioavailability, therapeutic drug monitoring, pharmacokinetics and also drug abuse.
- Saliva sampling offers simple, fast, non-invasive and cheap method as compared with plasma sampling with no contamination risk.
- The role of plasma protein binding on salivary excretion has been widely discussed.

Previous screened drugs

(Saliva and plasma mean (%CV) pharmacokinetics)

Drug	AUC0→t (ng/ml h) SALIVA	Cmax (ng/ml) SALIVA	Tmax (h) SALIVA	Half life (h) SALIVA	AUC0→t (ng/ml h) PLASMA	Cmax (ng/ml) PLASMA	Tmax (h) PLASMA	Half life (h) PLASMA
Cinacalcet	23.2 (123)	10.3 (145)	2.3 (137)	2.59(51)	97.4 (50)	15.0 (29)	1.3(88)	4.65(23)
Sitagliptin	592 (57)	111 (75)	6 (0)	2.98(4)	3717(56)	585(72)	1.5 (0)	6.19(23)
Diacerhin	NSE	NSE	NSE	NSE	22724(53)	5748 (20)	2.3 (53)	4.1(27)
Tolterodine	2.47 (48)	1.11 (69)	1.22 (69)	1.88(27)	11.75 (95)	3.60 (50)	0.8 (33)	1.98(40)
Losartan	NSE	NSE	NSE	NSE	1405(49)	610(79)	1.75(2)	2.38(18)
HCT	265 (16)	89.6 (70)	2.39 (28)	5.2(8)	646(32)	113(34)	2.14(34)	3.9(25)
Tamsulosin	NSE	NSE	NSE	NSE	176(46)	6.3(38)	5.7(61)	38(16)
Montelukast	NSE	NSE	NSE	NSE	2690(44)	395(37)	3.2(38)	4.7(28)
Lornoxicam	NSE	NSE	NSE	NSE	2063(35)	587(24)	2.0(37)	3.9(27)
Metformin	990 (38)	166 (46)	4.1 (68)	4.2(40)	8711 (14)	1392(18)	1.8 (55)	2.7(6)
Cloxacillin	31518(111)	36620(76)	0.58(25)	0.66(79)	17859(24)	14051(27)	0.58(49)	1.22(3)
Azithromycn	5624 (49)	2263 (82)	4.33 (66)	--	1003(36)	134(42)	4.2(28)	--
Rosuvastatin	23.4 (95)	4.19 (94)	4.5 (40)	4.3(31)	279(60)	24.9(56)	4.3(24)	5(20)

Salivary Excretion Classification System (SECS)

Parameter / Class	P_{eff}	fu	Salivary excretion
Class I	High	High	Yes
Class II	Low	High	Yes
Class III	High	Low	Yes
Class IV	Low	Low	No

Mol Pharm. 2012 Aug 6;9(8):2358-63

Previous screened drugs

(Simcyp optimized P_{eff})

Drug	Log P	fu	P_{eff} x 10^{-4} (cm/sec)	Fa	SECS Class
Cinacalcet	5.7	0.03	44.16	1.00	III
Sitagliptin	1.3	0.62	13.75	1.00	I
Tolterodine	5.77	0.37	10.74	0.99	I
Losartan	4.36	0.01	1.11	0.75	IV
HCT	-0.02	0.33	0.16	0.18	II
Tamsulosin	2.14	0.01	0.71	0.58	IV
Montelukast	5.8	0.01	1.13	0.75	IV
Lornoxicam	0.77	0.1	0.39	0.38	IV
Metformin	-1.82	0.99	1.44	0.83	II
Cloxacillin	2.83	0.05	10.04	0.99	III
Azithromycin	3.33	0.71	29.74	1.00	I
Rosuvastatin	0.42	0.1	32.15	1.00	III
Diacerhein	3.13	0.01	0.84	0.65	IV

Objectives

* Compare & correlate BA/BE or TDM parameters of 10 selected drugs **based on SECS** calculated from saliva samples with those from plasma samples.

- Suggest saliva matrix instead of plasma as a surrogate in such studies.

Study Design & Methods

- **1. Clinical Part:**

- **6 BE pilot studies** of parcetamol, metformin, rosuvastatin, HCT/valsartan, azithromycin and tolterodine on 12-18 health humans were conducted under fasted state as per the ICH, GCP, and Helsinki declaration guidelines after CROs IRB and Jordan FDA approvals.
- **3 TDM studies** of tacrolimus (Jordan University Hospital), pregabalin (Islamic Hospital) and mycophenolate (RMS- Queen Rania Pediatric Hospital) were done on Jordanian patients after hospitals IRB approvals.
- **1 ADME pilot** study of paracetamol in saliva was done at high altitude.
-

Study Design & Methods

2. Analytical Part:

All samples were deep freezed until assayed by validated LC-MSMS assay methods.

3. Data Analysis Part (pharmacokinetics):

Saliva and plasma primary PK parameters (AUC, C_{max}, T_{max}) were calculated by non-compartmental analysis (NCA) using Kinetica or Winnonlin programs.

3. Data Analysis Part (TDM):

Statistics for Saliva and plasma TDM parameters (C^{ss}_{max} , C^{ss}_{min}) were calculated by Excel.

Study Design & Methods

3. Data Analysis Part (absorption kinetics):

Absorption kinetics and effective intestinal permeability (P_{eff}) values were estimated by Nelder-Mead algorithm of Parameter Estimation module using SimCYP or PK-Sim programs.

- This was done by searching for the **best parameter values that produce plasma concentration that matches the actual plasma concentration at the same time**.
- The objective function is the weighted sum of squared differences of observed and model predicted values.
- Physicochemical factors used in calculations such as LogP, MW and fu were obtained from literature and were kept constant during the minimization processes.

Study Design & Methods

3. Data Analysis Part (Dimensional Analysis):

AUC^{*} = saliva AUC_t/ plasma AUC_t

T_{max}^{*} = saliva T_{max}/ plasma T_{max}

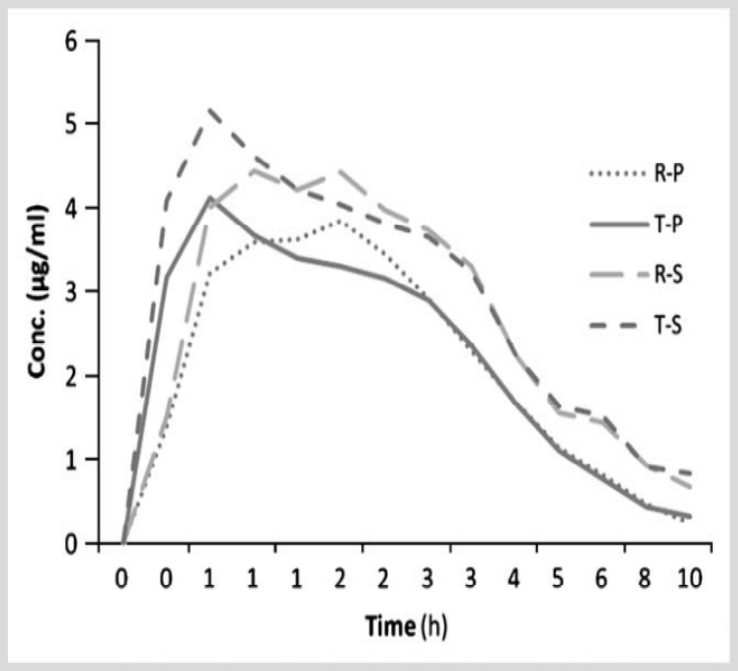
C_{max}^{*} = saliva C_{max}/ plasma C_{max}

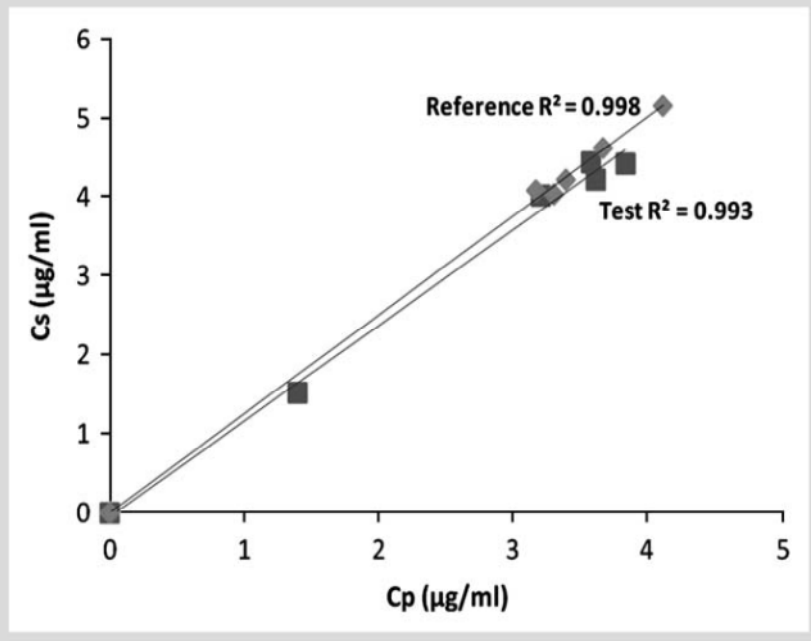
C^{*}= Saliva Concentration/ Plasma Concentration = C_s/C_p

P_{eff}^{*} = dimensionless effective permeability = $(R.\ P_{eff})/\ D$
, where D is drug diffusivity and R is intestinal radius.

BA/BE RESULTS

Paracetamol plasma and saliva mean profiles & correlations

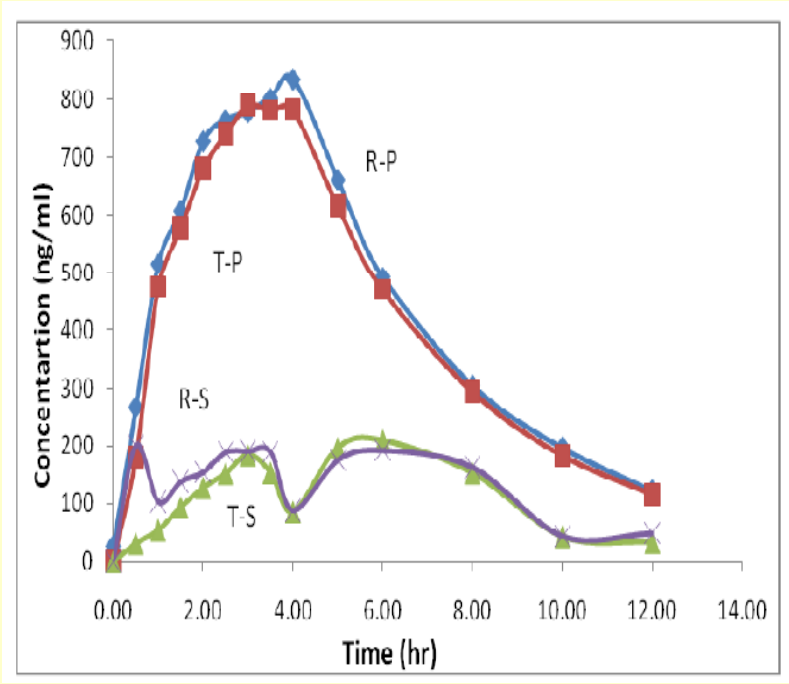


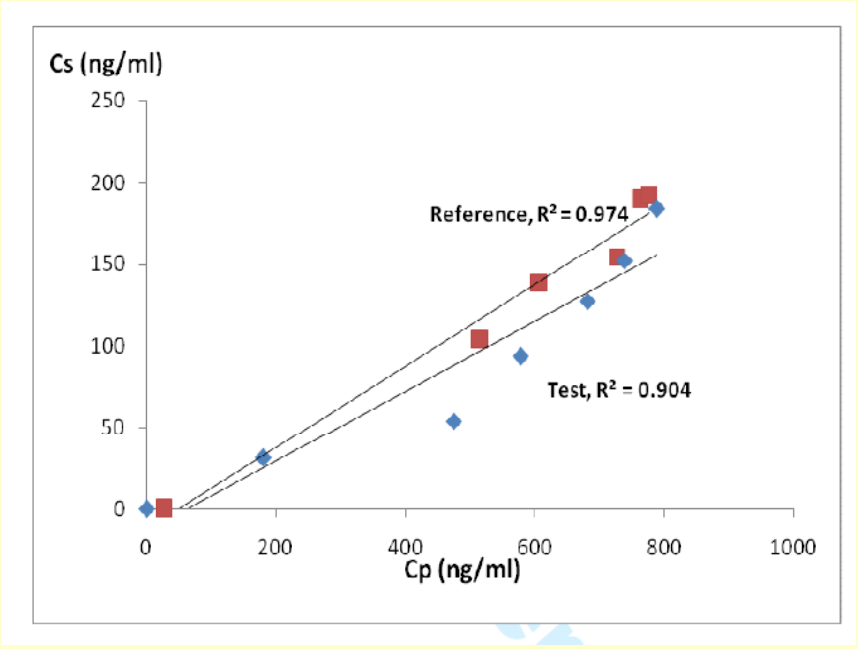


Drug Res (Stuttg). 2014; Nov;64(11): 559–562

BA/BE RESULTS

Metformin plasma and saliva mean profiles & correlations

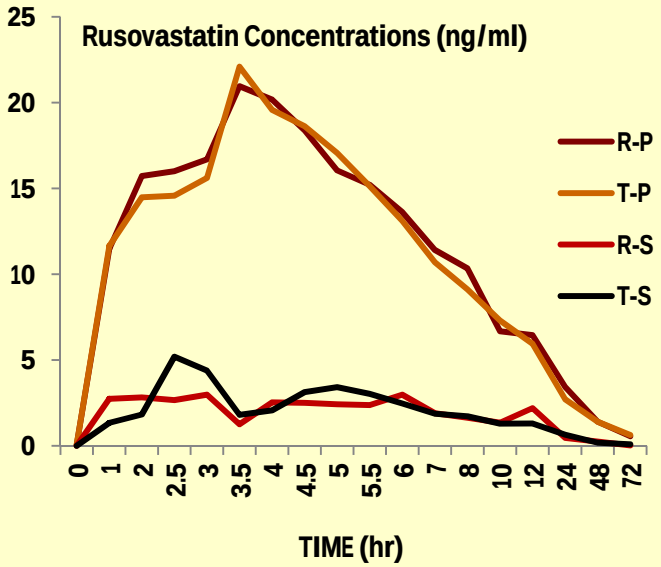


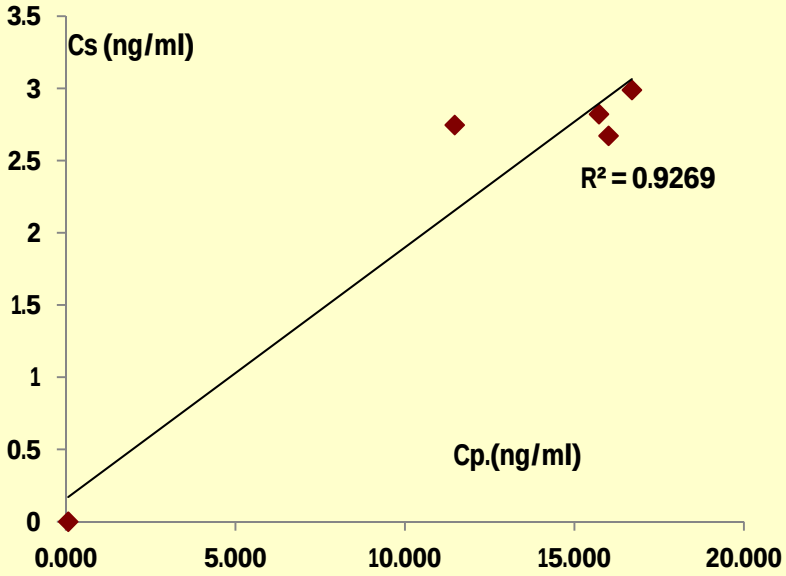


Drug Res (Stuttg). 2014 Nov;64(11):599-602

BA/BE RESULTS

Rosuvastatin plasma and saliva mean profiles & correlations

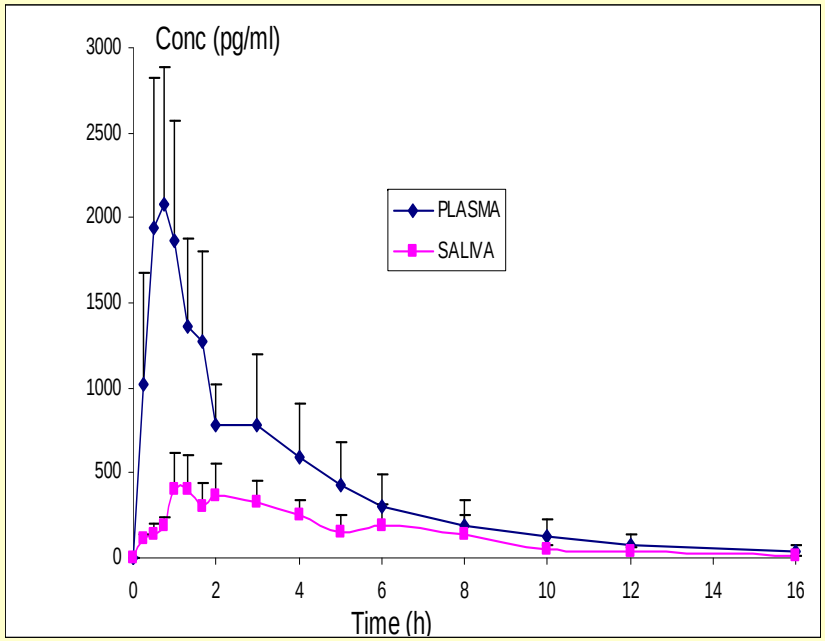


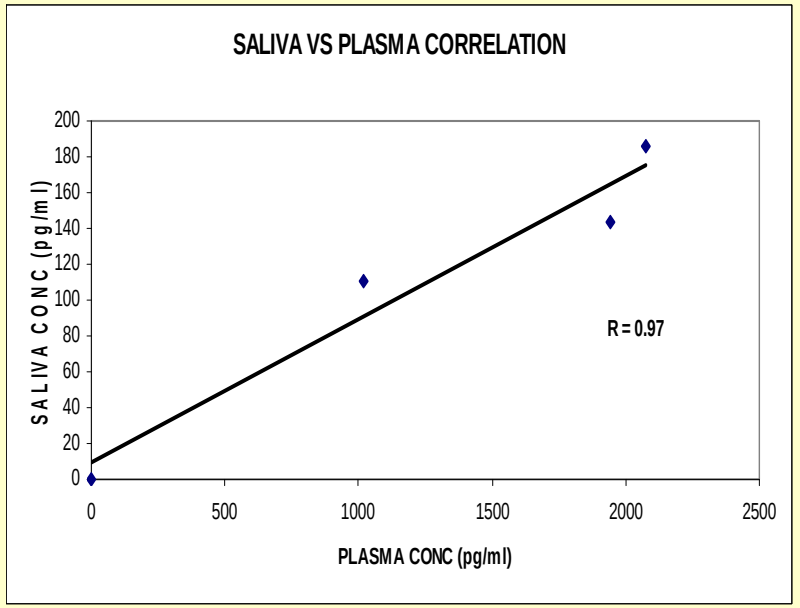


Drugs R&D. 2015 Mar;15(1):79-83.

BA/BE RESULTS

Tolterodine plasma and saliva mean profiles & correlations

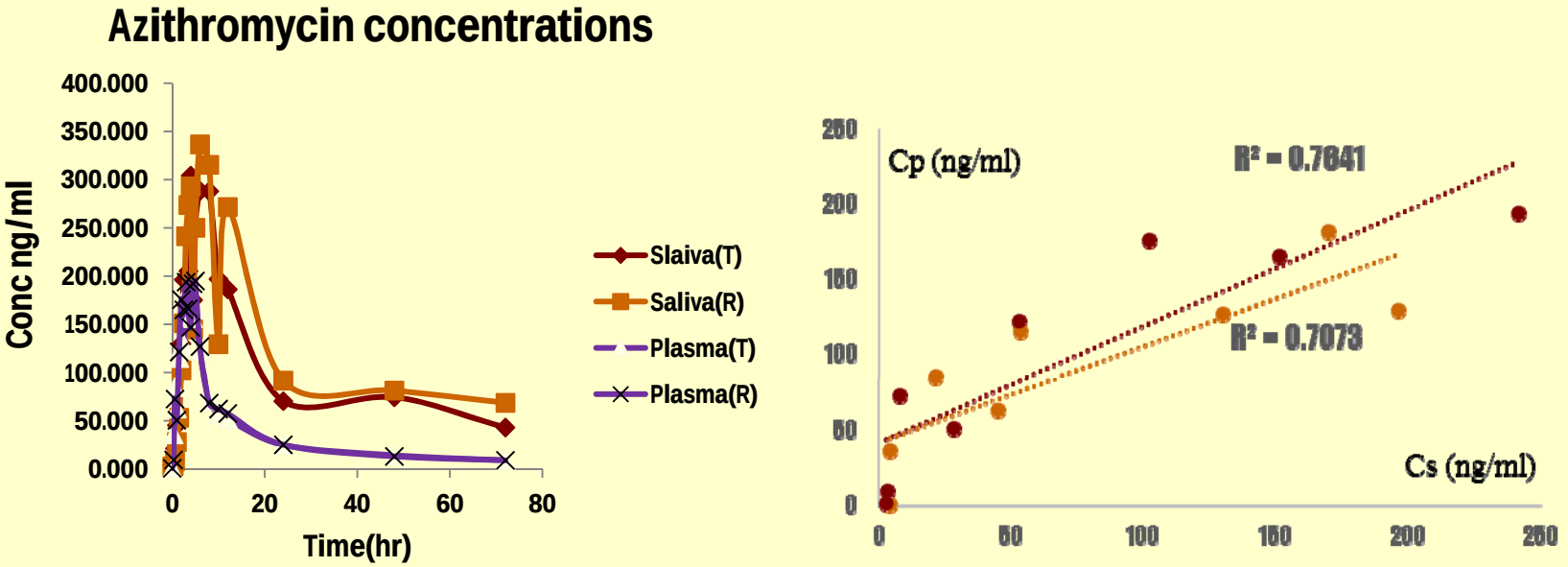




Drug Res (Stuttg). 2016 Jun;66(6):312-5

BA/BE RESULTS

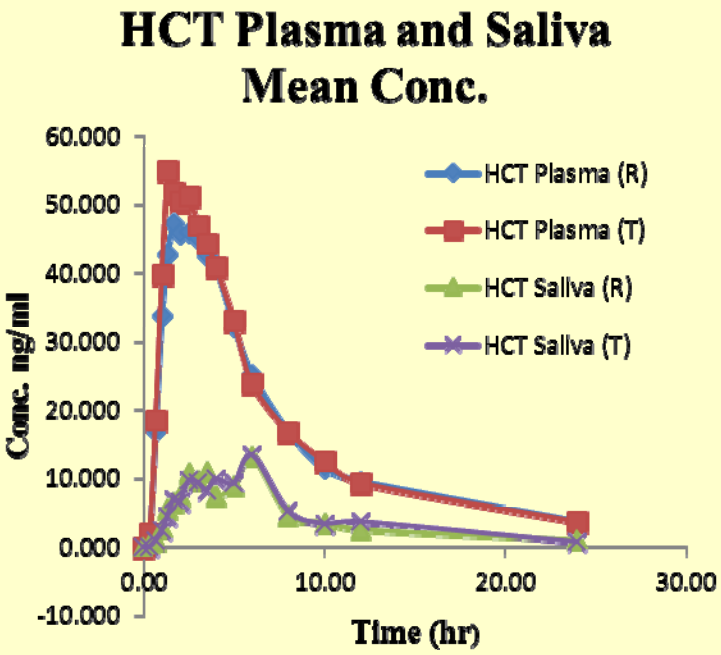
Azithromycin plasma and saliva mean profiles & correlations

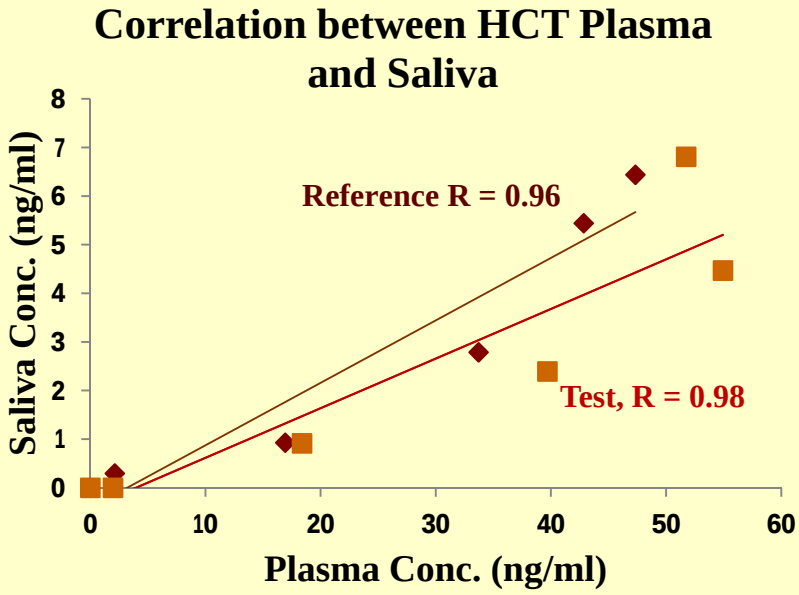


Drugs R&D. 2017 Mar;17(1):219-224

BA/BE RESULTS

HCT plasma and saliva mean profiles & correlations





Drug Res (Stuttg). 2018 Jan;68(1):54-59

BA/BE RESULTS
Saliva / Plasma: Dimensional Analysis

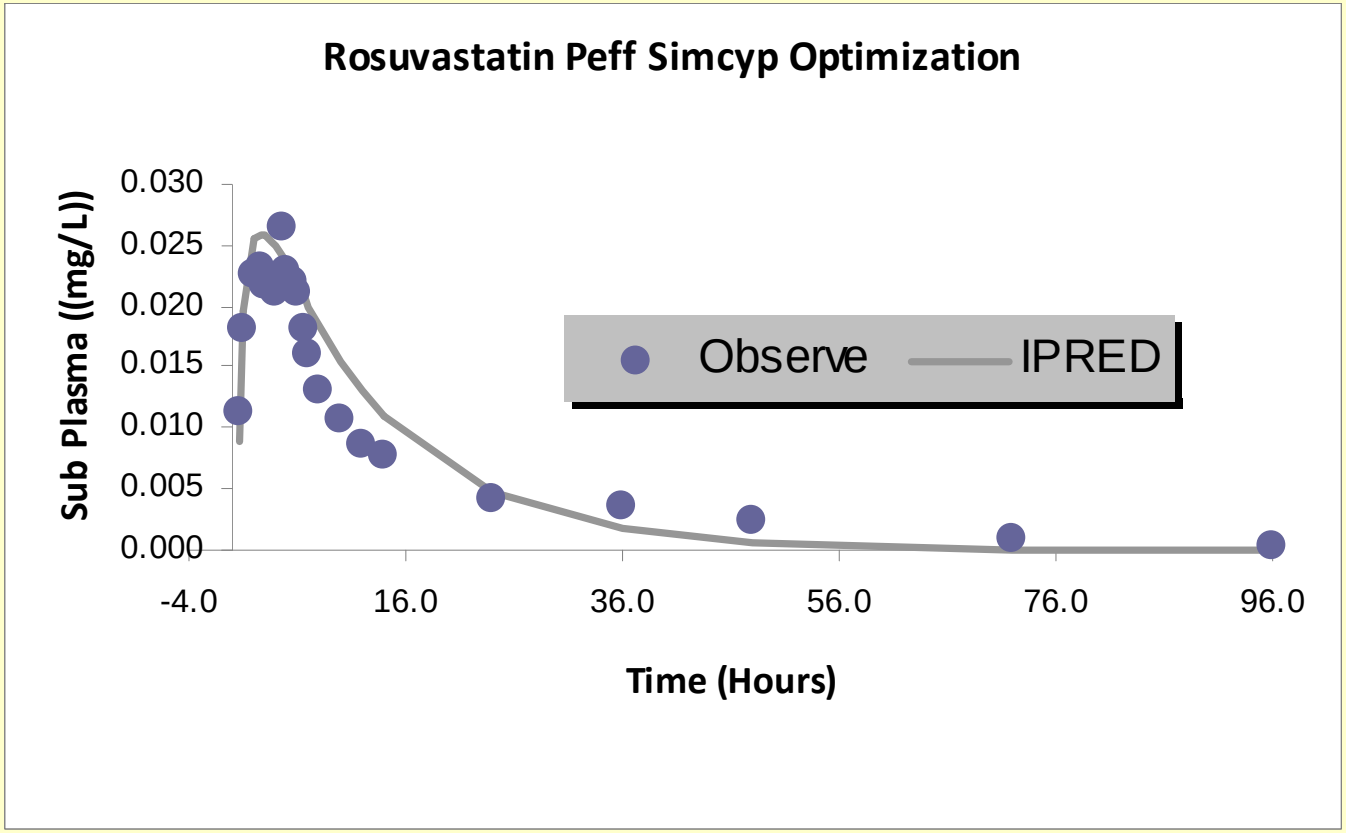
Drug (SECS Class)	HCT (II)	Azithromycin (I)	Tolterodine (III)	Paracetamol (I)	Metformin (II)	Rosuvastatin (III)
AUC*	0.25	3.37	0.42	1.36	0.27	0.17
Cmax*	0.38	1.57	0.34	1.14	0.38	0.35
Tmax*	2.05	2.86	2.37	1.47	1.29	1.47
C*	0.22	2.33	0.34	1.46	0.39	0.18

BA/BE RESULTS

Saliva vs Plasma: Statistical Metrics

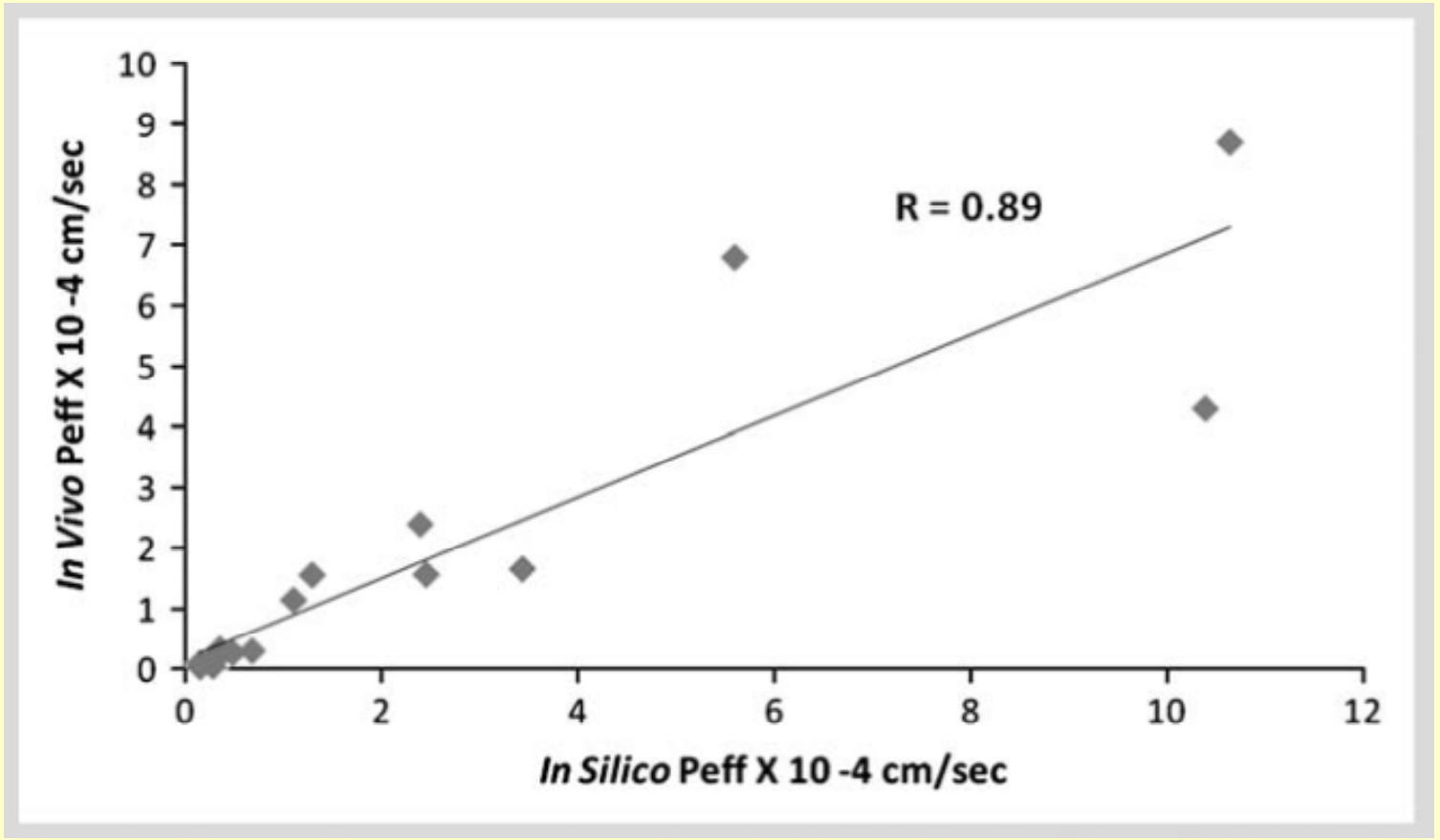
Matrix	Plasma	Plasma	Saliva	Saliva
Parameter	ISCV	N	ISCV	N
HCT	27	26	35	42
Azithromycin	52	84	52	84
Tolterodine	38	48	41	55
Paracetamol	25	24	46	68
Metformin	38	48	57	99
Rosuvastatin	46	68	48	73

BA/BE RESULTS
Simcyp optimized Peff



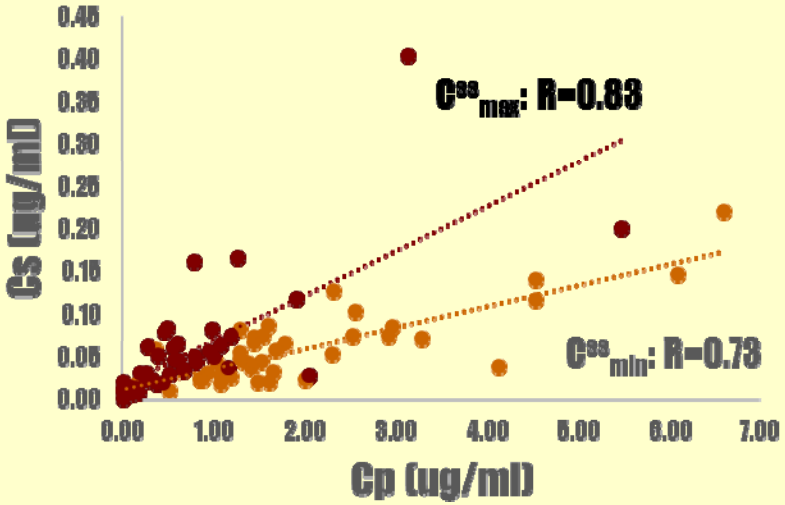
Drugs R&D. 2015 Mar;15(1):79-83.

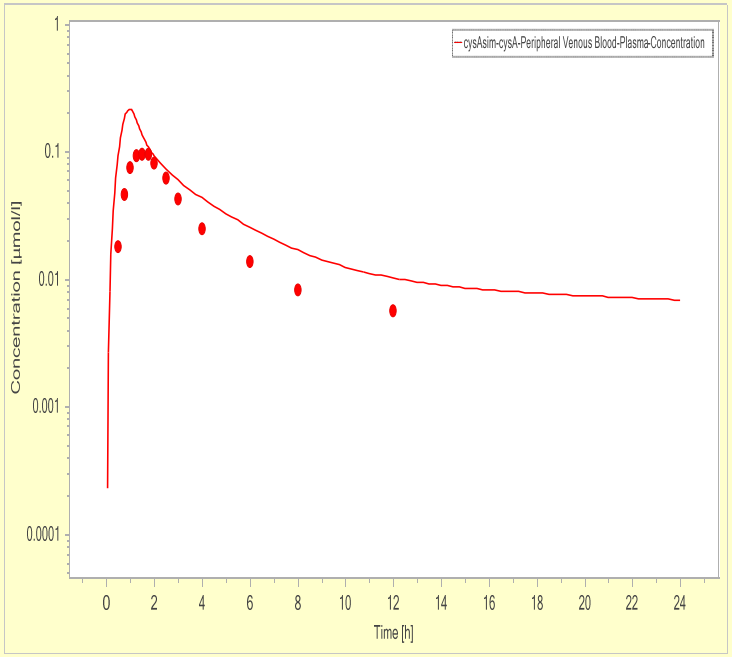
BA/BE RESULTS
Simcyp optimized Peff



Drug Res (Stuttg). 2014 Dec;64(12):693-4

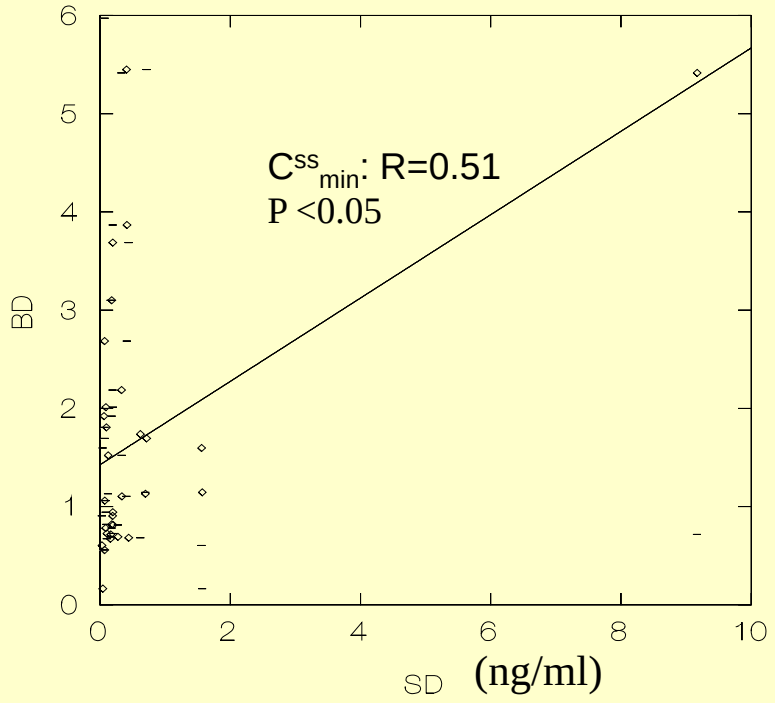
TDM RESULTS: Pregabalin Saliva vs Plasma correlation & Pk-Sim Optimization

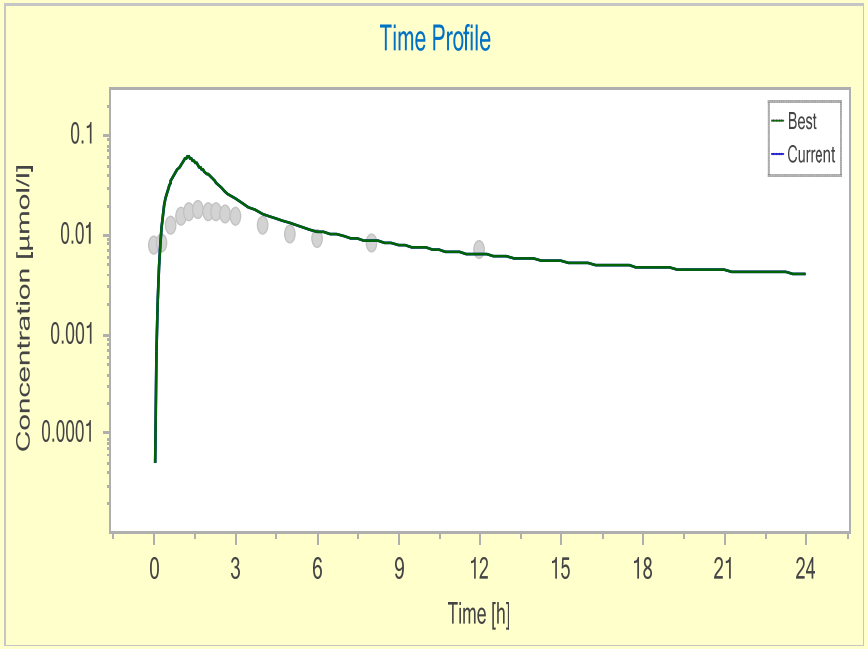




Drug Res (Stuttg). 2018 Apr 23

TDM RESULTS: Tacrolimus Saliva vs Plasma correlation & Pk-Sim Optimization





Accepted in: Novel Approaches in Drug Designing & Development, Sep 2018

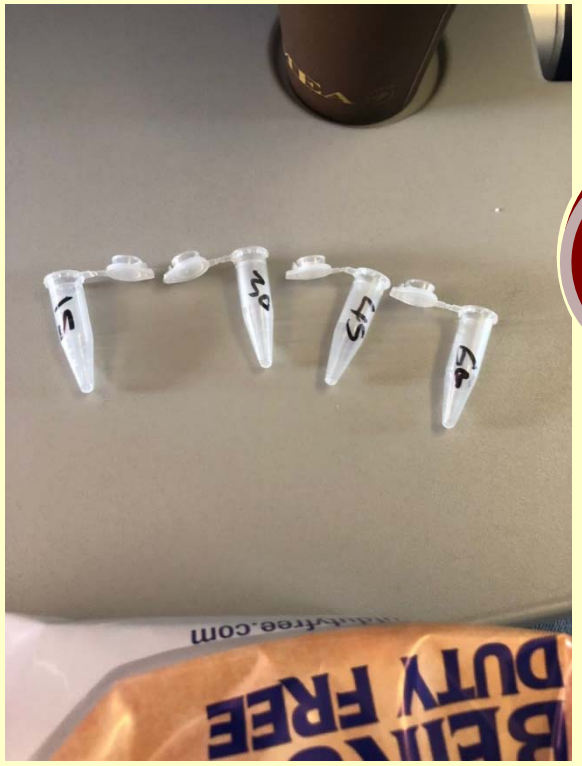
TDM RESULTS

Saliva vs Plasma: Therapeutic ranges

Drug (SECS Class)	Pregabalin (I)	Tacrolimus (III)	Mycophenolate (III)
C^{ss}_{min} (CV%)	Plasma: 0.7 µg/ml (135%) Saliva: 0.055 µg/ml (133%)	Plasma: 2.73 -3.82 ng/ml(18%) Saliva: 0.93-1.3 ng/ml (72%)	Clinical phase
C^{ss}_{max}(CV%)	Plasma: 1.84 µg/ml (79%) Saliva: 0.145 µg/ml (77%)	XXXX	

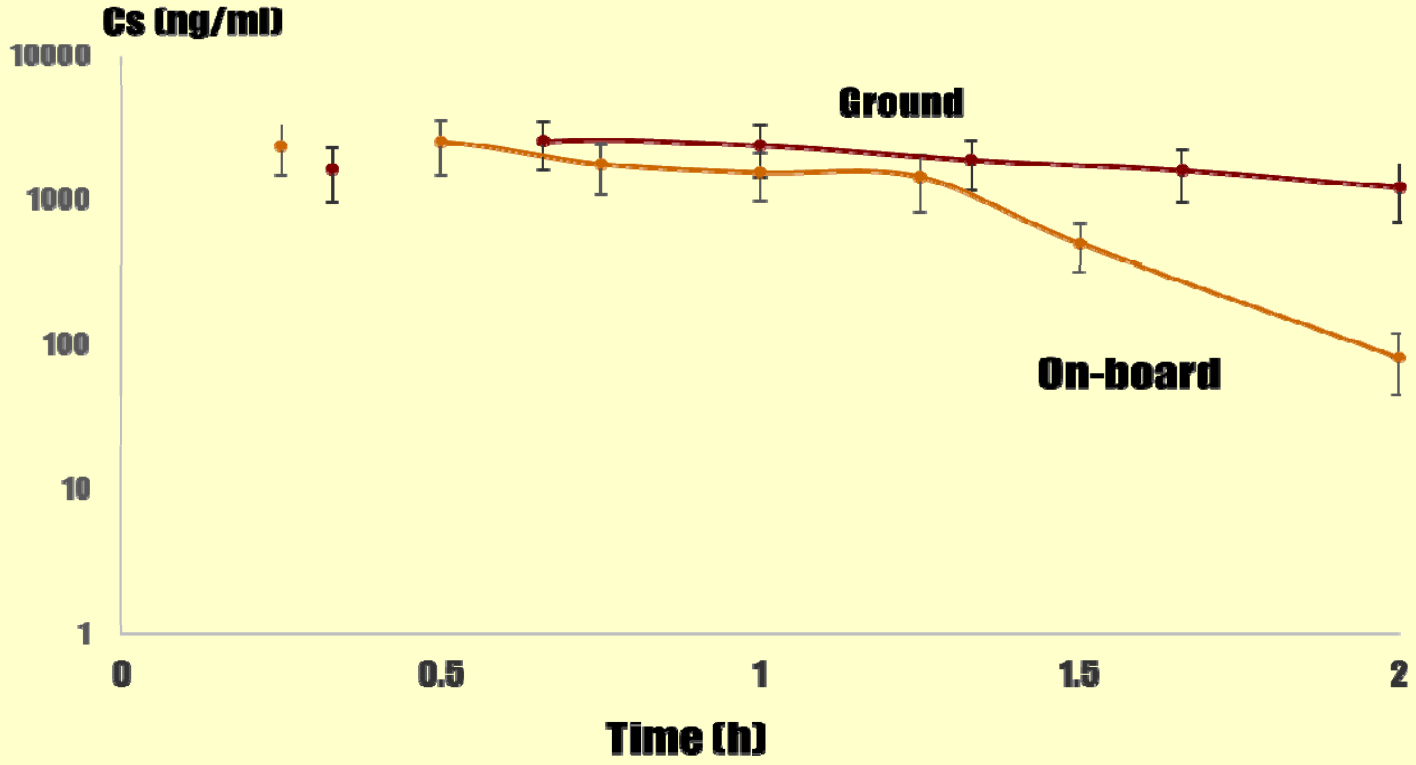
ADME STUDY

On-board vs Ground Early Exposure of Paracetamol



ADME RESULTS

On-board vs Ground: Paracetamol early exposure levels comparison



Submitted to: High Altitude Medicine & Biology, Sep 2018

ADME RESULTS

On-board vs Ground: Paracetamol early exposure levels comparison

Pharmacokinetic parameter	On-Board/ Ground Ratio	P-values
Ka	0.81	-
Peff	1.20	-
AUC0→2	0.38	0.006
AUC0→1	0.62	0.133
Cmax	0.79	0.268
Tmax	1.01	0.496
MRT0→ 2	0.75	0.026

CONCLUSIONS

* Saliva is considered an accessible biological matrix for drugs that fall into SECS classes I, II or III, and hence suggested to be used as a surrogate for BA/BE, TDM and ADME studies when all requirements are met.

* **The use of saliva instead of plasma in such studies is more ethical** since being non-invasive, easy, with less clinical cost, less clinical staff and less clinical burden.

*The proposed Salivary Excretion Classification System (SECS) can be used as a guide for drug salivary excretion.

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