Effect of Controlled Heat Application on Topical Diclofenac Formulations Evaluated by *In Vitro* Permeation Tests (IVPT) using Porcine and Human Skin

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INTRODUCTION

Elevated temperature can alter the pharmacokinetic profile and hence influence the safety and clinical efficacy of transdermal and topical drug products. Heating pads and electric blankets are widely used for pain relief and to provide warmth respectively. Their unintentional application simultaneously with a transdermal or topical drug delivery system can result in unexpectedly higher drug levels in systemic circulation. Topical products usually have a higher safety margin (with respect to systemic toxicity), but it has not been well characterized whether elevated plasma levels could still arise in certain instances of the off label use of certain products with external heat. Heat could influence products with the same active pharmaceutical ingredient (API) but different inactive ingredients to a different extent. This may result in an altered pharmacokinetic profile for either patch or semi-solid topical or transdermal formulations. *In vitro* permeation tests with excised porcine or human skin can provide insights into the effect of heat on these formulations. The purpose of this study was to evaluate the influence of heat on the permeation of a model lipophilic, weakly acidic drug (Table 1), diclofenac, through human skin, compared among four topical products (diclofenac epolamine topical patch 1.3%, diclofenac sodium solution 2%, diclofenac sodium gel 1% and diclofenac sodium gel 3%) in the presence of heat (Table 2).

METHODS

Study Design

In vitro permeation tests (IVPT) were performed using PermeGear flow-through In-Line diffusion cells. Dermatomed Yucatan mini-pig skin from a single donor with three to four replicates per treatment group was used in a pilot study. Human skin from three donors with three to four replicates per donor were used for each treatment group in the pivotal study. (Donor 1a, 1b, 1c, 2 and 3 indicate different human skin donors). For the diclofenac epolamine patch product, a 0.97 cm^2 circular disc was applied to the permeation area of the diffusion cell. For the diclofenac sodium products (Table 2), clinically relevant doses of 2% solution (5 mg/cm^2), 1% gel (10 mg/cm^2) and 3% gel (20 mg/cm^2) were applied to the skin. Skin temperature was maintained at either 32 ± 1°C or 42 ± 1°C to mimic normal and elevated skin temperature conditions, respectively. Receptor solution was collected every two or three hours for 12 h and analyzed using a validated high performance liquid chromatography (HPLC) method.

Statistical Analysis

Student's t-test was used for comparing the differences in the means of flux and cumulative amount and significant differences were declared at $p \leq 0.05$.

Table1. Comparison of diclofenac to other topical and transdermal drug substances based on logP and pKa values

Group	##logP	#pKa	Example
1	Moderate	WB	*Lidocaine*
2	High	WB	*Oxybutynin; Buprenorphine*
3	Moderate	WA	*Salicylic acid*
4	High	WA	*Diclofenac*

WB: weak base; WA: weak acid
logP > 3 denoted as high

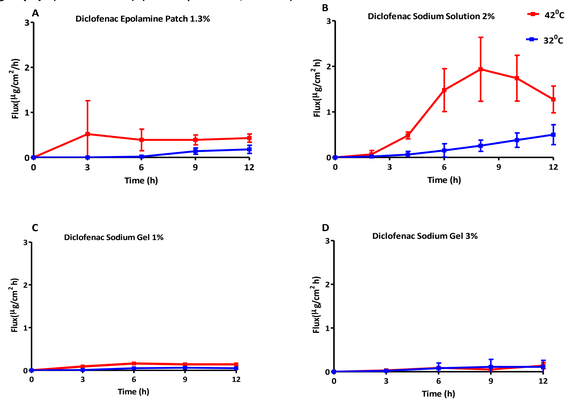
Table 2. Comparison of four topical diclofenac products with varying formulations and dosage forms

	1.3% patch	2% solution	1% gel	3% gel
Inactive ingredients	Adhesive in aqueous base containing polyacrylate, carboxy methyl cellulose	DMSO, Hydroxy propyl cellulose, Ethyl alcohol	Carbomer homopolymer, Coroyl capryl caprate, Isopropyl alcohol	Hyaluronate sodium, Benzyl alcohol
Dose applied (Equivalent amount of diclofenac)	- (878mg/cm^2)	5mg/cm^2 (approx. 100µg/cm^2)	10mg/cm^2 (approx. 100µg/cm^2)	20mg/cm^2 (approx. 600µg/cm^2)

RESULTS

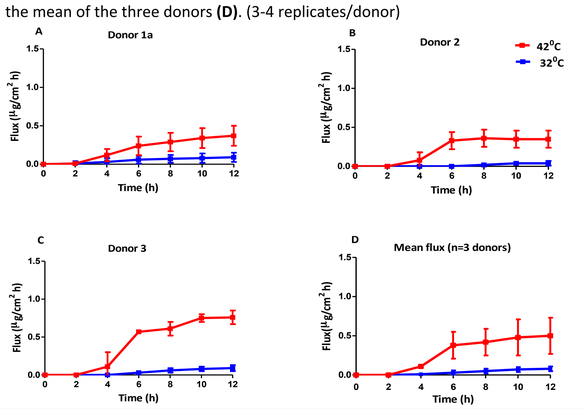
Permeation of diclofenac from different formulations (porcine skin)

Figure 1. Flux profile from porcine skin for patch **(A)**, solution **(B)**, 1% gel **(C)** and 3% gel **(D)**. (mean ± SD) (3-4 replicates/donor)



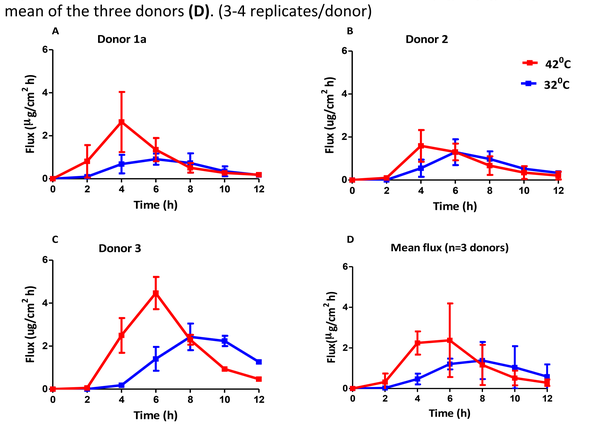
Permeation of diclofenac from the 1.3% topical patch (human skin)

Figure 2. Flux profiles (mean ± SD) for human skin donor 1a **(A)**, 2 **(B)**, 3 **(C)** and the mean of the three donors **(D)**. (3-4 replicates/donor)



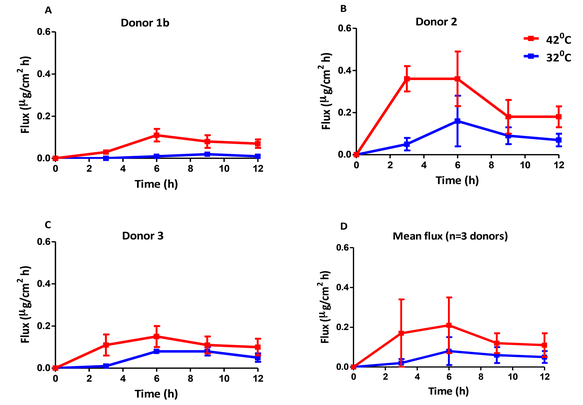
Permeation of diclofenac from the 2% topical solution (human skin)

Figure 3. Flux profiles (mean ± SD) for human skin donor 1a **(A),** 2 **(B),** 3 **(C)** and the mean of the three donors **(D)**. (3-4 replicates/donor)



Permeation of diclofenac from the 1% topical gel (human skin)

Figure 4. Flux profiles (mean ± SD) for human skin donor 1b **(A)**, 2 **(B)**, 3 **(C)** and the mean of the three donors **(D)**. (3-4 replicates/donor)



Permeation of diclofenac from the 3% topical gel (human skin)

Figure 5. Flux profiles (mean ± SD) for human skin donor 1c **(A)**, 2 **(B)**, 3 **(C)** and the mean of the three donors **(D)**. (3-4 replicates/donor)

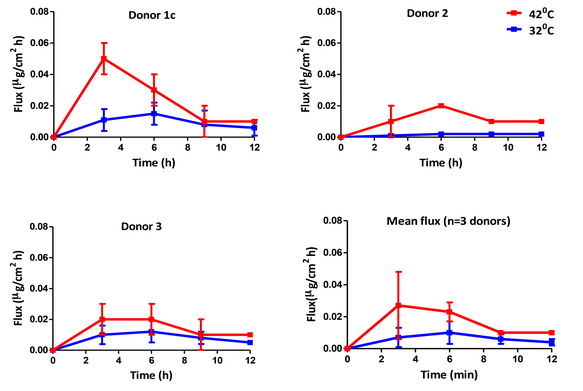


Table 3. Summary of heat enhancement on porcine skin

Formulation	Heat Enhancement Ratio (Heat/No Heat)		##*p* value (Heat vs No Heat)	
	J_{max}	Cum. Amt.	J_{max}	Cum. Amt.
Patch	2.3	5.0	0.034	0.104
Solution	4.0	5.0	0.006	0.002
1% Gel	2.6	3.0	0.001	<0.001
3% Gel	1.0	0.87	0.961	0.883

##*p* values were obtained from unpaired t test

Table 4. Summary of heat enhancement on human skin

Formulation	Donor (human skin)	Heat Enhancement Ratio (Heat/No Heat)		##*p* value (Heat vs No Heat)	
		J_{max}	Cum. Amt.	J_{max}	Cum. Amt.
Patch	1a	4.1	4.0	0.010	0.022
	2	8.7	15.9	0.002	<0.001
	3	8.0	10.4	< 0.001	0.001
	Mean (n=3 donors)	6.5	8.0	0.079	0.067
#Solution	1a	3.8	4.4	0.044	0.057
	2	2.8	3.0	0.058	0.053
	3	14.3	14.0	0.002	0.002
	Mean (n=3 donors)	4.7	5.1	0.043	0.048
1% Gel	1b	7.0	6.8	0.002	0.001
	2	2.2	2.9	0.020	0.011
	3	1.8	2.0	0.070	0.045
	Mean (n=3 donors)	2.3	2.8	0.097	0.127
3% Gel	1c	3.5	2.8	0.001	0.001
	2	8.3	6.3	0.001	0.002
	3	1.6	1.4	0.056	0.046
	Mean (n=3 donors)	2.7	2.5	0.123	0.115

Heat enhancement in J_{max} and Cum. Amt. at 4 h was calculated
##*p* values were obtained from unpaired t test for individual donors and paired t test for mean of three donors

CONCLUSIONS

- The highest levels of diclofenac permeation under elevated temperature were seen for the patch and the 2% solution in both porcine and human skin donors. Both these formulations showed a decrease in T_{lag} or T_{max} at elevated temperature. (Figures 1, 2 and 3)
- The relatively large drug reservoir and closed environment of the patch design may enable it to maintain pseudo-zero order release kinetics even under the exposure of 12 h of heat (Figure 2).
- In case of the semisolid formulations, diclofenac permeation was increased during the initial few hours of heat application, after which it decreased and reached a plateau (Figures 3, 4 and 5). A possible explanation is that an initial heat-induced increase in drug delivery when the vehicle (solution or gel) is present in its native form is followed by faster drying, whereby the drug delivery and permeation rate decrease as a consequence, regardless of the influence of elevated temperature.
- Diclofenac is highly lipophilic (logP > 3) and protein bound, and so permeates into and clears from the stratum corneum slowly. All four formulations except the 2% solution containing DMSO (which is a permeation enhancer) had total skin concentration (data not shown) to cumulative amount permeated ratios of diclofenac > 1. This slow permeating nature of the drug could have caused the higher variability in heat induced enhancement seen among different human skin donors.

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