



Research paper

Using laser microporation to improve transdermal delivery of diclofenac: Increasing bioavailability and the range of therapeutic applications

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ABSTRACT

The objective of the study was to investigate the effect of laser microporation, using P.L.E.A.S.E.[®] technology, on diclofenac delivery kinetics. Skin transport of diclofenac was studied from aqueous solution, propylene glycol and marketed formulations across intact and laser-porated porcine and human skins; cumulative permeation and skin deposition were quantified by HPLC. After 24 h, cumulative diclofenac permeation across skins with 150, 300, 450 and 900 shallow pores (50–80 μm) was 3.7-, 7.5-, 9.2- and 13-fold superior to that across untreated skin. It was also found to be linearly dependent on laser fluence; Permeation ($\mu\text{g}/\text{cm}^2$) = $11.35 \times \text{Fluence} (\text{J}/\text{cm}^2) + 352.3$; $r^2 = 0.99$. After 24 h, permeation was 539.6 ± 78.1 , 934.5 ± 451.5 , 1451.9 ± 151.3 and $1858.6 \pm 308.5 \mu\text{g}/\text{cm}^2$, at 22.65, 45.3, 90.6 and $135.9 \text{ J}/\text{cm}^2$, respectively. However, there was no statistically significant effect of laser fluence on skin deposition. Diclofenac delivery from marketed gel formulations was also significantly higher across laser-porated skins (e.g. for Solaraze[™], cumulative permeation after 24 h across treated (900 pores/ $135.9 \text{ J}/\text{cm}^2$) and untreated skin was 974.9 ± 368.8 and $8.2 \pm 3.8 \mu\text{g}/\text{cm}^2$, respectively. Diclofenac delivery from Solaraze[™] across laser-porated porcine and human skins was also shown to be statistically equivalent. The results demonstrated that laser microporation significantly increased diclofenac transport from both simple and semi-solid formulations through porcine and human skin and that pore depth and pore number could modulate delivery kinetics. A similar improvement in topical diclofenac delivery *in vivo* may increase the number of potential therapeutic applications.

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1. Introduction

Diclofenac (MW 296.15 Da; log P 4.06) is one of the most widely used nonsteroidal anti-inflammatory agents. Although it is almost completely absorbed, an extensive hepatic first-pass effect means that systemic bioavailability following oral administration is ~50%; furthermore, rapid clearance results in a short half-life and the potential need for multiple dosing [1]. Although generally well tolerated, the most common adverse drug reaction is its impact on the gastric mucosa; indeed, a recent study using endoscopic examination of a series of orthopaedic outpatients demonstrated that 83.3% and 73.5% of patients receiving diclofenac and diclofenac SR, respectively, manifested gastric mucosal lesions [2]. Topical administration should decrease the risk of these side effects and such dosage forms are available [3].

Furthermore, clinical studies have shown that topical administration resulted in higher diclofenac levels in the dermis and mus-

cle as compared to oral administration, providing evidence for the efficacy of local administration [4,5]. For example, following application of two tapes containing a total of 30 mg diclofenac, concentrations in the subcutaneous fat and muscle were reported to be 13.46 ± 11.31 and $9.29 \pm 8.34 \text{ ng/ml}$, respectively (cf. 3.85 ± 2.28 and $0.66 \pm 1.11 \text{ ng/ml}$ after oral administration of a 30 mg diclofenac capsule) [5]. However, the converse was true for drug levels measured in the synovial fluid and membrane (topical: 1.96 ± 0.68 , $4.99 \pm 3.84 \text{ ng/ml}$ and oral: 16.76 ± 12.00 , $15.07 \pm 9.17 \text{ ng/ml}$) [5]. It follows that oral administration is the preferred option for the treatment of rheumatoid and osteoarthritis, whereas topical application is suitable for the relief of pain symptoms in minor strains, sprains and contusions. Pharmacokinetic studies have also shown that diclofenac levels measured in synovial fluid after topical administration from ipsi- and contralateral knee joints were not significantly different; thus, it was likely that drug was principally entering the synovial space from the systemic circulation [6]. Therefore, in order to improve efficacy in the treatment of rheumatoid and osteoarthritis using topical diclofenac dosage forms, it will probably be necessary to increase systemic bioavailability while minimising the risk of adverse drug reactions.

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Several different formulation strategies have been investigated to improve diclofenac transport [7–11]. However, the excellent barrier function of the stratum corneum limits the rate and extent of topical drug delivery [12,13], and focus has moved to the development of new technologies to reversibly impair barrier function and so enhance transport [14]. Several approaches to ablate the stratum corneum have been studied, including mechanical ablation by way of microneedles [15–18] to the use of more sophisticated energy-based strategies to selectively remove the stratum corneum and to facilitate drug entry into the epidermis [19–21].

The aim of this study was to use laser-assisted microporation to create transport channels in the skin and so enable controlled enhancement of diclofenac delivery. The laser system employed in these studies (P.L.E.A.S.E.[®]; Precise Laser Epidermal System) contains an Er:YAG laser that emits light at 2.94 μm [22,23]. This corresponds to a major water absorption peak; the excitation and subsequent evaporation of the water molecules in the epidermis lead to micropore creation without inducing thermal damage to the surrounding tissues [22]. The applied laser energy per unit area (fluence) controls the depth of each micropore, and due to the device's high repetition rate, it is possible to create several hundred micropores with controlled depth in the space of a few seconds. Since the number of pores created in the skin and the depth can be easily varied (in principle, from 1 to nearly 5000), this provides a simple means to control the dose delivered and to individualise therapy; in contrast, other microporation technologies lack this capacity since they create a fixed number of pores dependent on the number of “porating” elements in the device placed in contact with the skin.

The specific objectives of the project were (i) to study the effect of pore number and fluence on diclofenac delivery, (ii) to demonstrate that diclofenac could be delivered rapidly and in significant amounts across P.L.E.A.S.E.[®] porated porcine skin from both simple and marketed formulations and (iii) to compare transport across P.L.E.A.S.E.[®] porated porcine and human skins.

2. Materials and methods

2.1. Chemicals

Diclofenac sodium, propylene glycol and sodium dihydrogen phosphate were purchased from Sigma (Buchs, Switzerland). Acetonitrile, methanol (Chromasolv HPLC gradient grade) and nylon membrane filters (0.22 μm) were purchased from VWR (Nyon, Switzerland). Sodium chloride and potassium dihydrogen phosphate were purchased from Acros Organics (Chemie Brunschwig; Basel, Switzerland). Marketed diclofenac formulations: Voltaren Dolo[®] Emugel[®] 1% w/w (VDE; Novartis SA), Flector[®] gel 1.3% w/w (FG) and Flector[®] EP Tissugel 1.3% w/w (3.0 cm^2 –3.4 mg diclofenac epolamine) (FTG; Institut Biochimique SA (IBSA)) were purchased direct from pharmacies. Solaraze[™] gel 3% w/w (Almirall Hermal GmbH) was kindly provided by Dr. R. Strohal (Federal Academic Hospital of Feldkirch, Dept. of Dermatology and Venereology, Feldkirch, Austria). Deionised water (resistivity > 18 $\text{M}\Omega\text{ cm}$) was used to prepare all the solutions.

2.2. Skin

Full thickness (1.0–1.5 mm) porcine skin was used to study the effect of P.L.E.A.S.E.[®] poration on diclofenac delivery. Porcine ears were supplied by a local abattoir (CARRE; Rolle, Switzerland) shortly after sacrifice. After cleaning under cold running water, the whole skin was removed carefully from the outer region of the ear and separated from the underlying cartilage with a scalpel.

Full thickness porcine skin samples were wrapped in Parafilm[™] and maintained at -20°C for no longer than a period of 2 months before use.

Human skin samples were collected immediately after surgery from the Department of Plastic, Aesthetic and Reconstructive Surgery, Geneva University Hospital (Geneva, Switzerland); fatty tissue was removed and the skin was wrapped in Parafilm[™] before storage at -20°C for a maximum period of 3 days. The study was approved by the Central Committee for Ethics in Research (CER: 08-150 (NAC08-051); Geneva University Hospital).

2.3. Diclofenac stability in the presence of skin

Solution stability of diclofenac in contact with porcine skin was assessed by preparing (a) 10 mg/ml diclofenac in water and (b) 10 mg/ml diclofenac in pH 7.4 phosphate-buffered saline (PBS, pH 7.4). Solutions (a) and (b) were placed in contact with full-thickness epidermal and dermal skin surfaces, respectively, for 6 h. Samples were diluted in PBS (pH 7.4) and analysed by HPLC. Experiments were performed in triplicate.

2.4. Laser microporation

Skin samples were equilibrated in 0.9% NaCl for 30 min prior to poration using the P.L.E.A.S.E.[®] device. After removing surface moisture, skin samples mounted in a custom-designed assembly were placed at the focal length of the laser to create the micropores. Laser poration parameters, i.e., the pore number and the fluence (determined by the number of energy pulses applied to create each pore), were fixed by the user.

2.5. Experimental protocol to study diclofenac delivery kinetics

Skin samples (either intact (untreated) or P.L.E.A.S.E.[®] porated) were mounted in Franz diffusion cells ($A = 3.0 \pm 0.1 \text{ cm}^2$); silicone grease was applied to ensure a watertight seal. The receptor compartment ($\sim 10 \text{ ml}$) was filled with PBS (pH 7.4). After equilibration, the formulations (details given below) were placed in the donor compartment. The receptor phase was stirred at room temperature throughout the experiment; 0.4 ml of the receptor phase was withdrawn hourly for 6 h and then again after 24 h, and each aliquot was replaced with an equivalent volume of fresh PBS buffer.

At the end of the permeation experiment, the diffusion cells were dismantled and the skin surface washed in running water to remove residual donor formulation. The skin samples were then cut into small pieces and soaked in mobile phase (6 ml; see below for composition) for 4 h under constant agitation at ambient temperature so as to extract diclofenac deposited in the membrane during the permeation experiment. After dilution in PBS (pH 7.4), samples were filtered through 0.22 μm nylon membrane filters prior to HPLC analysis.

Four separate series of experiments were performed:

2.5.1. Effect of P.L.E.A.S.E.[®] device parameters on diclofenac delivery

Diclofenac transport (permeation and deposition) from 1 ml of aqueous solution (10 mg/ml) through P.L.E.A.S.E.[®] porated porcine skin was investigated as a function of (i) pore number (0, 150, 300, 450 and 900 pores; fluence fixed at 22.65 J/cm^2) and (ii) fluence (22.65, 45.3, 90.6 and 135.9 J/cm^2), which determines the pore depth – this was done using 900 pores.

2.5.2. Effect of formulation on diclofenac delivery

Diclofenac transport into and across porcine skin using aqueous and propylene glycol formulations at equivalent concentration (10 mg/ml) was compared in order to investigate the effect of

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