Blood and Plasma: a Magic Twin or Single in Human Pharmacokinetics ?

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EBF Workshop

Connecting Strategies on Dried Blood Spots

Recent Regulatory Guidance

- **only plasma concentration-time profiles:**
  - 2010 EMEA Guideline on the Investigation of Bioequivalence
  - 2010 EMEA draft Guideline on the Investigation of Drug Interactions
- **blood concentrations in some sections and plasma concentrations in other sections:**
  2009 FDA draft Guidance on the Contents of the Clinical Pharmacology Section of the Labeling for Drugs
- **plasma or whole blood, if appropriate:**
  2010 Draft FDA Guidance on Pharmacokinetics in Patients with Impaired Renal Function

A commentary.
Use of Dried Blood Spots in Drug Development: Pharmacokinetic Considerations.

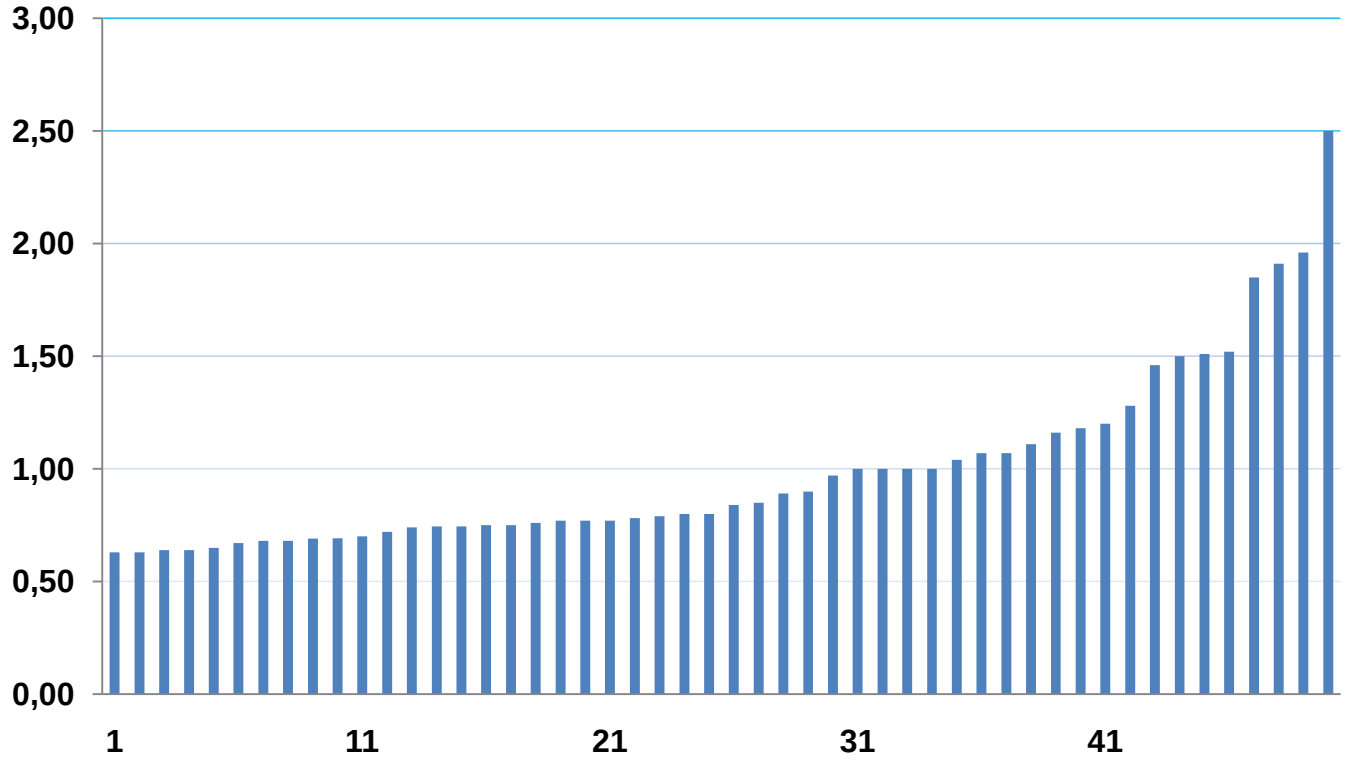
Malcolm Rowland and Gary T Emmons
The AAPS Journal, 2010

"This commentary considers the pharmacokinetic issues that arise and compares these with those attached to plasma, the mainstay matrix. A common implicit use of these matrices is as a surrogate for plasma water, and to this extent, the critical assumption made is constancy in fraction unbound for plasma and, additionally for blood, constancy of hematocrit and blood cell affinity of compound. Often, these assumptions are reasonable and either matrix suffices, but not always.

….

Most of these issues can be explored and addressed in vitro prior to the main development program."

Blood : Plasma Drug Concentration Ratios of 50 structurally diverse compounds



De Buck S, Sinha VK, et al. DMD 35: 649-659, 2007

Relevance of Blood in physiologically (mechanistically) based PK

Hepatic Clearance is expressed in blood flow and unbound drug in blood

$$Cl_{H,blood} = \frac{Q_{H,blood} \times fu_{blood} \times Clu_{\text{int},H}}{Q_{H,blood} + fu_{blood} \times Clu_{\text{int},H}}$$

Hepatic Clearance	First Pass Extraction	Absolute Oral Bioavailability
Close to $Q_{H,blood}$	High	Low (e.g . < 10%)
Low compared to $Q_{H,blood}$	Low	High (e.g. > 85%)

Blood and Plasma Drug Concentrations

Malcolm Rowland and Gary T Emmons
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$$C_{plasma} = \frac{C_u}{fu}$$

$$C_{blood} = \left[\frac{1 - H}{fu} + H \times R \right] C_u$$

R : blood cell to unbound plasma concentration ratio

Whole Blood concentration is sensitive to

- **Hematocrit**
- **Unbound fraction in plasma**
- **R, which can change, e.g. due to saturation of binding affinity in red blood cells**

Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase

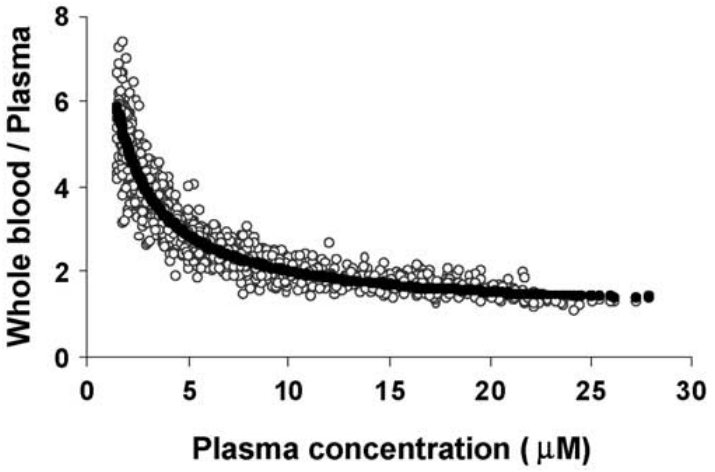


Fig. 2. Plot of the whole blood/plasma concentration ratio for TPM as a function of the plasma concentration. The open circles represent individual results of 1278 blood samples obtained from 27 male subjects. The curvilinear line formed by the filled circles represents values predicted by a curve-fit analysis of the data assuming two saturable binding sites as defined in Eq. (1).

2.4. Analysis of the binding of TPM to erythrocytes

TPM dissociation binding constant (K_d) and maximum binding rate (B_{max}) values for its saturable binding to erythrocytes were obtained by a curve-fit analysis of the data applied to forms of Eq. (1) that contained one or two saturable sites.

$$C_b = \frac{B_{max}1 \times C_{pu}}{C_{pu} + K_d1} + \frac{B_{max}2 \times C_{pu}}{C_{pu} + K_d2} + CF \times C_p \quad (1)$$

Shank RP, Doose DR, et al. Epilepsy Research 63: 103-112, 2005

Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase

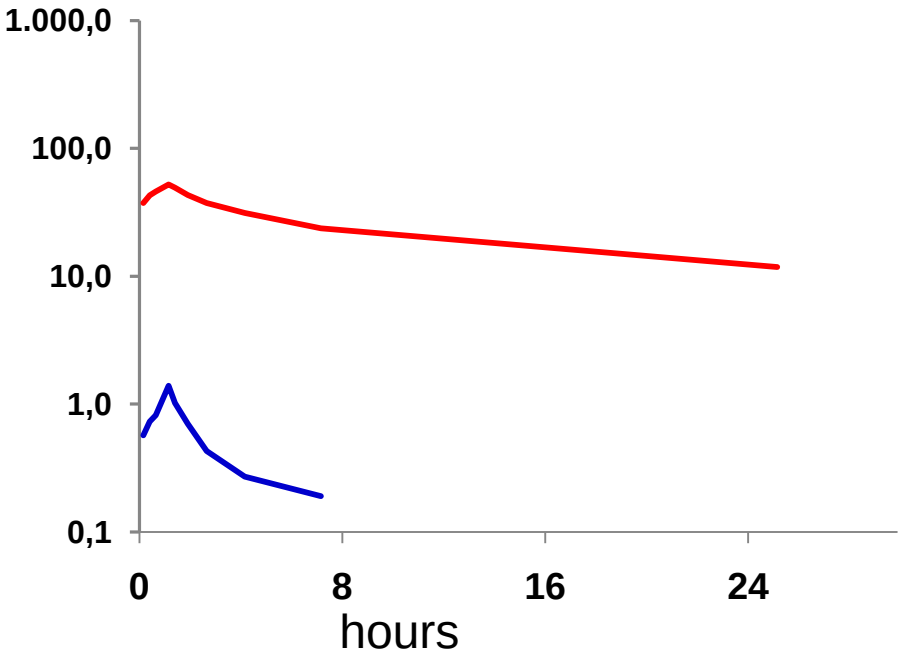
	Plasma				Whole Blood		
	100 mg	200 mg	400 mg		100 mg	200 mg	400 mg
CL/F (L/h)	1.5	1.5	1.5		0.2	0.3	0.5
Vss/F (L)	80	69	65		22	33	43
$t_{1/2}$ (h)	47	33	30		71	78	58
C_{max} (mg/L)	1.6	3.5	7.3		4.9	7.1	11.5

Shank RP, Doose DR, et al. Epilepsy Research 63: 103-112, 2005

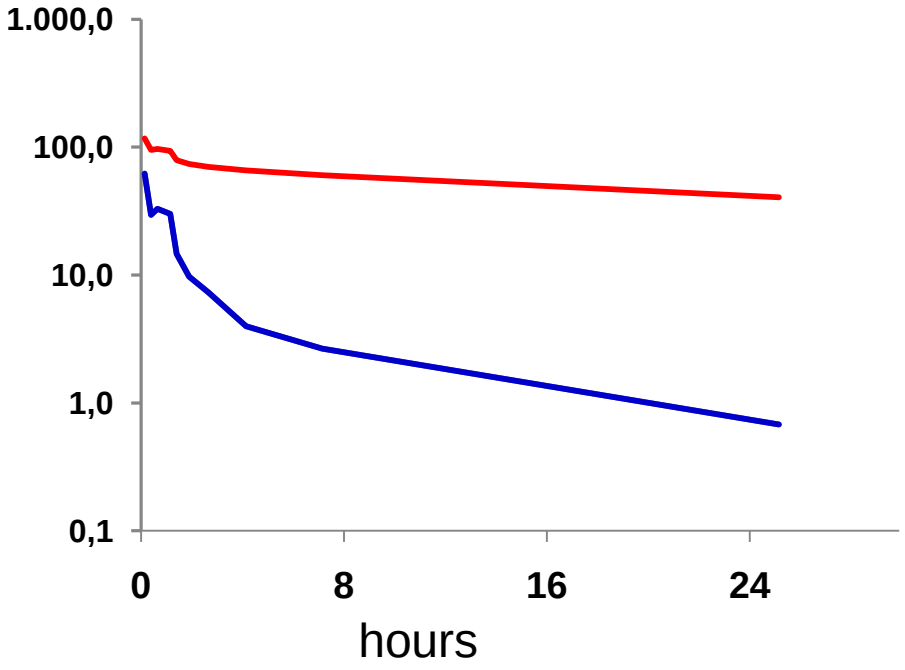
Implication of non-linear red blood cell partitioning for the PK of the nucleoside transport inhibitor draflazine

Draflazine concentration (ng/ml) in whole blood and plasma

0.25 mg over 15 min followed by
0.25 mg over 1 hour infusion

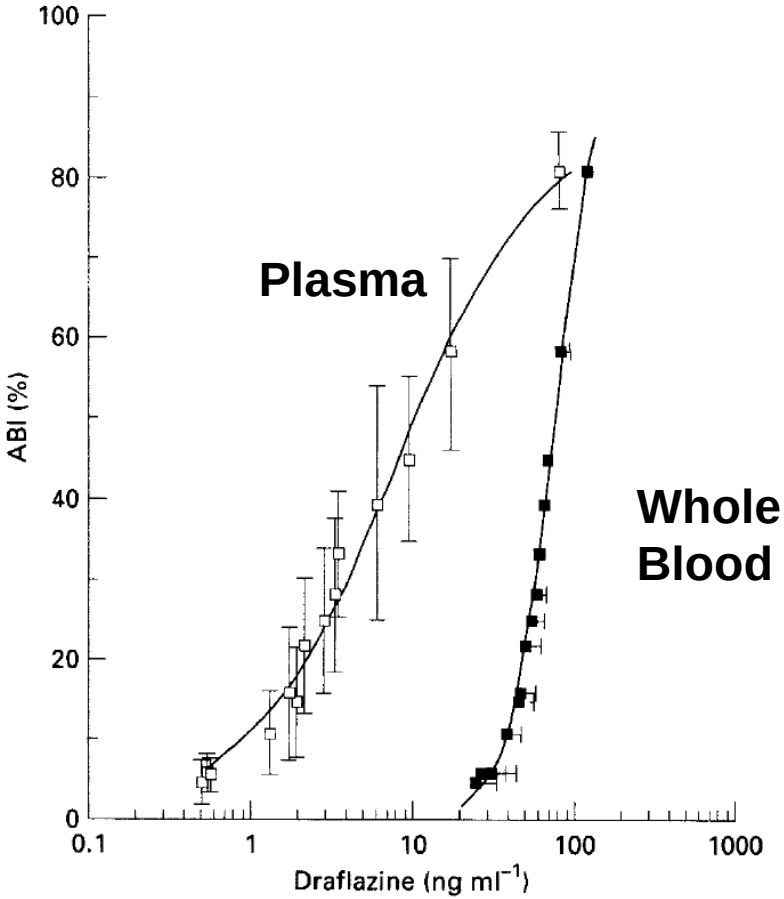


2.5 mg over 15 min followed by
2.5 mg over 1 hour infusion

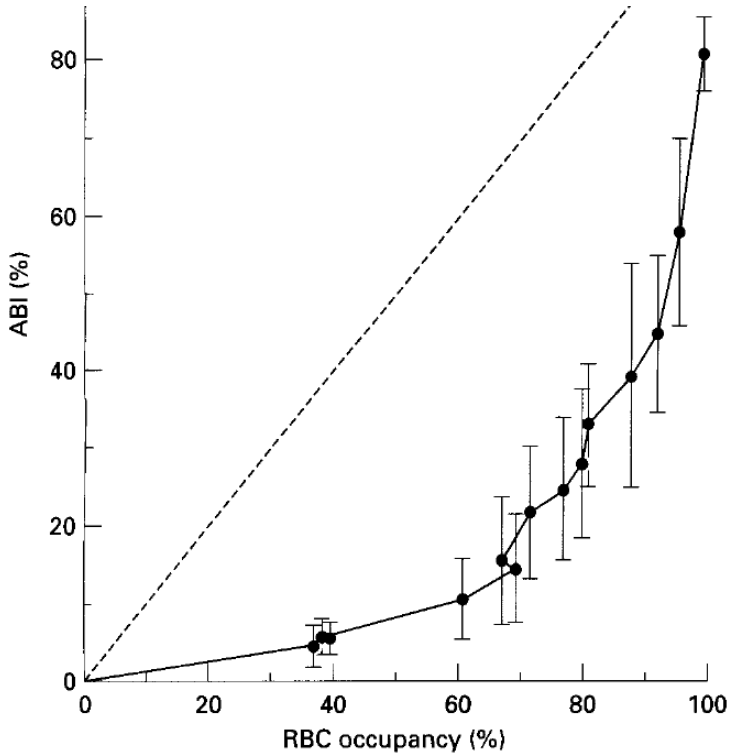


Based upon
Snoeck E, Piotrovskij V, et al. Br J Clin Pharmacol 43: 603-612, 1997

Concentration-response relationship between inhibition of nucleoside transport and draflazine concentrations in plasma, whole blood and RBC



$$C_{RBC} = \frac{C_b - (1 - H) \cdot C_p}{H}$$



Snoeck E, Piotrovskij V, et al. Br J Clin Pharmacol 43: 603-612, 1997

Blood and Plasma Pharmacokinetics of Cyclosporin in Diabetic Kidney Transplant Recipients

Mendoza AE et al., Clin Pharmacokinet 47: 733-742, 2008

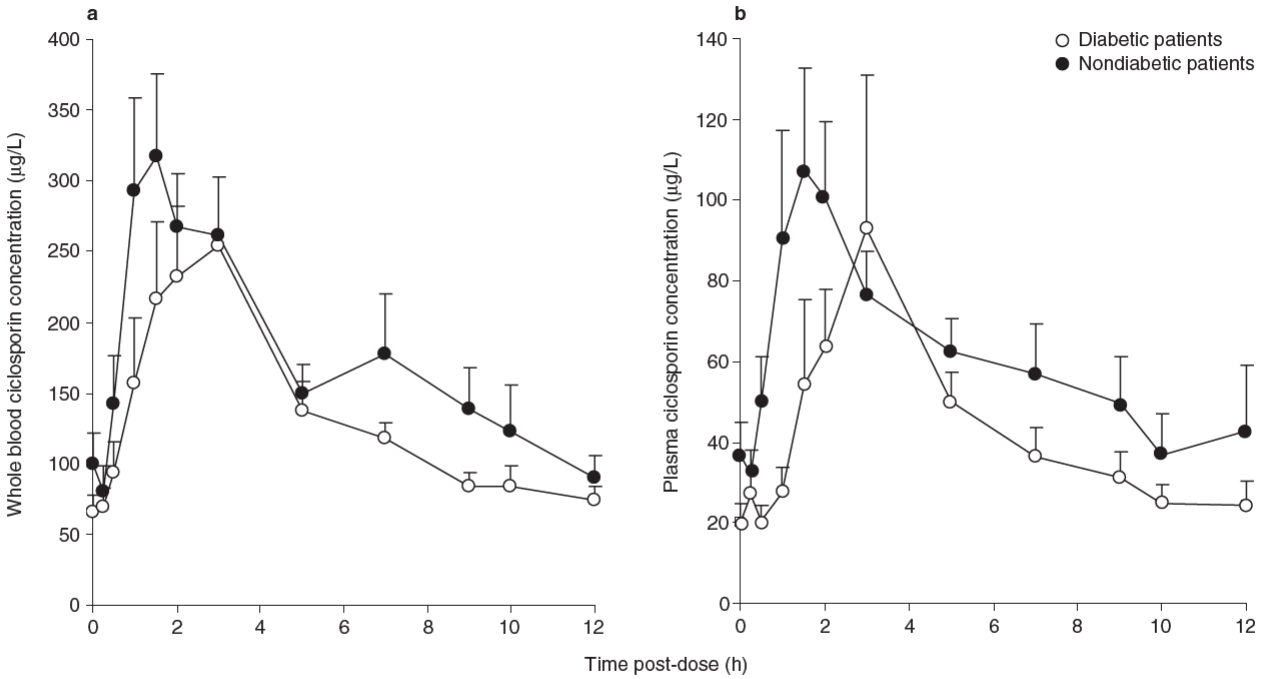


Fig. 1. Mean (standard error of the mean) concentration-time profiles of ciclosporin (**a**) in whole blood and (**b**) in plasma from diabetic and nondiabetic stable kidney transplant recipients.

B : P ratio varied at each time point

4.2 ± 3.9 for diabetic (n = 67 determinations in six subjects)
3.4 ± 1.7 for non-diabetic (n = 80 determinations in seven subjects)

Blood and Plasma Pharmacokinetics of Cyclosporin in Diabetic Kidney Transplant Recipients.

Mendoza AE et al., Clin Pharmacokinet 2008: 47 (11): 733-742

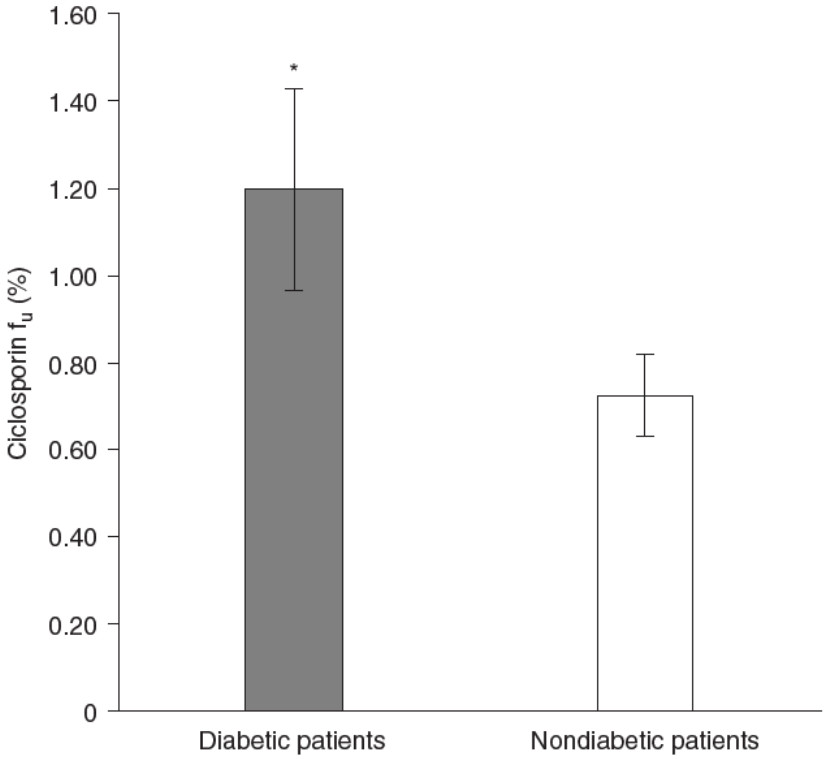


Fig. 2. Ciclosporin fraction unbound (f_u) in diabetic and nondiabetic stable kidney transplant recipients. The error bars denote the standard error of the mean. * p = 0.066 vs nondiabetic patients.

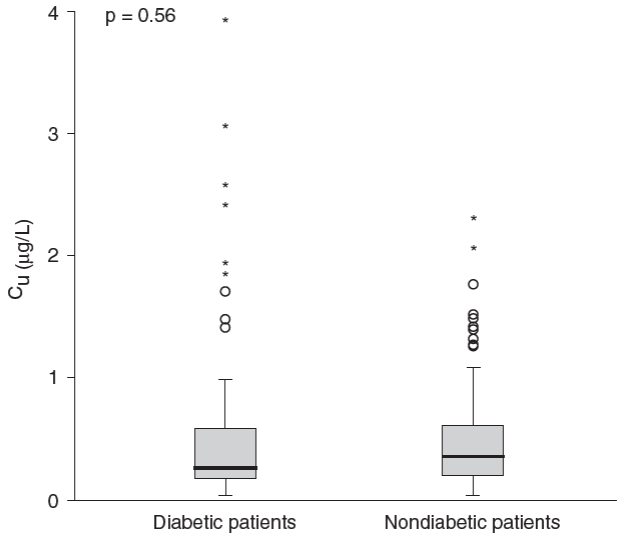


Fig. 3. Box plot of unbound ciclosporin concentrations (C_u) in plasma from diabetic and nondiabetic kidney transplant recipients. The C_u was calculated using the equation $C_u = f_u \times C_p$, where f_u is the unbound fraction and C_p is the ciclosporin concentration in plasma. The central line in the box represents the median value, the lower and upper lines represent the 25th and 75th percentiles, respectively, the whiskers represent values <1.5 times the interquartile range (IQR), values of >1.5 IQRs but <3 IQRs from the end of the box are labelled as outliers (o), and values more than 3 IQRs from the end of a box are labelled as extreme, denoted with an asterisk (*).

Conclusions

- **Specific and saturable drug binding to erythrocytes is a source of non-linear pharmacokinetics, causing deviations in concentration-time profiles between blood and plasma.**
  Think of the relevance for the drug action.
- **Verify constancy in unbound fractions in plasma and blood, in biochemistry (haematocrit, proteins, free fatty acids, … , associated with certain diseases)**
- **Early in vitro assessments of**
  - **Blood to plasma concentration ratios**
    - **in human blood over a broad range of drug concentrations**
    - **some animal species may miss the binding target in blood**
  - **Concentration dependency of protein binding**