IBUPROFEN DERMATOPHARMACOKINETICS: STUDY OF THE CLEARANCE PHASE

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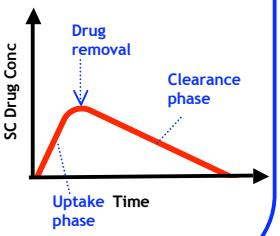
INTRODUCTION

The dermatopharmacokinetics approach suggested by the FDA proposes to evaluate the level of a topically applied drug in the stratum corneum (SC) during its uptake and clearance so as to calculate classic pharmacokinetic parameters (1).
Assumption: SC concentration-time curves are directly related to concentration-time curves in the epidermis and dermis.

Previous studies (2) have characterized the uptake phase of ibuprofen into the SC from a propylene glycol : water vehicle.
The goal of this work was to study the clearance phase of ibuprofen from the SC after 30 minutes of infinite dose application.

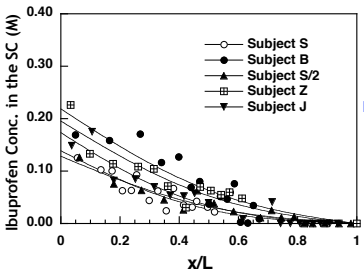


METHODOLOGY

TAPE STRIPPING
- Donor solution: Ibuprofen saturated solution in PG/water (75:25 v/v).
- Application time:30 min
- Application area: 4.91 cm²
- Sequential tape stripping (area: 3.14 cm²) @ 0, 0.5, 1, 2, 3, 4 hours after formulation removal
- Tapes weighted to quantify the SC removed
- TEWL measurement to determine SC thickness

ATR-FTIR (Attenuated total reflectance-IR spectroscopy)
- Donor solution: Ibuprofen saturated solution in PG/water (75:25 v/v).
- Application time:30 min
- ATR-FTIR Spectra of skin surface recorded at different times after formulation removal

RESULTS



Ibuprofen concentration profiles as a function of SC position after 30 minutes of application of a saturated solution

D/L^2 (h^{-1})	0.21 ± 0.04
K	2.99 ± 0.66
AUC (M)	0.059 ± 0.017

Appropiate solution of Fick's second law of diffusion:

$$C_x = K\,C_{veh}\left\{1 - \frac{x}{L} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(n\pi\,\frac{x}{L}\right)\exp\left(-\frac{D}{L^2}\,n^2\pi^2 t\right)\right\}$$

C_x : ibuprofen concentration (M)
K: SC-vehicle partition coefficient
L : SC thickness (μm)
X:depth into the SC (μm)
C_{veh}: donor concentration (M)
D: drug diffusion coefficient ($cm^2\,h^{-1}$)

X/L: relative depth of drug penetration

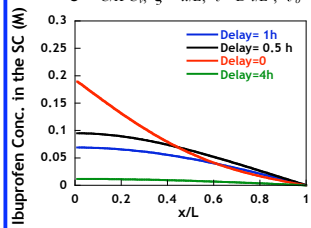
D/L^2: diffusional parameter (h^{-1})

Study of the Clearance Phase:

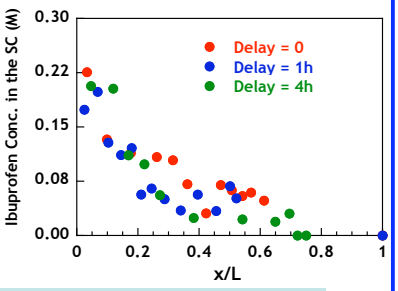
$$\tilde{C} = 2\sum_{n=0}^{\infty}\left(\frac{1}{\lambda_n^2} - 2\sum_{m=1}^{\infty}\frac{\exp\left[-\lambda_n^2\tau_o\right]}{m^2\pi^2 - \lambda_n^2}\right)\cos(\lambda_n\xi)\exp\left[-\lambda_n^2(\tau-\tau_o)\right] \quad \lambda_n = (2n+1)\pi/2$$

$\tilde{C} = C/K\,C_v,\ \xi = x/L,\ \tau = D\,t/L^2,\ \tau_o = D\,t_o/L^2$ = start of clearance phase ,

Theoretical curves (3)



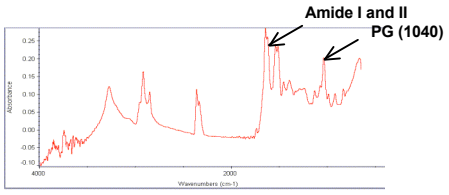
Experimental profiles



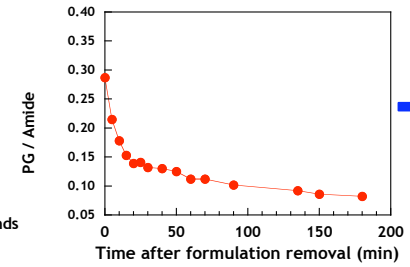
Surprisingly, very little change in the profile occurred during the 4 hours post-termination of delivery

Hypothesis:
rapid diffusion of PG (4), relative to the drug, results in the, at least transient, maintenance of a saturated ibuprofen concentration at the SC surface even after removal of the original formulation

ATR-FTIR analysis of propylene glycol elimination from SC surface



The AUC of PG was normalized with respect to the amide I+II bands



The absorbance (C-O stretch) characteristic of PG at 1040 cm^{-1} decreased rapidly during the 15 minutes post-removal of the formulation, indicating a fast elimination of PG from the skin surface.

CONCLUSIONS

- Ibuprofen clearance from the SC after 30 minutes of infinite dose application of a saturated solution in PG:H2O (75:25) was slow.
- ATR-FTIR analysis demonstrated that PG clearance from the skin surface is very rapid, and this could cause ibuprofen precipitation in the outermost layers of the SC, thus maintaining a saturated drug concentration after the formulation removal
- The role of excipients in topical delivery and bioavailability studies deserves further investigations

REFERENCE

(1) FDA (1998) Guidance for Industry:topical dermatological drug product NDAs and ANDAs - in vivo bioavailability, bioequivalence, in vitro release and associated studies (Draft).
(2) Herkenne C., Naik A., Kalia Y., Guy R. In vivo prediction of topical drug bioavailability AAPS Annual meeting, Baltimore Nov 8-11, 2004
(3)N'Dri-Stempfer B., Bunge A., Improving Dermatopharmacokinetics (DPK) evaluation of dermal penetration, AAPS Annual meeting, Baltimore Nov 8-11, 2004.
(4) Trottet L., Merly C., Mirza M., Hadgraft, Davis A.F., Effect of finite doses of propylene glycol on enhancement of in vitro permeation of loperamide hydrocloride. Int J Pharm 274 (2004) 213-219