A COMPARISON *IN VITRO* STUDY OF PERMEATION OF SELECTED DRUGS FROM LIPOPHILIC SOLUTIONS TROUGH HUMAN SKIN

ABSTRACT

The aim of the study was to compare the permeation of testosterone (TST), caffeine (CAF), flufenamic acid (FA) and benzoic acid (BA) from highly liquid paraffin through human heat-separated epidermis (HSE).

For evaluation of saturation concentration of the drugs in the vehicle(c_{sat}), an excess of BA, CAF, FA or TST was suspended in 5 ml of highly liquid paraffin in a screw top scintillation vial (500 rpm, 32 °C; 24 h). After sedimentation of non-dissolved substance, samples were drawn from the supernatant, diluted 1:10 with dichloromethane and analyzed via UV/VIS-spectroscopy: (Lambda 35; Perkin Elmer, BA 228 nm; CAF 277 nm; FA 287 nm; TST 238 nm).

Permeation experiments over human HSE of two donors (6 pieces of each) were performed in Franz diffusion cells at 32 °C. The donor was composed of TST, FA, BA (0.4 mg/ml), CAF (0.1 mg/ml) dissolved in paraffin. Samples of 0.4 ml were collected over the time, replaced by fresh acceptor solution (Soerensen phosphate buffer pH 7.4) and quantified by validated HPLC methods.

The steady state flux (J) was evaluated from the linear part of cumulative amount versus time plots and dividing it by donor concentration (c_{don}), the apparent permeability coefficient (k_P) was obtained**.** The k_P, were calculated by multiplying diffusion coefficient (D) and the stratum corneum-donor partition coefficient ($K_{sc/don}$); dividing this by the thickness of HSE (h), maximum flux (Jmax) was also calculated

Based on $K_{sc/don}$ is established the partitioning of drug between highly liquid paraffin and SC lipids. $K_{sc/don}$ was determined from the decrease of c_{don} after 24 h incubation of SC with BA, CAF, FFA, or TST in highly liquid paraffin at 32 °C
(3 different c_{don} each, skin 1 and skin 2). The remaining amount of drug in paraffin (c_{Rest}) was analyzed using UV-spectrophotometer by wavelength determined from UV spectrum of drug. °The results obtained are summarized in Table 1.

TABLE 1	**TST**	**CAF**	**FA**	**BA**
$C_{sat.}$ ± SD (µg/ml)	498.15 ± 55.3	134.1± 3.3	1176.7 ± 5.2	9852.4±826
Log $K_{oct/water}$	3.47	-0.08	4.80	1.90
K_P (cm/s) ×10-7	2.50 ± 0.56	11.43 ± 5.2	7.11 ± 0.8	29.68 ± 9.9
J_{MAX} (µg/cm²/h)	0.45	0.53	3.02	105.25
$K_{SC/don}$	168.3 ± 47.9	103.74 ± 39.1	52.5 ± 23.4	61.7 ± 34.4

The potential of vehicle to influence the permeation of model drugs is present in my work. Normally, the permeability is higher for hydrophilic drug using the lipophilic donor in comparison to the aqueous. However, for testosterone the permeation was very similar. This may lead to the conclusion, that skin absorption of testosterone is not dependent on the vehicle used. Generally, we can assert that hydrophilic drugs show high permeabilities out of lipophilic vehicle and vice versa.

The maximum flux **(**J_{MAX}) is primarily dependent on solubility of drug in vehicle **(**C_{sat}**)**, which corresponds well to lipophilicity of drugs expressed as the octanol/water partition coefficient (log $K_{oct/water}$).