DERMATOPHARMACOKINETICS: DRUG CLEARANCE FROM THE STRATUM CORNEUM

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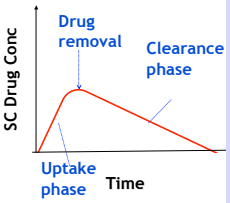
INTRODUCTION

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.

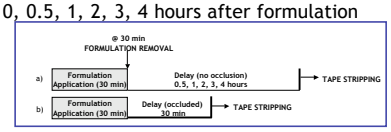
Previous studies [(2,3)] have characterized the uptake phase of ibuprofen into the SC from a propylene glycol : water vehicle.

The goal of this work was to study the clearance phase of ibuprofen from the SC after 30 minutes of infinite dose application.

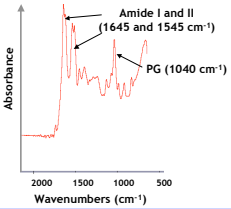


METHODOLOGY

TAPE STRIPPING
- Formulation: 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) @ time 0, 0.5, 1, 2, 3, 4 hours after formulation removal
- Tapes weighed to quantify SC removed
- TEWL measurement to determine SC thickness
- Subjects: 5 volunteers, 3 female and 2 male



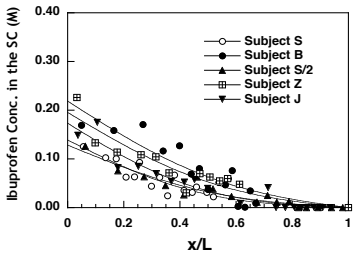
ATR-FTIR (Attenuated total reflectance-IR spectroscopy)
- Formulation: Ibuprofen saturated solution in PG/water (75:25 v/v).
- Application time:3 0 min
- ATR-FTIR spectra of skin surface recorded at different times after formulation removal
- ATR-FTIR spectra of tapes collected @ 0 and 0.5 hours after formulation removal



RESULTS

IBUPROFEN CONCENTRATION PROFILES AFTER 30 MINUTES OF APPLICATION OF A SATURATED SOLUTION

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



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 ($cm^2\,h^{-1}$)

Appropiate solution of Fick's second law of diffusion

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

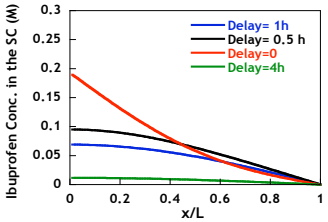
X/L: relative depth of drug penetration
D/L^2: diffusional parameter (h^{-1})

STUDY OF THE CLEARANCE PHASE:

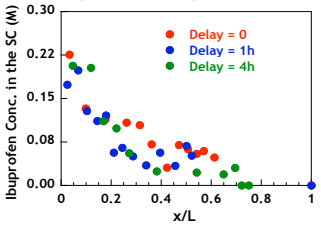
$$\tilde{C} = 2\sum_{n=0}^{\infty}\left(\frac{1}{\lambda_n^2} - 2\sum_{m=1}^{\infty}\frac{\exp\left[-\lambda_n^2\tau_o\right]}{m^2\pi^2 - \lambda_n^2}\right)\cos(\lambda_n\xi)\exp\left[-\lambda_n^2(\tau-\tau_o)\right] \qquad \lambda_n = (2n+1)\pi/2$$

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

Theoretical curves [(4)]



Experimental profiles



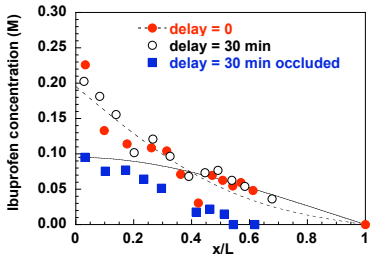
Surprisingly, very little change in the profile occurred during the 4 hours post-termination of delivery.

HYPOTHESIS:

Rapid diffusion and/or evaporation of PG [(5)] results in the, at least transient, maintenance of a saturated ibuprofen concentration at the SC surface even after removal of the original formulation

IBUPROFEN CLEARANCE IN THE PRESENCE OF OCCLUSION

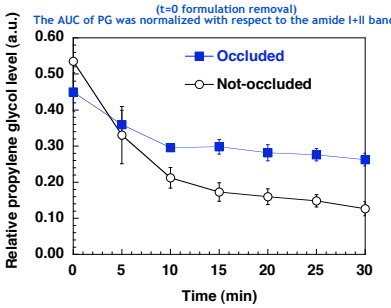
Ibuprofen concentration profile in the SC



When the treated site was occluded during the delay period (propylene glycol was prevented from evaporative loss), ibuprofen remained able to diffuse from the SC.

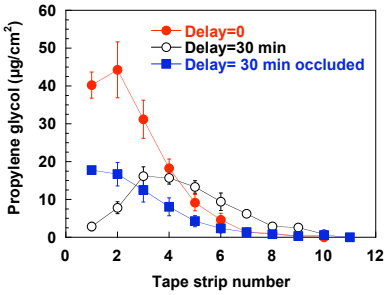
ATR-FTIR ANALYSIS OF PG ELIMINATION FROM SC

Elimination of PG from the skin surface
(t=0 formulation removal)
The AUC of PG was normalized with respect to the amide I+II bands



PG was lost by both evaporation and diffusion into and through the SC
- **30% by diffusion (occluded site)**
- **60% by diffusion + evaporation (unoccluded site)**

PG concentration profile in the SC



- **Delay = 0: Steep PG concentration gradient**
- **Delay = 30 min occluded: PG profile decreased**
- **Delay = 30 min unoccluded: Altered profile shape; significantly less PG in the surface SC layers**

CONCLUSIONS

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

REFERENCES

(1) FDA (1998) Guidance for Industry:topical dermatological drug product NDAs and ANDAs - in vivo bioavailability, bioequivalence, in vitro release and associated studies (Draft).
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