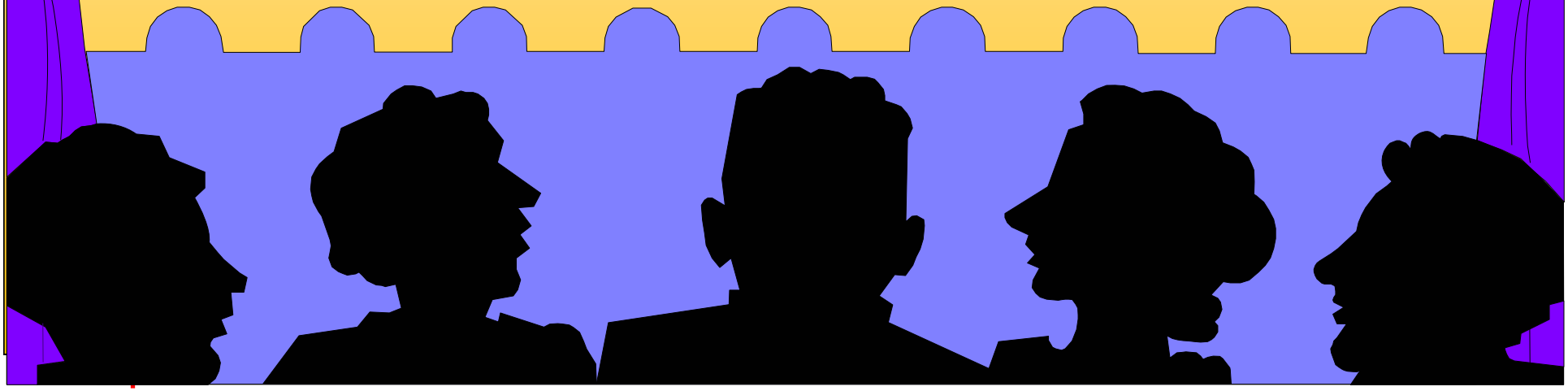
Pharmacokinetics and bioavailability derived from various body fluids

Saliva samples instead of plasma samples

Willi Cawello, Schwarz BioSciences, Monheim am Rhein



Overview

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- Introduction
- Sampling tissues/fluids to characterize PK
- Model of saliva sampling
- Examples
- Discussion, Conclusion / Perspectives

Definitions

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- Regulatory Definition (21 CFR 320.1(a)):

  "Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action."

- Regulatory Definition (21 CFR 320.1(e)):

  "Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study…."

Collected from a presentation of Kofi A. Kumi, Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmaceutical Evaluation III, ACPS 7/20/2001

Definitions

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- ***21 CFR 320.24***

The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product:

- Blood/plasma/serum drug conc. measurement in humans
- Urinary excretion in humans
- In vivo pharmacological effect
- Well-controlled clinical trials
- In-vitro test
- Any other approach deemed adequate by FDA

Collected from a presentation of Kofi A. Kumi, Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmaceutical Evaluation III, ACPS 7/20/2001

Pharmacokinetics

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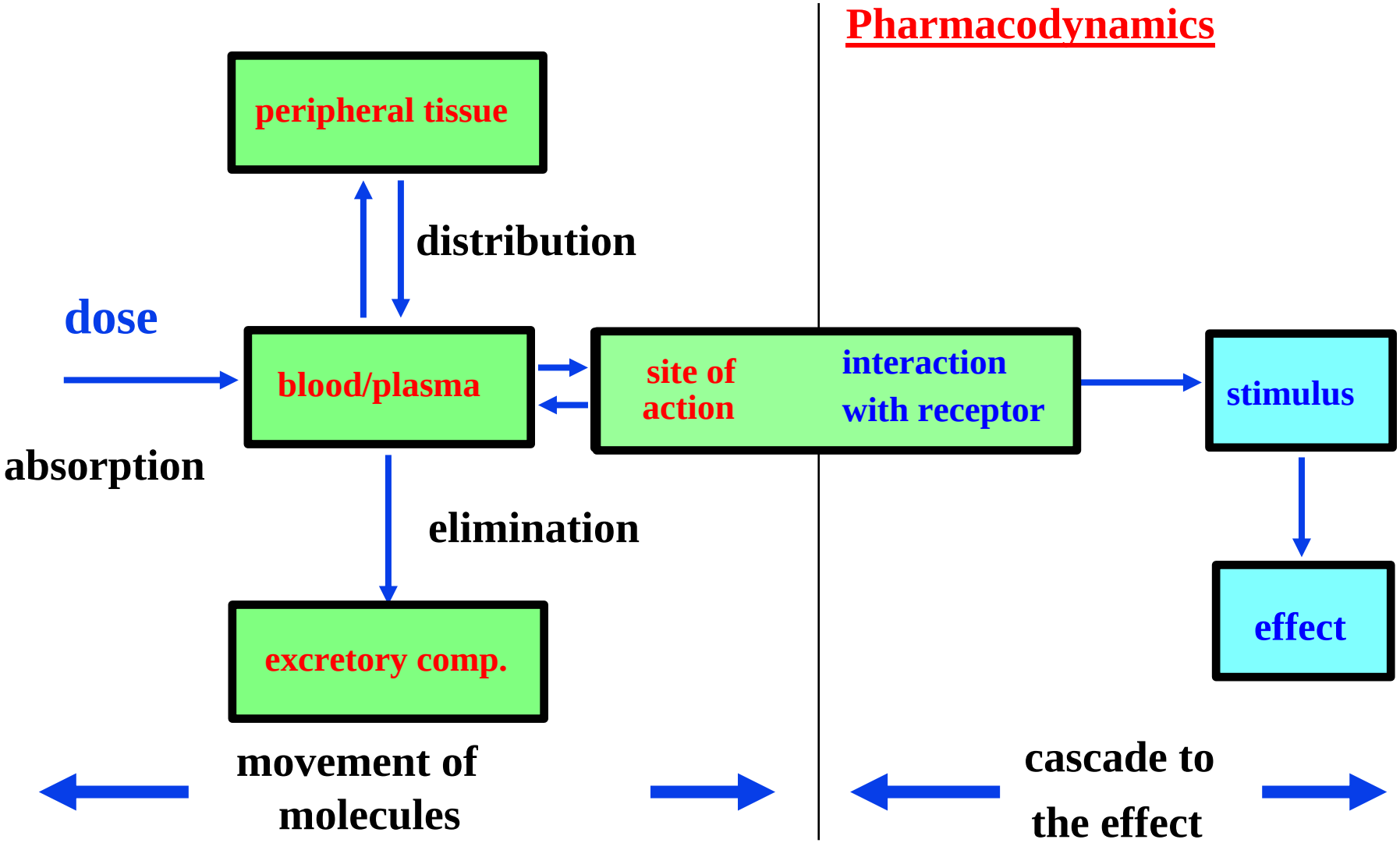

Excretion

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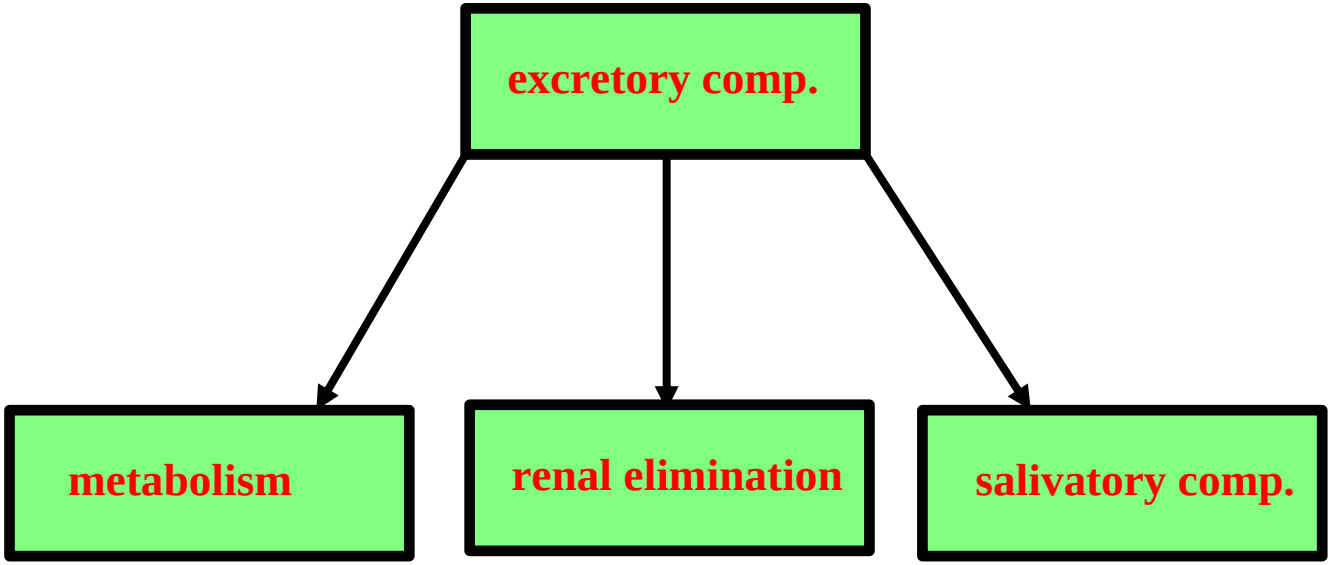

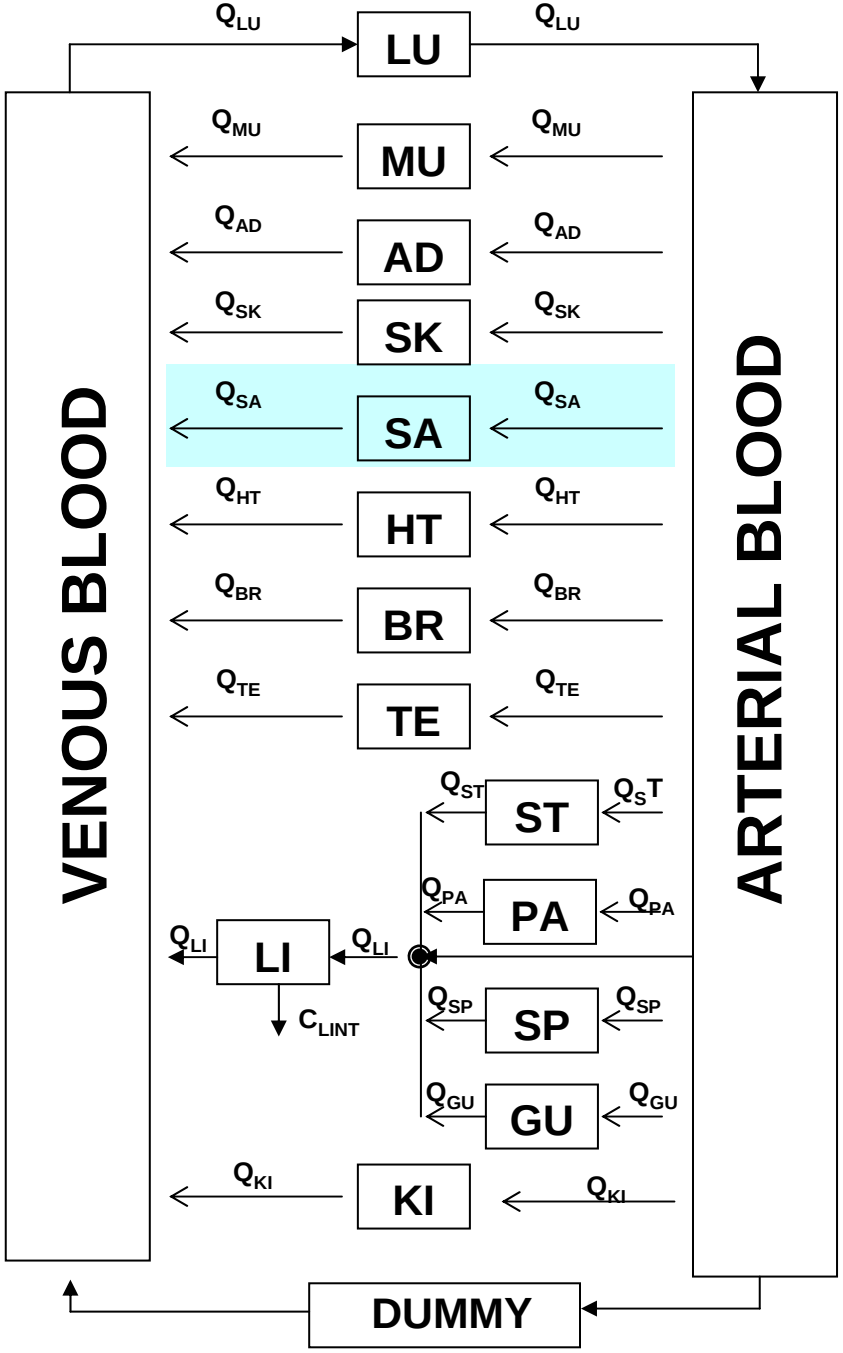

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Tissues

MU	musculature
SA	salivatory gland
SK	skin
TE	testis
GU	thin intestine
ST	stomach
SP	spleen
LI	liver
PA	pancreas
LU	lung
HT	heart
BR	brain
AD	fat tissue
KI	kidney

Pharmacokinetics in saliva

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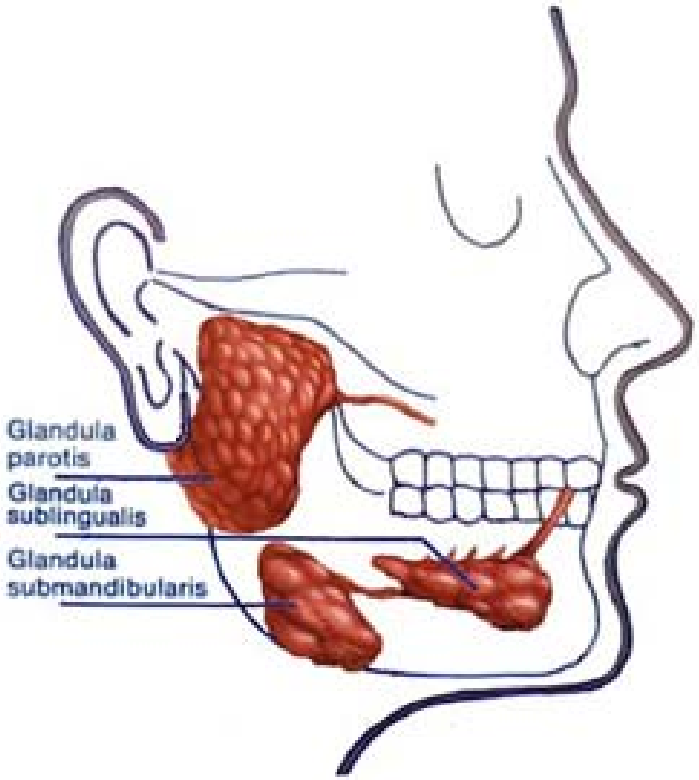
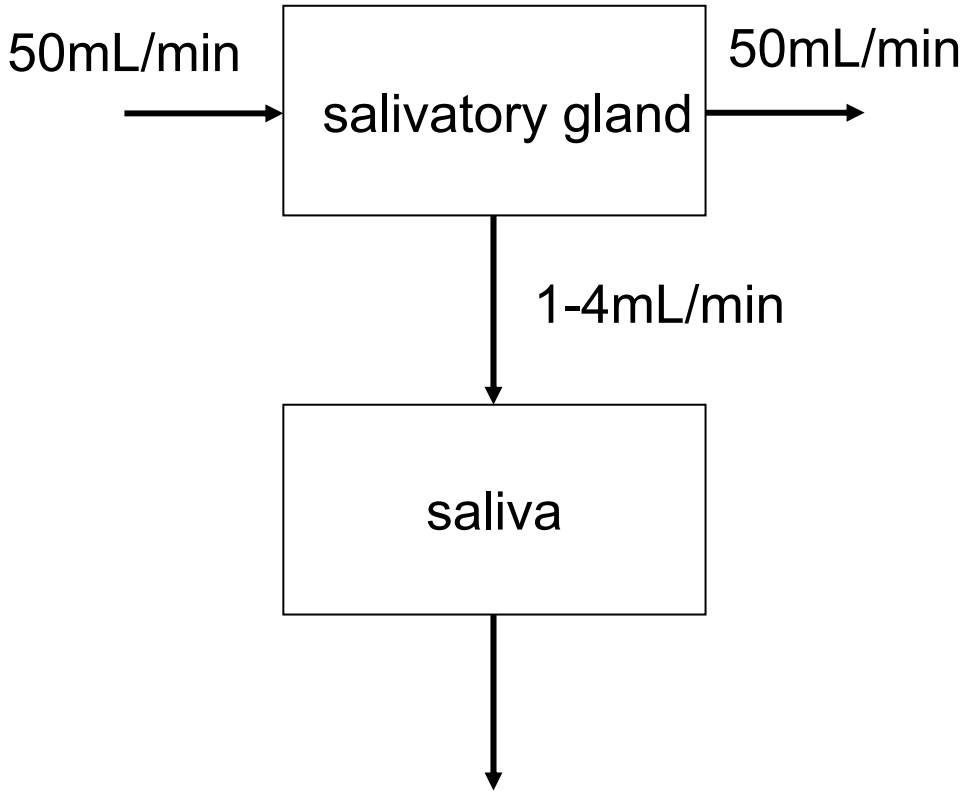
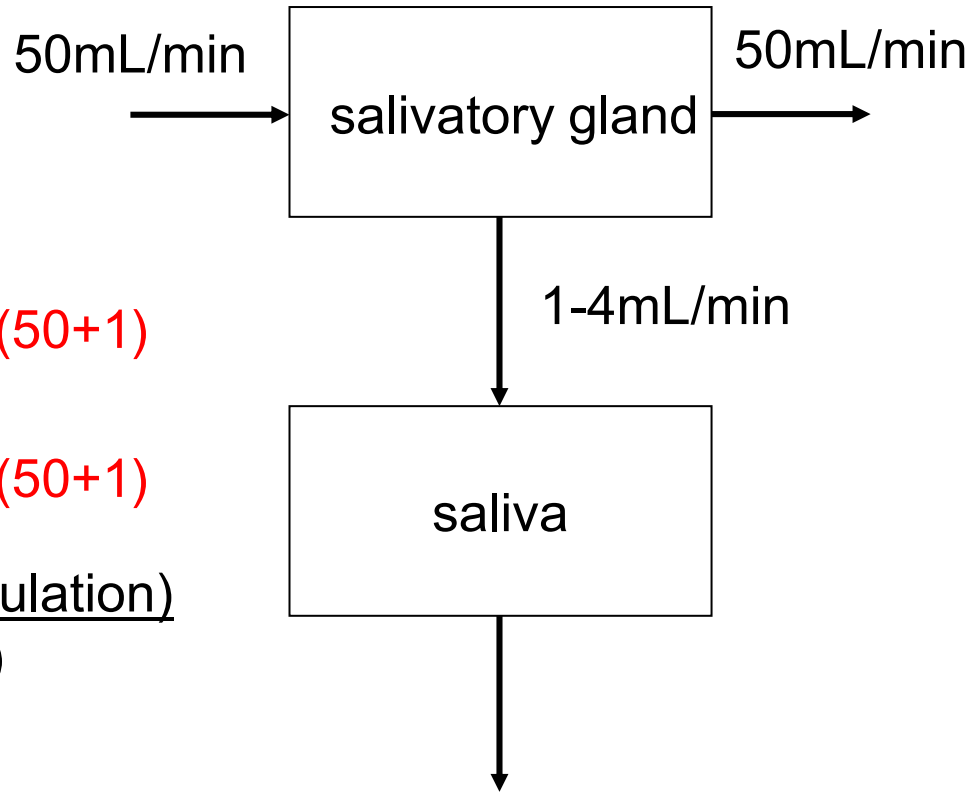




Mass of saliva glands: 30-50g
Approximated Blood flow: 50-200mL/min

What about mass balance during extraction to saliva?

Having a 1:1 extraction:
Concentration in plasma and in saliva is the same.



Plasma
Before 'extraction' 5µg/mL
After 'extraction' 4.902µg/mL =5*50/(50+1)

Saliva
Concentration 4.902µg/mL =5*50/(50+1)

Total Amount in Plasma (central circulation)
Before: 12.5mg (2500ml * 5µg/mL)
After: 12.495mg = 4.998µg/mL

Prediction of extraction into saliva

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Ratio of saliva vs. plasma concentrations

$$R = \frac{1+10^{pH_{saliva}-pKa}}{1+10^{pH_{plasma}-pKa}} \cdot \frac{f_{u,plasma}}{f_{u,saliva}}$$

pH_{plasma} is almost constant,
f_u=fraction unbound, $f_{u,saliva}$ is 1 for most drugs,
pKa is the negative logarithm of acid dissociation constant

Equation derived from: a) Kozjek F, et al, Biopharm Drug Dispos 20: 183-191 (1999)
b) Drobitch RK and Svensson CK, Clin Pharmacokinet 23: 365-379 (1992)

Elimination by saliva

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Examples of drug elimination by saliva (ratios collected from the literature)

drug	ratio of saliva conc vs plasma conc	protein binding %
Aminophenazon	0.79	>99
Amphetamin	2.76	
Antipyrin	0.89 - 1.00	
Carbamazepine	0.26-0.44	75
Coffein	0.55	<10
Diazepam	0.029	95-98
Digoxin	0.66 - 1.68	20-30
Isoniazid	1.02	10
Levetiracetam	1.3	<10
Lithium	2.86 - 3.43	
Paracetamol	1.40	20-50
Penicillin	0.015	>80
Phenacetin	0.60	35
Phenobarbital	0.30 - 0.43	59
Phenytoin	0.09 - 0.24	83-94
Sulfanilamid	0.87 - 1.08	20
Theophyllin	0.49 - 0.77	56

Examples of saliva sampling for PK evaluation

SCHWARZ PHARMA

Study of bioavailability and pharmacokinetics of theophylline following administration of two sustained release dosage forms as assessed by salivary data: Part II

N. Ohmori[1], N. Inotsume[1], M. Matsukura[2], A. Higashi[2], R. Iwaoku[1], Y. Tobino[1], M. Nakano[1] and I. Matsuda[2]

[1]Department of Pharmaceutical Services, Kumamoto University Hospital and [2]Department of Pediatrics, Kumamoto University Medical School, 1-1-1 Honjo, Kumamoto 860, Japan

Abstract. Bioavailability and pharmacokinetics of theophylline following administration of a marketed sustained release tablet (Theo-Dur®) and a newly designed sustained release tablet (E-0686) have been studied in fifteen healthy volunteers by measuring plasma and salivary concentrations. The theophylline level in saliva was 42.3 ± 0.008 (s.e.m.) % of the plasma level and its correlation coefficient was 0.908. This observation suggests that salivary levels are considered to be a good indicator of the plasma concentration of theophylline. Inter-

International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 24 No. 4 – 1986 (pp. 196–201)

Examples of saliva sampling for PK evaluation

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$Conc_{saliva} \approx 0.423 * conc_{plasma}$, r=0.908

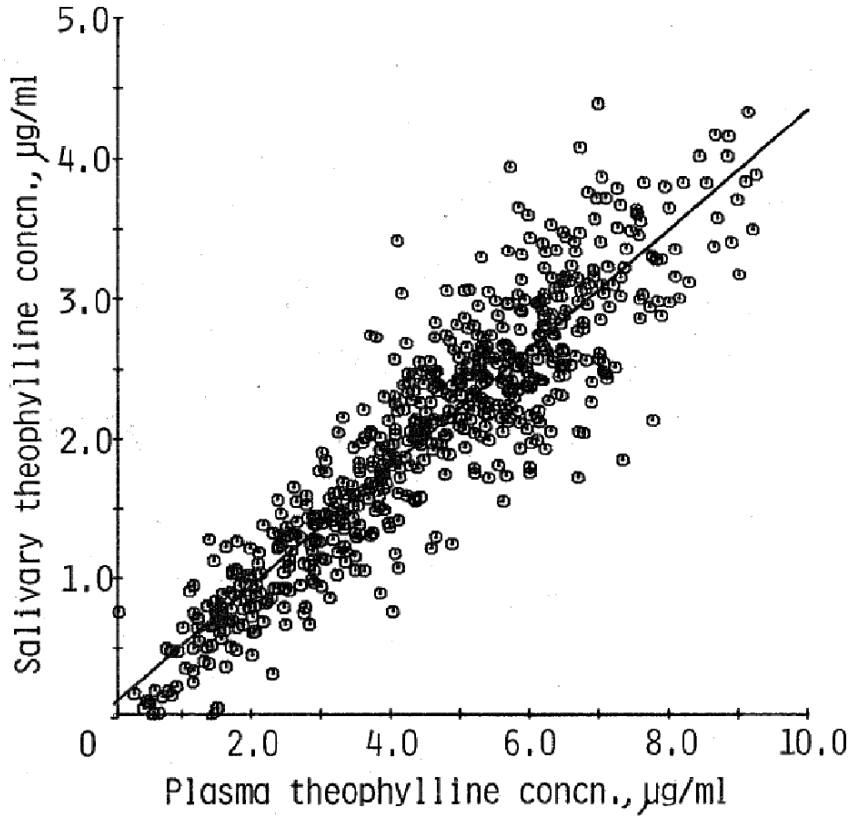

Fig. 1 Relationship between theophylline concentrations in 600 plasma and salivary specimens.

Ohmori N., et al, Int J Clin Pharmacol Therapy and Toxicol, (1986) 24: 196-201

Examples of saliva sampling for PK evaluation

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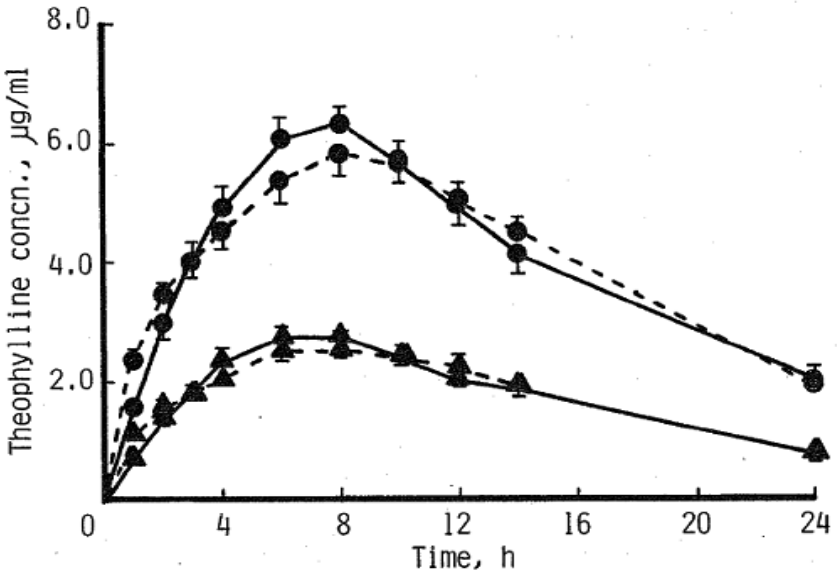

Fig. 2 Mean plasma (●) and salivary (▲) theophylline concentrations after administration of 300 mg Theo-Dur under fasting (– – –) and non-fasting (——) conditions in 15 healthy subjects.

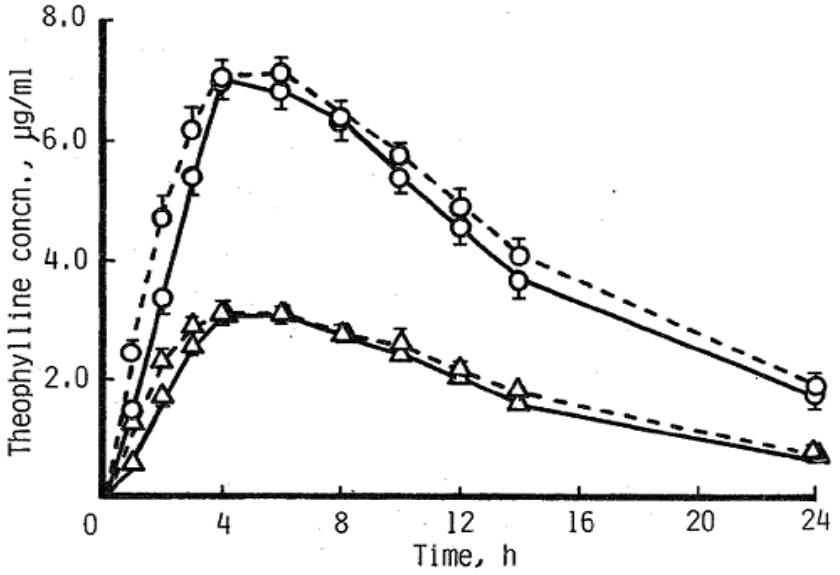

Fig. 3 Mean plasma (○) and salivary (△) theophylline concentrations after administration of 300 mg E-0686 under fasting (– – –) and non-fasting (——) conditions in 15 healthy subjects.

Ohmori N., et al, Int J Clin Pharmacol Therapy and Toxicol, (1986) 24: 196-201

Examples of saliva sampling for PK evaluation

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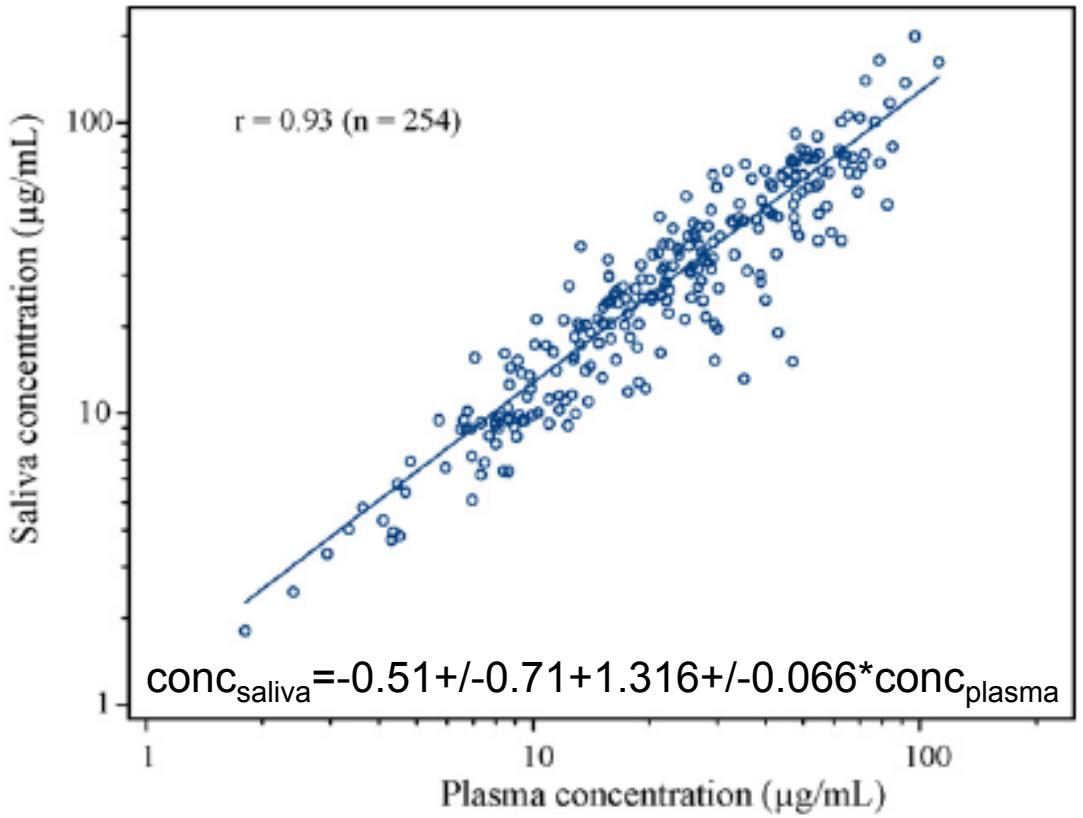

Figure 3 Levetiracetam saliva vs. plasma concentrations relationship. The line represents the least-squares regression line.

Published by: Fontain N.B., et al, Epilepsy Research 2007, in press

Examples of saliva sampling for PK evaluation

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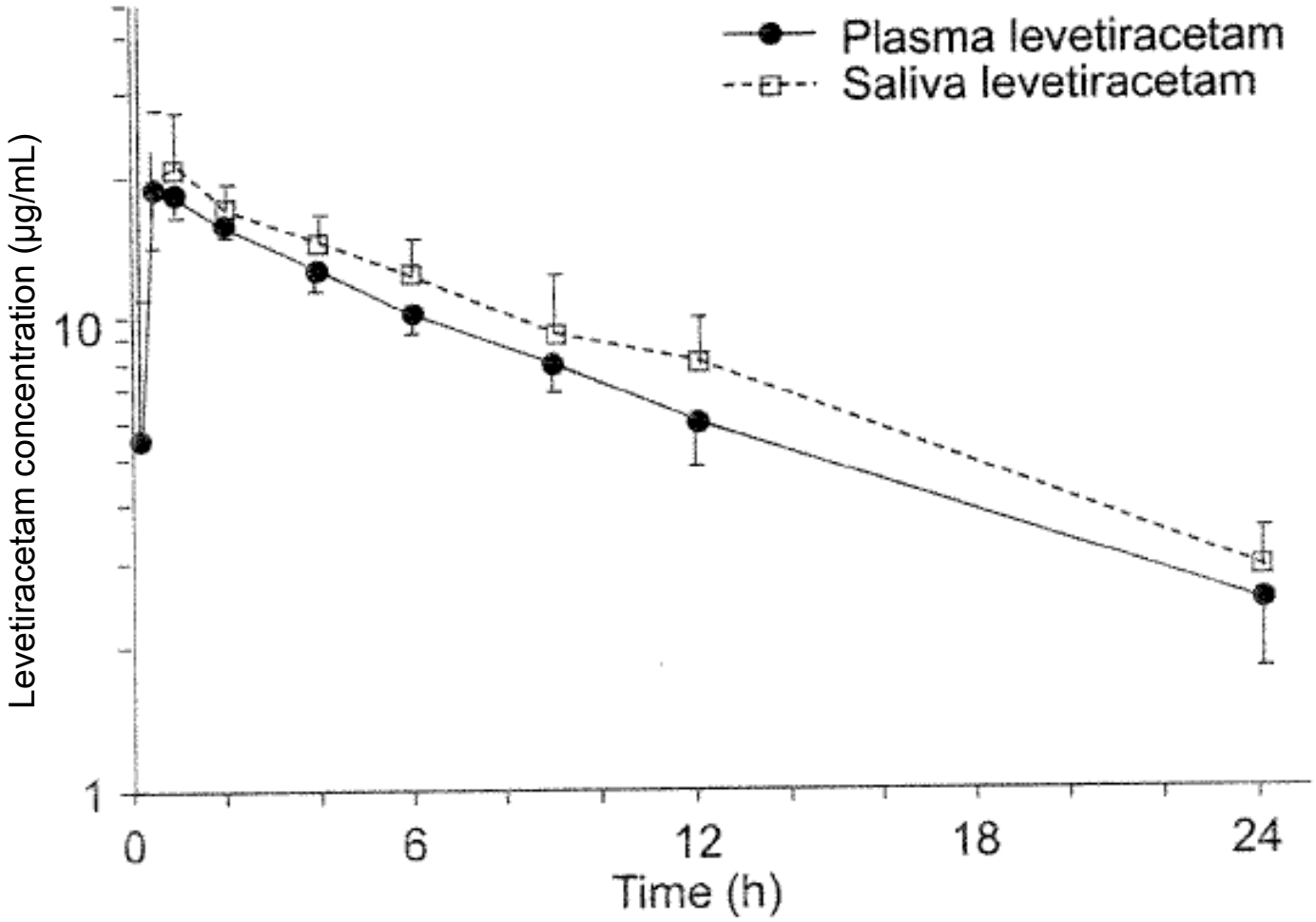

Concentrations after single oral dose of 750mg Levetiracetam (three 250mg tablets)
Extract from: Lins RL, et al. IntJClinPharmacol&Thera; 45(1), 2007, 47-54

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Example: drug RED

Comparison of plasma PK and saliva PK

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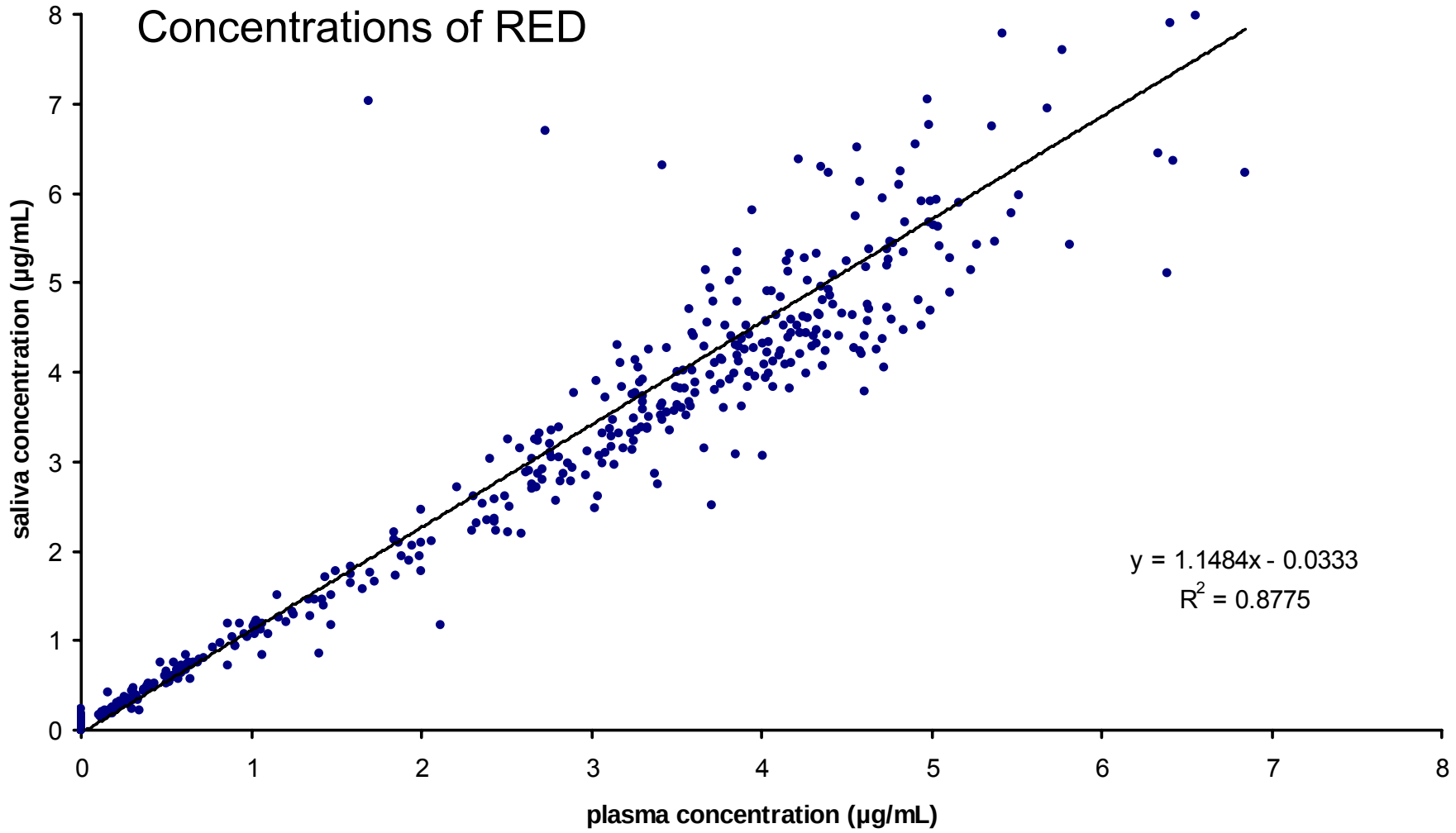
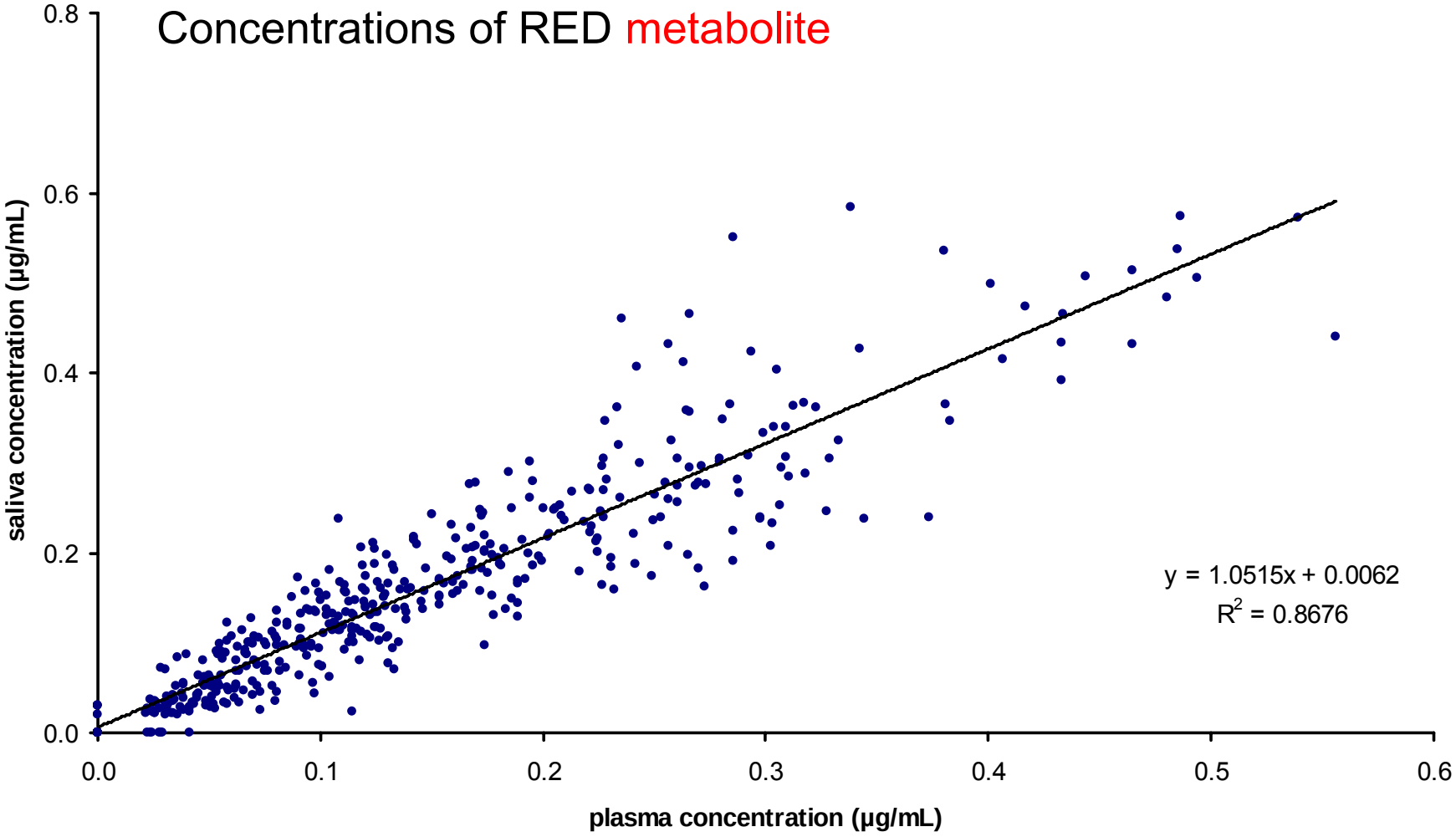


Comparison of plasma PK and saliva PK



Parameters of pharmacokinetics evaluation of bioequivalence

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Treatment drug	AUC Plasma	AUC Saliva	BE % plasma BE % saliva	90%CI plasma 90%CI saliva
A RED	86.4/18.3	95.3/20.3	101.4 99.9	89.0-115.5 88.1-113.3
B RED	85.1/17.6	94.9/18.6		
A metabolite	10.05/4.11	11.02/4.82	101.4 102.6	75.7-134.9 74.1-142.1
B metabolite	9.98/4.11	10.73/4.45		

Arithmetic mean/sd, n=16, BE and 90% CI after log transformation

Model dependent PK with plasma or saliva samples

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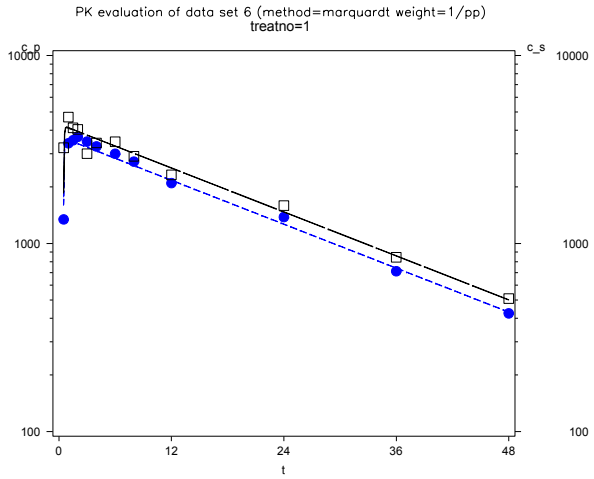

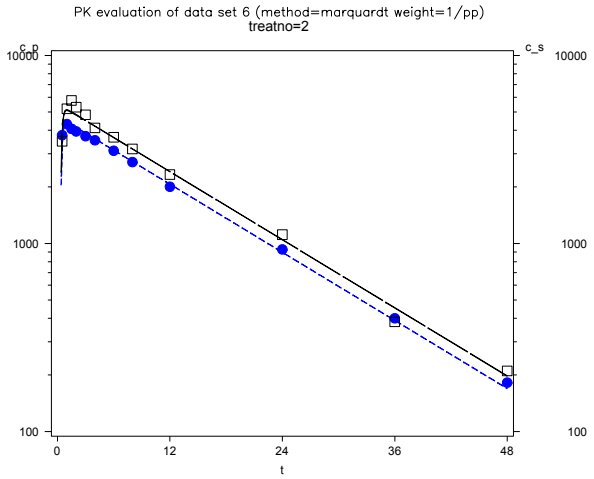

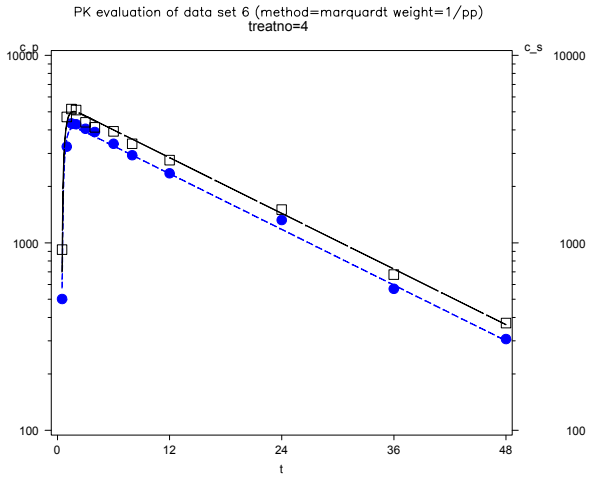

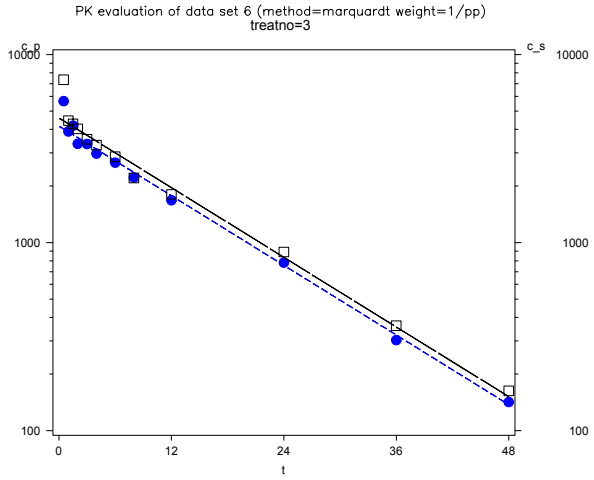

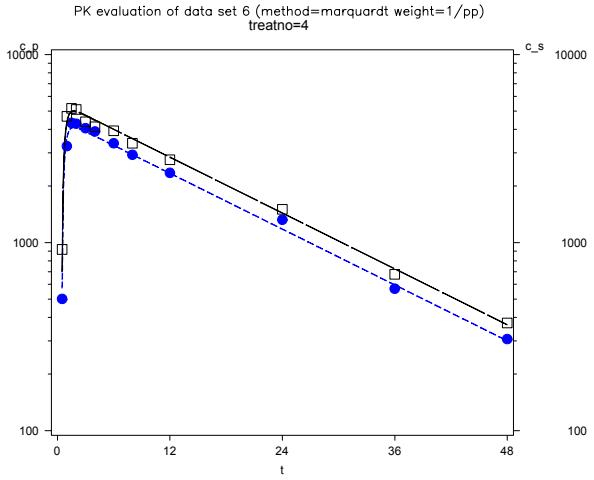

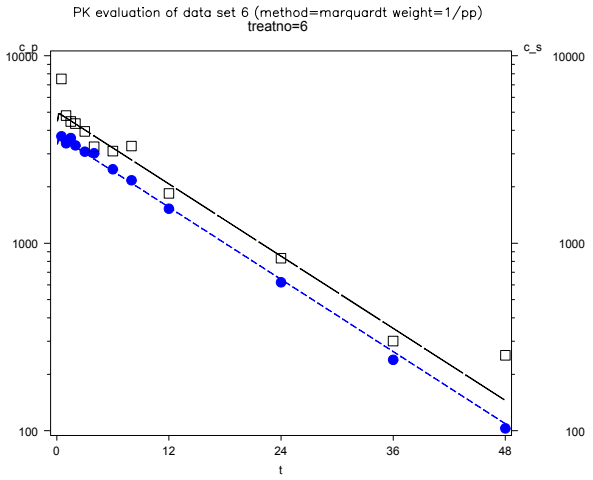

PK Parameters of RED

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One compartment model with first order absorption and first order elimination
(Bateman function with parameters k_a, k_e, dose, and V_d)

Saliva samples	**Plasma samples**
k_e = 0.0622 h^{-1}	k_e = 0.0635 h^{-1}
$t_{1/2}$ = 11 h	**$t_{1/2}$ = 11 h**
t_{lag} = 0.245 h	t_{lag} = 0.187 h
V/f = 42.2 L	**V/f = 49.6 L**

Comparison of plasma PK and saliva PK

SCHWARZ PHARMA

- Data from saliva samples are sufficient to characterize PK profile, model dependent PK and useful for BE evaluation.
- Rate constant of elimination resp. $t_{1/2}$ is the same.
- Approximation of the volume of distribution using saliva samples results in about 15% lower values corresponding to 15% higher concentrations in saliva than in plasma.
- Similar results for the metabolite of RED.

Pharmacokinetics of RED in saliva is a good approximation (a surrogate) for the pharmacokinetics in plasma.

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Example: drug BLUE

Correlation between BLUE concentrations in saliva and plasma

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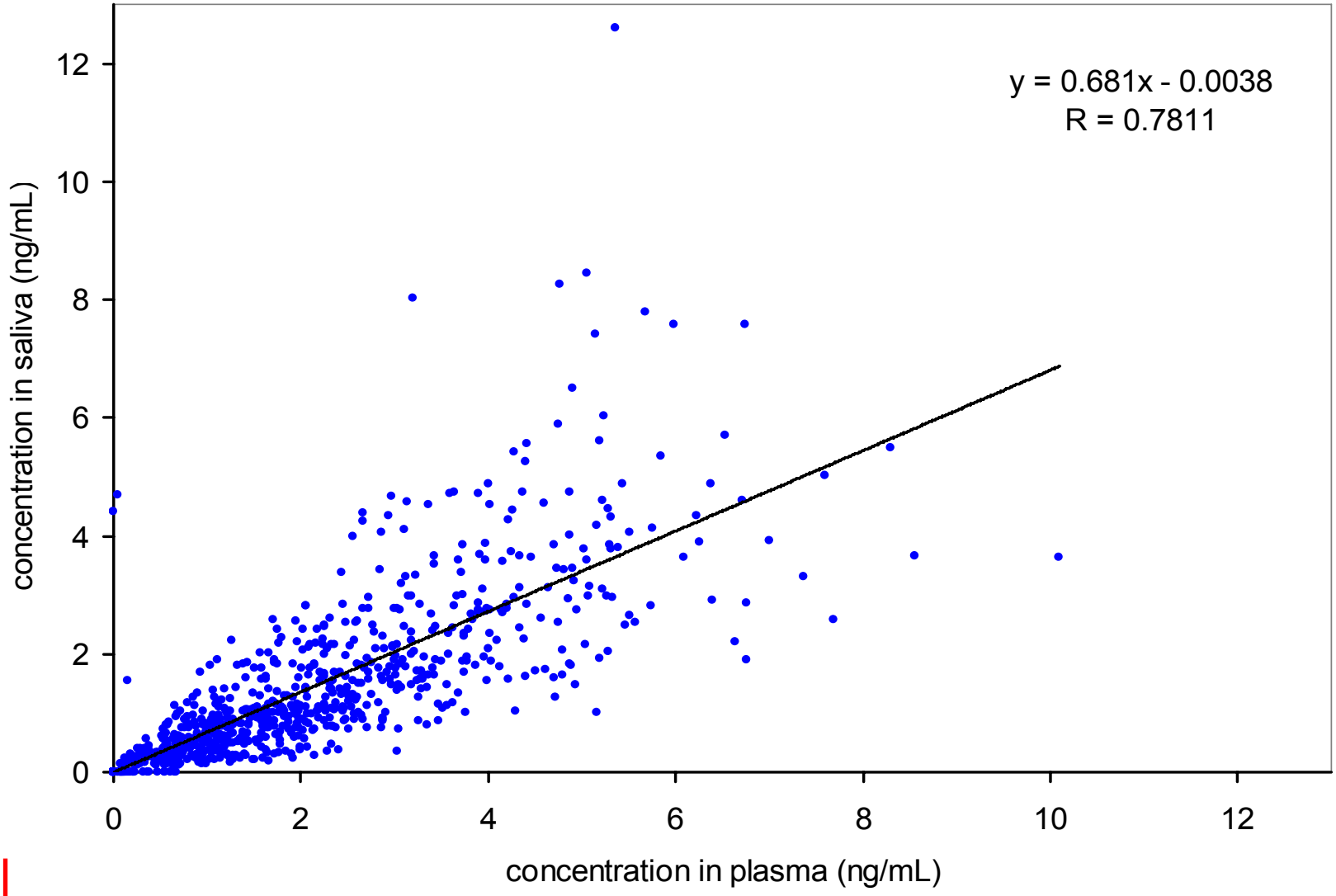

Correlation between BLUE concentrations in saliva and plasma

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Individual factor for correlation between plasma and saliva concentration

C_{saliva} = intercept + factor * C_{plasma}

parameter	intercept	factor
arithmetic mean	-0.018	0.671
SD	0.242	0.273
range	-1.04 - 0.586	0.297 – 1.424

Correlation between BLUE concentrations in saliva and plasma (after individual correction)

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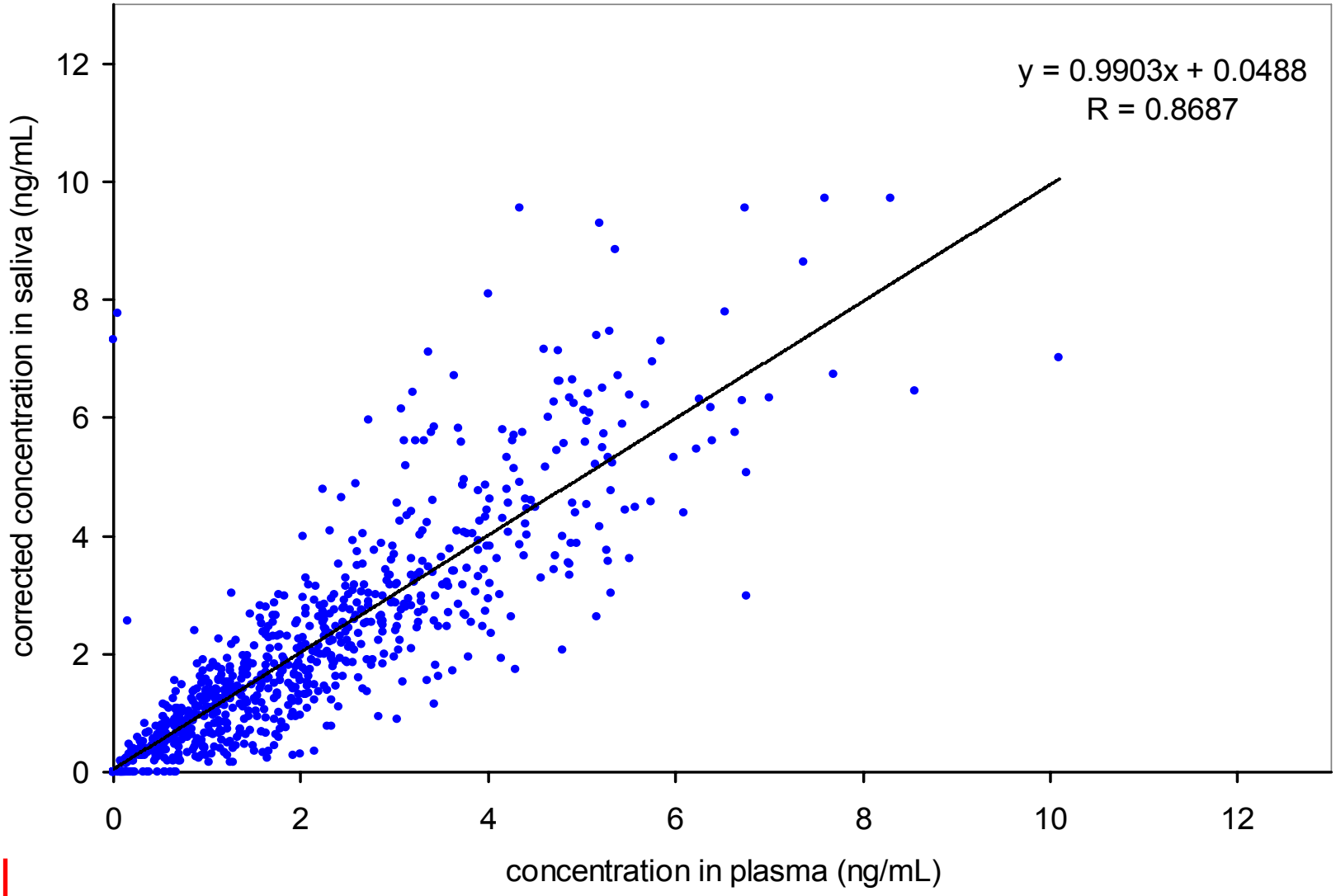

Results of „BE“ evaluation

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Parameter	Medium	8mg BLUE - reference	8mg BLUE - test
C_{max}	Plasma Saliva	3.69(45.1) 3.17(63.5)	4.16(43.7) 3.47(65.2)
$AUC_{(0\text{-}tz)}$	Plasma Saliva	44.9(43.8) 33.3(65.2)	47.5(41.5) 34.4(63.0)
t_{max}	Plasma Saliva	5(3-6) 5(3-8)	5(3-6) 5(3-8)

C_{max} and $AUC_{(0\text{-}tz)}$: Mean (CV), t_{max}: range

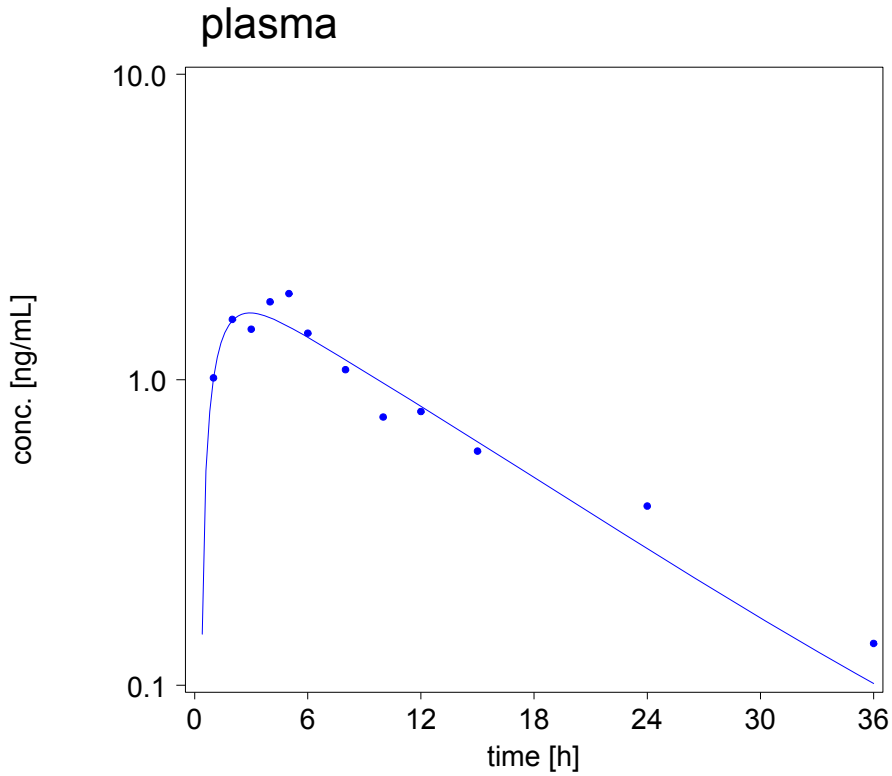
Results of „BE“ evaluation

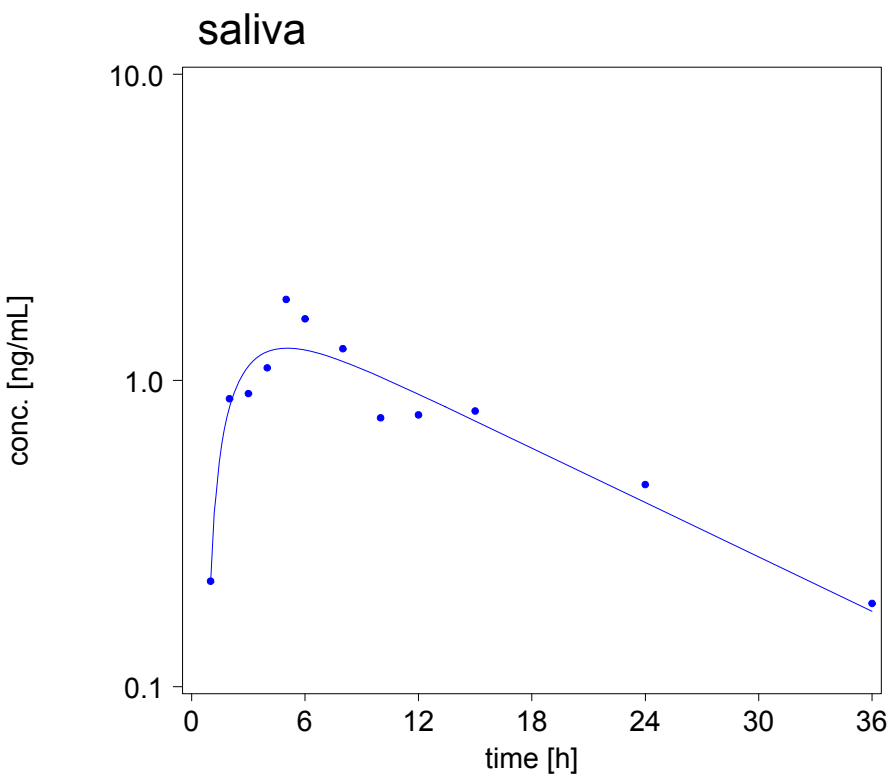
SCHWARZ PHARMA

Parameter	Saliva point estimate	 90% CI	Plasma point estimate	 90% CI
C_{max}	112.0	98.4 – 127.5	112.3	101.8 – 123.9
AUC(0-tz)	105.7	94.9 – 117.8	106.6	99.3 – 114.5

ANOVA results relative bioavailability

PK modelling





PK modelling

SCHWARZ PHARMA

PK model: one compartment model with first order absorption and elimination (Bateman function)

k_e (1/h)	treatment A (n=33)	treatment B (n=33)
plasma	0.1548-/+0.2084	0.1357+/-0.0596
saliva	0.1319+/-0.0792	0.1309+/-0.0595

Comparison of plasma PK and saliva PK

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- Saliva samples are a good surrogate for model independent PK and PK modelling (for drug BLUE in plasma).

- BE evaluation based on the saliva samples fit with the results of the evaluation based on plasma samples (especially after normalization using individual factors).

Use saliva samples instead of plasma samples for characterization of BLUE PK (after validation of the correlation and characterization of variability and maybe use of individual value of R estimeted with 1 or 2 plasma samples).

Discussion and Conclusion

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- Using saliva samples instead of / in addition to plasma samples was shown to be a feasible tool to characterize the PK of a drug in plasma.

- Using a drug specific ratio for saliva over plasma concentrations can result in useful values for model dependent and model independent parameters of PK and BE testing.

- The BE evaluation based on saliva samples fits with the results based on plasma samples (especially after normalization using individual factors).

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Future perspectives

- Saliva samples not only for therapeutic drug monitoring but for PK / popPK evaluation

- Decreased costs for sample collection

- Increased explanatory power of Population PK with possible (more) sampling out of clinics (at more relevant time points after admin.)

- Increased acceptance for studies in children (by patients, parents, ethics committees, and authorities)

- Increased comfort for the patients/subjects by non-invasive sampling

…