TRANSDERMAL FLUX PREDICTIONS FOR HIGHLY LIPOPHILIC COMPOUNDS: COMPARISON WITH EXPERIMENTAL RESULTS

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BACKGROUND & AIMS

- To evaluate the feasibility of delivering transdermally a series of **highly lipophilic** compounds (**log P ~ 4-7**), comprising several selective estrogen receptor modulators (**SERMs**) and a modified testosterone (**danazol**).
- To explore whether the fluxes achieved might be sufficient to allow for 'local' application and drug delivery to underlying subcutaneous tissues, avoiding thereby undesirable systemic side-effects when treating breast cancer.
- To compare the ***in vitro*** **experimental fluxes** of the drugs considered with their **predicted transport** using the **Potts & Guy algorithm**.

METHODS

Prediction model & experimental studies

Step 1: Calculation of lipophilicity and aqueous solubility of compounds

- **Log $P_{o/w}$** and aqueous solubilities **(log *S*)** of the drugs were estimated with the **"ALOGPS 2.1 Programme" [1].**

Step 2: Prediction of maximum drug flux (J_{max}) across skin

$$J_{max} \cong \frac{D}{h} * K_{skin\ /\ vehicle} * C^{sat}_{vehicle}$$

$$K_p = \frac{D * K_{skin\ /\ water}}{h}$$

- Calculate permeability coefficient **(K_p)** of each drug across skin from aqueous solution using the **Potts & Guy equation [2]:**

$$\log K_p = -2.7 + 0.71 * \log P - 0.0061 * MW$$

- Calculate corrected permeability coefficient **(K_{pcorr})** following **Cleek & Bunge [3]** for highly lipophilic species for which viable epidermis can contribute to rate-control:

$$K_p^{corr} = \frac{K_p}{1 + \frac{K_p \bullet \sqrt{MW}}{2.6}}$$

Step 3: Determine J_{max} from K_p x estimated solubility of drug in water

Step 4: *In vitro* permeation studies

- *In vitro* experimental fluxes **(J_{expt})** from saturated hydroalcoholic solutions (70:30; ethanol:water) were determined in side-by-side diffusion cells (area: 0.71 cm2; volume: 3.2 ml) through dermatomed (750 µm) pig skin at 37±0.5°C. Samples were analyzed by HPLC.

***J_{max}*: maximum flux; *D*: diffusion coefficent; *K*: *stratum corneum*-vehicle partition coefficent, *h*: *stratum corneum* path lenght; *$C_{sat\ veh}$*: saturated drug solubility; *K_p*: permeability coefficient; *MW*: molecular weight**

RESULTS & DISCUSSION

Table: Estimated physicochemical properties and predicted skin permeability parameters of the compounds considered.

Compound[a]	MW	Model[b]	Log $K_{o/w}$	$10^2 x C_{sat}$ (mg.cm^{-3})	Log K_p (cm. h^{-1})	$10^2 x K_p$ (cm. h^{-1})	$10^2 x K_{pcorr}$ (cm. h^{-1})	J_{max} (µg.cm^{-2}.h^{-1})	J_{expt} (µg.cm^{-2}.h^{-1})
Clomiphene	405.97	AlogPs	6.08	0.04	-0.819	15.2	6.97	0.03	0.1±0.09
		Average logPs	6.89	0.25	-0.244	57.0	10.5	0.26	
Danazol	337.46	AlogPs	3.61	1.76	-2.162	0.69	0.66	0.12	0.30±0.08
		Average logPs	4.02	0.76	-1.871	1.35	1.23	0.09	
Droloxifene	387.52	AlogPs	5.43	0.31	-1.170	6.76	4.47	0.14	0.06±0.03
		Average logPs	6.03	1.77	-0.744	18.00	7.62	1.35	
Endoxifen	373.5	AlogPs	5.32	0.09	-1.164	6.85	4.54	0.04	1.55±1.28
		Average logPs	5.64	0.39	-0.937	11.60	6.22	0.24	
4-OH Tamoxifen	387.52	AlogPs	5.44	0.30	-1.163	6.87	4.52	0.14	0.52±0.26
		Average logPs	5.92	1.12	-0.822	15.10	7.04	0.79	
Tamoxifen	371.52	AlogPs	5.93	0.10	-0.719	19.10	7.91	0.08	0.14±0.08
		Average logPs	6.46	0.30	-0.343	45.40	10.40	0.31	
Toremifene	405.97	AlogPs	5.65	0.04	-1.124	7.51	4.75	0.02	0.21±0.13
		Average logPs	6.45	0.15	-0.556	27.80	8.81	0.14	

[a] Theoretical calculations presented are based only on parent drug.
[b] AlogPs model, in which ALOGPs and ALOGpS values predicted by the algorithm were taken as log $K_{o/w}$ and C_{sat}, respectively. Average AlogPs model uses average values of these two parameters derived from several different algorithms.

- Predicted fluxes were in good general agreement with the experimental results **(Figure).**

- Experimental values (except droloxifene) were typically greater thanthe predicted fluxes.
- Possibly due to the fact that prediction of J_{max} is based on an aqueous vehicle, whereas experimental formulation was a ethanol/water (70:30).
- Higher experimental fluxes could be due to the action of ethanol as a skin penetration enhancer.

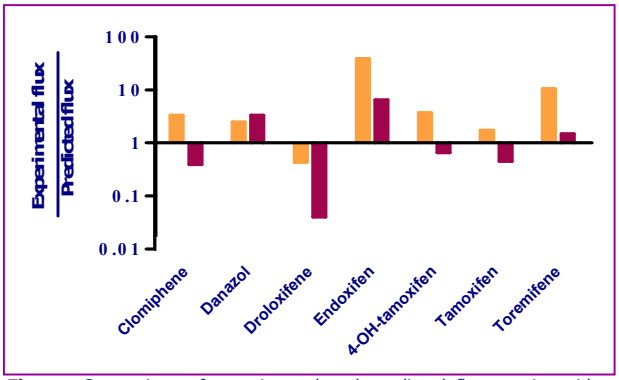

Figure: Comparison of experimental and predicted fluxes using either ALOGPs values (orange bars) or average ALOGPs values (red bars).

CONCLUSIONS

- Fluxes of **highly lipophilic** compounds can be **reasonably predicted**.
- From previous clinical studies **[4, 5]** and experimental fluxes observed, **topical** delivery of therapeutically useful doses of certain compounds to cancerous breast tissue and/or to treat benign breast diseases (such as mastalgia) may be feasible.

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