

# Importance of the formulation in the skin delivery of topical diclofenac: not all topical diclofenac formulations are the same

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**Purpose:** The current study aimed to compare 2 topical diclofenac products (diclofenac diethylamine [DEA] 1.16% emulsion and diclofenac sodium [Na] 5% gel). The quantitative evaluation of skin permeability and the qualitative evaluation of their physical characteristics were performed.

**Methods:** The skin permeability of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel was compared in vitro using Franz diffusion cells following a single, fixed, 10 mg/cm<sup>2</sup> dose of product applied to a 0.64 cm<sup>2</sup> area of the stratum corneum surface of ex vivo human skin samples. The physical characteristics of the 2 formulations were assessed by rheological measurement and microscopy observation.

**Results:** Diclofenac DEA 1.16% emulsion exhibited a statistically significant higher permeation through human skin at 24 hrs than diclofenac Na 5% gel (554 vs 361 ng/cm<sup>2</sup>, respectively; ratio of adjusted geometric means, 1.54 [95% CI, 1.14–2.07]). When expressed as a percentage of the applied dose of diclofenac that permeated through human skin, a 7-fold difference was observed between the diclofenac DEA 1.16% emulsion (0.54%) and the diclofenac Na 5% gel (0.077%). Qualitative composition and physical characterization showed differences between the formulations that may explain some of the permeation data observed. Based on rheological assessments, diclofenac Na 5% gel had a higher viscosity (24.82 Pa.s) than diclofenac DEA 1.16% emulsion (10.29 Pa.s).

**Conclusion:** A topical diclofenac product with a higher concentration of the active ingredient does not necessarily lead to greater absorption relative to a product with lower concentration of the active ingredient but different characteristics. These observations highlight the importance of considering parameters beyond drug concentration, such as composition, which may influence the solubility of the drug and permeation of topical nonsteroidal anti-inflammatory drugs.

**Keywords:** topical application, excipients, nonsteroidal anti-inflammatory drug, physicochemical properties, Voltaren

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat acute and chronic pain,<sup>1,2</sup> but their long-term use may be limited by systemic side effects such as gastrointestinal toxicity and the potential for certain cardiovascular and cerebrovascular complications.<sup>2–6</sup> Topical administration of NSAIDs offers clinical efficacy similar to oral NSAIDs, fewer systemic adverse events, and a reduced risk of drug–drug interactions.<sup>7–10</sup> The NSAID diclofenac has demonstrated efficacy in

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treating a variety of acute and chronic pain conditions.<sup>2,11</sup> Diclofenac is a good choice of topical NSAID based on a number-needed-to-treat of 1.8 for acute pain<sup>12</sup> and 9.8 for chronic pain,<sup>13</sup> as reported in a recent Cochrane meta-analysis. Topical diclofenac is available in several different forms, including gel, spray, emulsion, aqueous solution, cream, and transdermal patch.<sup>2,10</sup>

Although it may be assumed that the skin permeation will be directly proportional to the drug concentration, according to Fick's law, other drug physicochemical parameters may influence drug permeation. According to O'Connor et al, diclofenac sodium seems to have a higher rate of transport than diclofenac DEA, which is related to the higher saturation solubility of diclofenac sodium.<sup>14</sup> Formulation composition such as choice of vehicle (solutions, gels,<sup>15</sup> emulsions, microemulsions,<sup>16,17</sup> particles,<sup>18</sup> liposomes,<sup>19,20</sup> and transfersomes<sup>21</sup>) and inclusion of penetration enhancers and characteristics such as water solubility and acidity may influence the ability of topical formulations to permeate the skin and deeper tissues.<sup>10</sup> To demonstrate the importance of the formulation parameters and composition regardless of the drug concentration, an *in vitro* skin permeation study was undertaken to compare the permeability of 2 commercially available topical products: diclofenac diethylamine (DEA) 1.16% emulsion (GlaxoSmithKline, Munich, Germany), which corresponds to 1% of diclofenac sodium (Na), and diclofenac Na 5% gel (Sandoz, Holzkirchen, Germany). The qualitative composition and physical characteristics of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel were also assessed in order to provide further insight, which could explain observed differences in skin permeation.

## Materials and methods

### Permeability assessment

The *in vitro* study used Franz diffusion cells<sup>22</sup> to compare the permeability of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel through *ex vivo* human skin obtained from the abdominal region of 5 patients during their plastic surgery. The skin collection was approved by two ethical committees (Lothian Research Ethics Committee, Edinburgh, UK, and West of Scotland Research Ethics Services, Glasgow, UK). Written informed consent was obtained from all donors after explaining the purpose of the collection. After collection, skins were frozen at  $-20^{\circ}\text{C}$  until their use for the percutaneous permeation study. The day of the experiment, skins were thawed and dermatomed at  $\sim 400\ \mu\text{m}$  thickness, starting from the stratum corneum. The barrier integrity of each skin sample

was confirmed before application of each formulation using the electrical resistance method, and those skin samples with an electrical resistance of  $>10.9\ \text{k}\Omega$  were included. A single, fixed,  $10\ \text{mg}/\text{cm}^2$  dose (corresponding to the single-application dose for topical products recommended in the patient information leaflets) of each diclofenac formulation was applied to a  $0.64\ \text{cm}^2$  area of the stratum corneum surface of skin samples, which were maintained at  $32\pm 1^{\circ}\text{C}$  and mounted in static diffusion cells. Each formulation was applied to 15 skin samples (ie, 3 replicates were performed for each donor; 30 samples in total). No formal sample size calculation was performed, and the sample size was chosen for exploratory purposes. Receptor fluid (PBS with 5% w/v bovine serum albumin) samples were collected at 0, 2, 4, 8, 16, and 24 hrs after application and analyzed by liquid chromatography/tandem mass spectrometry to quantify permeation of diclofenac (lower limit of quantification,  $1\ \text{ng}/\text{mL}$ ).

### Data and statistical analysis

Because skin permeability data have been shown to be log-normally distributed,<sup>23</sup> log-transformed mean cumulative absorption of diclofenac at 24 hrs was compared post hoc between the 2 formulations using a restricted maximum likelihood estimation-based, mixed-effects model, with formulation as a fixed effect and donor as a random effect. Ninety-five percent CIs for the geometric mean ratios on the original scale were derived by back-transforming the CIs for the differences between formulations on the log-transformed scale. The percentage of applied dose was calculated as follows:  $CA_{24\text{h}}/(Q \times P/A)$ , where  $CA_{24\text{h}}$  is the cumulative absorption at 24 hrs ( $\text{mg}/\text{cm}^2$ ),  $Q$  is the quantity of topical product applied on the skin sample ( $\text{mg}$ ),  $P$  is the percentage of diclofenac in the topical product applied, and  $A$  is the surface area of the skin sample ( $\text{cm}^2$ ). Flux of diclofenac was calculated at each timepoint:

$$F_t = \frac{CA_t}{t}$$

### Physical characterization

The physical characteristics of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel were assessed via microscopic observation and rheological measurement.

### Microscopic observation

A few microliters of each topical product were inspected visually using a Nikon Ni-U microscope (Nikon Instruments, Inc, Melville, NY, USA).

## Rheological characterization

Rheological measurements of each product were performed on a rheometer MCR 302 (Anton Paar GmbH, Ostfildern, Germany) at 25°C using a cone-plate device (CP60-2, 60 mm diameter, angle 1.995°, truncation 252 µm). Samples were relaxed for 2 mins before measurement. The flow properties were obtained by recording shear rate ( $s^{-1}$ ) and viscosity values  $\eta$  (Pa.s) when shearing the sample at increasing shear rates ranging from  $1.10^{-3}$  to  $2,800 s^{-1}$  (logarithmic ramp) for 280 s.

## Results

### Permeability assessment

Diclofenac DEA 1.16% emulsion exhibited a statistically significant higher permeation through human skin than diclofenac Na 5% gel (geometric mean of cumulative absorption, 554 vs 361 ng/cm<sup>2</sup>; ratio of adjusted geometric means, 1.54 [95% CI, 1.14–2.07]; Table 2). When expressed as a percentage of the applied dose permeating human skin at 24 hrs, a 7-fold difference was observed between the diclofenac Na 5% gel and the diclofenac DEA 1.16% emulsion (0.077% vs 0.54%, respectively). Figure 1 shows that the flux of diclofenac Na 5% gel was slightly faster than the one of diclofenac DEA 1.16% emulsion before 8 hrs, after the trend reverted up to 24 hrs.

### Physical characterization

#### Microscopic observation

Diclofenac Na 5% gel appeared as a monophasic gel without droplets, whereas diclofenac DEA 1.16% emulsion

demonstrated oily droplets in an aqueous phase, with a narrow distribution of droplet size (mainly <10 µm).

### Rheological characterization

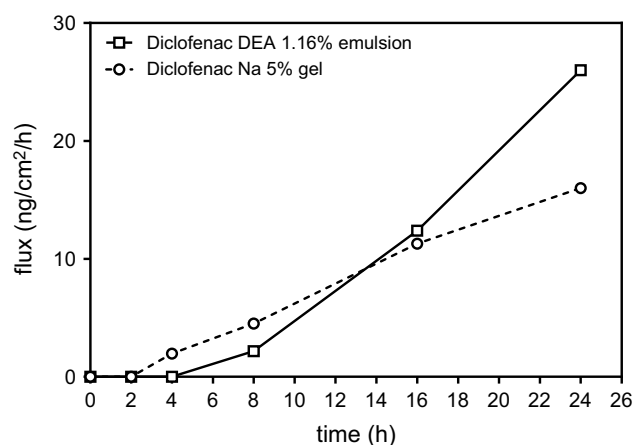
The viscosity of both products was obtained by applying a controlled shear rate from  $1.10^{-3}$  to  $2,800 s^{-1}$ . At  $10 s^{-1}$ , diclofenac Na 5% gel had a higher viscosity (24.82 Pa.s) than diclofenac DEA 1.16% emulsion (10.29 Pa.s). At higher shear rates, this trend was confirmed.

## Discussion

This in vitro study of human skin permeation of diclofenac, which mimicked the application of a single topical dose typically employed during clinical use, demonstrated significantly greater skin permeation with diclofenac DEA 1.16% emulsion compared with the higher concentration product, diclofenac Na 5% gel at 24 h. These results suggest that absorption of topical diclofenac may be influenced by parameters other than drug concentration, and thus, contrary to what might be expected, a higher concentration may not always lead to greater absorption through the skin.

Human skin permeation is likely influenced by the drug physicochemical characteristics (eg, drug salt, drug molecular weight,<sup>24,25</sup> and pKa<sup>26,27</sup>), the composition of the products (eg, excipients), and the pharmaceutical dosage form (eg, gel, emulsion). The two products contain different salts (diclofenac DEA and diclofenac Na). Therefore, differences in the physicochemical properties, solubility, dissolution rate, and membrane transport between salts can be expected. Despite diclofenac sodium having a higher rate of transport than diclofenac DEA, which is related to the higher saturation solubility of diclofenac sodium,<sup>14</sup> the data generated showed the opposite. It seems that other parameters could likely be responsible for those unexpected results.

The excipients in topical NSAID formulations likely affect the drug solubility,<sup>28</sup> diffusion into the formulation,<sup>29</sup> release from the formulation,<sup>30</sup> penetration into the stratum corneum,<sup>31,32</sup> and permeation through deeper skin layers,<sup>33</sup> thereby influencing its skin absorption. For example, organic solvents, such as isopropyl alcohol and ethanol are known to increase drug solubility and drug release from the formulation.<sup>32,33</sup> However, the solvent could not be the only influential parameter as it is contained in both formulations and the concentration of the excipients is unknown. The use of permeation enhancers such as propylene glycol (found in diclofenac DEA



**Figure 1** Median flux of diclofenac over 24 hrs.

**Abbreviations:** CI, confidence interval; DEA, diethylamine; Na, sodium.

**Table 1** Qualitative composition of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel

	<b>Diclofenac DEA 1.16% emulsion</b>	<b>Diclofenac Na 5% gel</b>
Gelling agent	Carbomer	Hypromellose
Emulsifier	Macrogol cetostearyl ether	Macrogol glyceryl cocoate
Emollient(s)	Liquid paraffin, cocoyl caprilocaprinate	Macrogol glyceryl cocoate
Permeation enhancer	Propylene glycol	–
pH adjusting	DEA	–
Solvents/co-solvents	Purified water, isopropyl alcohol	Purified water, isopropyl alcohol
Fragrance	Perfume cream 45	–

**Abbreviations:** DEA, diethylamine; Na, sodium.

**Table 2** Adjusted\* geometric mean cumulative absorption at 24 hrs by formulation

<b>Formulation</b>	<b>Geometric mean (95% CI), ng/cm<sup>2</sup></b>	<b>Diclofenac DEA 1.16% emulsion vs diclofenac Na 5% gel: ratio of geometric means (95% CI)</b>
Diclofenac DEA 1.16% emulsion	554 (265–1,158)	1.54 (1.14–2.07)**
Diclofenac Na 5% gel	361 (172–754)	

**Notes:** \*From mixed model analysis with formulation as a fixed effect and donor as a random effect. \*\*Two-sided *P*-value = 0.0067 for the superiority test of the null hypothesis that the geometric mean ratio is 1.

**Abbreviations:** DEA, diethylamine; Na, sodium.

1.16% emulsion only; Table 1) in combination with other excipients may result in increased skin permeation. The presence of emollients such as cocoyl caprylocaprinate and paraffin, both found in diclofenac DEA 1.16% emulsion, can also improve the skin level of hydration by occlusion, which favors drug absorption.<sup>34</sup>

Physical characterization of both diclofenac products was conducted in order to gain insight into the observation of greater skin permeation with diclofenac DEA 1.16% emulsion. Although both products are semi-solids, they exhibit physical differences that may potentially affect drug absorption.

Rheological measurements revealed that the formulations containing different gelling agents (carbomer in diclofenac DEA 1.16% emulsion and hypromellose in diclofenac Na 5% gel) behave differently. Diclofenac Na 5% gel has a higher viscosity at 10 s<sup>-1</sup> compared with diclofenac DEA 1.16% emulsion. The polymeric network created in gelified formulations, described by some parameters such as polymer molecular weight, polymer concentration, and viscosity, could retain the drug differently and could influence its release.<sup>35</sup> Interestingly, hypromellose seems to create a denser polymeric network in the formulation, which could limit the release of the drug according to the data generated. Further, the gelling agent and the pharmaceutical

dosage form (emulsion versus gel) appear to influence the drug release from the different formulations.<sup>29</sup>

The pharmaceutical dosage form may also influence the drug delivery and kinetics.<sup>29,36,37</sup> Usually, drug formulated in biphasic formulation (emulsion, cream, and ointment) needs to partition out of the internal phase through the external phase before reaching the skin surface. This observation has been confirmed by Stahl et al who noticed a faster drug release from gel compared to biphasic pharmaceutical form (eg, cream). Our flux data suggested that this would be likely the case. Regarding the drug delivery through the skin at 24 hrs, in this study, the emulsion seemed to favor higher drug permeation than gel. One explanation could be the dense polymeric network created by hypromellose in the gel product.

The potential effects of physicochemical properties, physical properties, and product composition (eg, excipients) on drug absorption were discussed above. However, multiple ingredients' interactions and physiological parameters also must be taken into account as they will together influence the drug absorption.

## Conclusion

We observed that a product with a higher concentration of diclofenac does not necessarily lead to greater skin

absorption relative to a product with lower concentration of the active ingredient but different characteristics.

Although our study was specific to topical diclofenac, the findings on the influence of the formulation could be applicable to other drugs. As such, these data support previous studies suggesting that development of a topical pain relief product should take into consideration parameters beyond drug concentration, such as formulation composition. As discussed, these critical parameters may influence the ability of a given NSAID to efficiently penetrate first through the stratum corneum and subsequently the lower layers of the skin to exert its local action at the level of soft tissues and/or joints.

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## Disclosure

All authors are GlaxoSmithKline Consumer Healthcare, Nyon, Switzerland employees. The authors report no further conflicts of interest in this work.

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