Activity Comparison of Diclofenac Gel And Diclofenac Diethylamine

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Abstract- *The objective of the current study was to compare two topical diclofenac products: the gel (diclofenac sodium [Na] 5% and the diethylamine [DEA] 1.16% emulsion). Both a qualitative assessment of their physical attributes and a quantitative assessment of skin permeability were carried out. Fran diffusion cells were used to examine the skin permeability of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel after a single, fixed, 10 mg/cm2 dose of product was administered to a 0.64 cm2 region of the stratum corneum surface of ex vivo human skin samples. Rheological measurement and microscope observation were used to evaluate the two formulations' physical properties.*

Between 554 and 361 ng/cm2, respectively, diclofenac DEA 1.16% emulsion showed a statistically significant greater penetration through human skin at 24 hours; the ratio of corrected geometric means was 1.54 [95% CI, 1.14–2.07]. Between the diclofenac DEA 1.16% emulsion (0.54%) and the diclofenac Na 5% gel (0.077%), there was a 7-fold difference in the percentage of the applied dose of diclofenac that penetrated into human skin. Disparities in the formulations were shown by qualitative composition and physical characterisation, which could account for some of the reported permeation data. Diclofenac Na 5% gel has a higher viscosity (24.82 Pa.s) than diclofenac DEA 1.16% emulsion (10.29 Pa.s) according to rheological evaluations.

Higher concentrations of the active ingredient in topical diclofenac products may not always translate into better absorption when compared to products with lower concentrations but distinct features. These findings emphasise how crucial it is to take into account factors other than drug concentration, like composition, which might affect the drug's solubility and penetration of topical nonsteroidal anti-inflammatory medications.

Keywords- Physicochemical properties, topical application, excipients, nonsteroidal anti-inflammatory medication, Voltaren

I. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat acute and chronic pain,1,2 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.2–6 NSAIDs applied topically have clinical efficacy comparable to that of oral NSAIDs, fewer systemic side effects, and a lower chance of drug-drug interactions.7–10. Diclofenac, an NSAID, has proven effective in treating a range of acute and persistent pain conditions.2,11 According to a recent Cochrane meta-analysis, diclofenac is a good option for a topical NSAID, with a number-needed-to-treat of 1.8 for acute pain12 and 9.8 for chronic pain13. There are various forms of topical diclofenac that can be purchased, such as gel, spray, emulsion, aqueous solution, cream, and transdermal patch.2,10

Fick's law states that other drug physicochemical parameters may affect drug permeation, despite the common assumption that skin penetration will be directly proportionate to drug concentration. O'Connor et al. state that because diclofenac sodium has a higher saturation solubility than diclofenac DEA, it appears to have a higher rate of transport.14 The ability of topical formulations to penetrate the skin and deeper tissues may be influenced by formulation composition, including the choice of vehicle (solutions, gels,15 emulsions, microemulsions,16,17 particles,18 liposomes,19,20, and transfersomes,21) and the inclusion of penetration enhancers and characteristics like water solubility and acidity.10 An in vitro skin penetration study was conducted to show the significance of the formulation parameters and composition independent of the drug concentration.

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) are two commercially available topical products whose permeabilities were compared. To further shed light on the observed variations in

skin permeation, the qualitative composition and physical characteristics of both products were evaluated.

II. MATERIALS AND METHODS

Premeability assessment

The permeability of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel through ex vivo human skin harvested from the abdominal region of five patients undergoing plastic surgery was compared in an in vitro study using Franz diffusion cells22. Two ethical committees (West of Scotland Research Ethics Services, Glasgow, UK, and Lothian Research Ethics Committee, Edinburgh, UK) gave their approval for the skin collection. All donors provided written informed consent after being informed of the reason for the collection. Skins were collected and then frozen at -20°C until they were needed for the percutaneous permeation investigation. On the day of the experiment, the skins were defrosted and dermatomed, beginning at the stratum corneum, at a thickness of about 400 µm. Before applying any formulation, the electrical resistance method was used to verify the barrier integrity of each skin sample. Skin samples that had an electrical resistance greater than 10.9 kΩ were included in the study. A 0.64 cm2 area of the stratum corneum surface of skin samples that were kept at 32±1°C and mounted in static diffusion cells received a single, fixed, 10 mg/cm2 dose of each diclofenac formulation (corresponding to the single-application dose for topical products recommended in the patient information leaflets). Thirty skin samples total—three duplicates of each donor—were used to apply each formulation to fifteen skin samples. The sample size was selected for exploratory reasons, and no formal sample size calculation was done. Samples of the receptor fluid (PBS containing 5% w/v bovine serum albumin) were taken at 0, 2, 4, 8, 16, and 24 hours following application. Liquid chromatography/tandem mass spectrometry was used tomeasure the amount of diclofenac that permeated (lower limit of quantification: 1 ng/mL).

III. DATA AND STATISTICAL ANALYSIS

The log-transformed mean cumulative absorption of diclofenac at 24 hours was compared post hoc between the 2 formulations using a restricted maximum likelihood estimation-based mixed-effects model, with donor as a random effect and formulation as a fixed effect. This was done because skin permeability data have been demonstrated to be log-normally distributed (23). By back-transforming the confidence intervals (CIs) for the variations between formulations on the log-transformed scale, ninety-five percent CIs were obtained for the geometric mean ratios on the original scale. The following formula was used to get the applied dose percentage: CA24h/(Q × P/A), where Q is the amount of topical product applied to the skin sample (mg), and CA24h is the cumulative absorption at 24 hours (mg/cm2). A is the skin sample's surface area (cm2), and P is the percentage of diclofenac in the topical product used. Diclofenac flux was determined at each timepoint using the formula

$$Ft=CAtt.$$

Physical characterization :-

Rheological analysis and microscopic inspection were used to evaluate the physical properties of diclofenac DEA 1.16% emulsion and diclofenac Na 5% gel.

Microscopic observation:-

Each topical product was visually examined in a few microliters using a Nikon Ni-U microscope (Nikon Instruments, Inc., Melville, NY, USA).

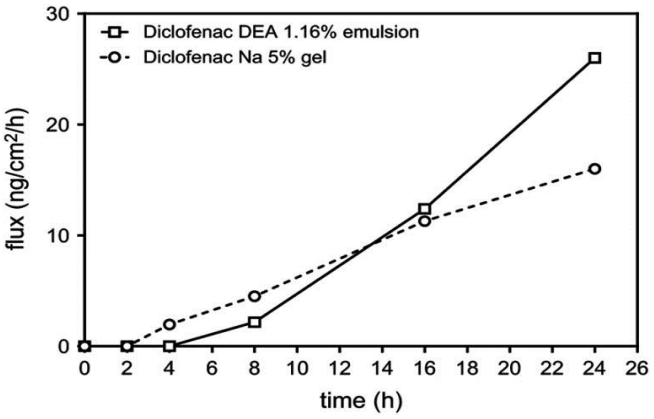
Rheological characterization :-

At 25°C, rheological measurements of every product were carried out using a cone-plate device (CP60-2, 60 mm diameter, angle 1.995°, truncation 252 µm) on a rheometer MCR 302 (Anton Paar GmbH, Ostfildern, Germany). Two minutes were spent relaxing the samples before measurement. The sample was sheared at increasing shear rates ranging from 1.10−3 to 2,800 s−1 (logarithmic ramp) for 280 s in order to determine the flow properties. Shear rate (s−1) and viscosity values ŭ (Pa.s) were recorded during this process.

Adjusted* geometric mean cumulative absorption at 24 hrs by formulation

Formulation	**Geometric mean (95% CI), ng/cm²**	**Diclofenac DEA 1.16% emulsion vs diclofenac Na 5% gel: ratio of geometric means (95% CI)**
Diclofenac DEA 1.16% emulsion	554 (265–1,158)	1.54 (1.14–2.07)**
Diclofenac Na 5% gel	361 (172–754)	

Abbreviations:- DEA, diethylamine; Na, sodium.



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

Solubility:-

While the diclofenac DEA 1.16% emulsion showed oily droplets in an aqueous phase with a narrow distribution of droplet size (mainly <10 µm), the diclofenac Na 5% gel appeared as a monophasic gel without droplets.

Viscosity:-

The viscosity of both products was measured at 10 s−1 at a controlled shear rate ranging from 1.10−3 to 2,800 s−1. This trend was confirmed at higher shear rates, with diclofenac Na 5% gel having a higher viscosity (24.82 Pa.s) than diclofenac DEA 1.16% emulsion (10.29 Pa.s).

IV. DISCUSSION

This in vitro study of diclofenac skin permeation in humans showed noticeably higher skin permeation with diclofenac DEA 1.16% emulsion at 24 hours than with the higher concentration product, diclofenac Na 5% gel. This study replicated the application of a single topical dose typically used during clinical use. These findings imply that factors other than drug concentration may affect topical diclofenac absorption. Consequently, a higher concentration may not always translate into more absorption through the skin.

The two products contain different salts (diclofenac DEA and diclofenac Na), so differences in the physicochemical properties, solubility, dissolution rate, and membrane transport between salts can be expected. Though diclofenac sodium has a higher rate of transport than diclofenac DEA, which is related to the higher saturation solubility of diclofenac sodium,14 the data generated showed the opposite. It seems that other parameters could likely be responsible for those unexpected results.

Topical NSAID formulations' excipients probably have an impact on the drug's solubility, diffusion into the formulation, release from the formulation, penetration into the stratum corneum, penetration through deeper layers of the skin, and ultimately, how well the drug is absorbed by the skin. For instance, it is well known that using organic solvents in formulations, like ethanol and isopropyl alcohol, can improve drug solubility and release.32, 33 Since the solvent is present in both formulations and the excipients' concentration is unknown, it is unlikely to be the only significant factor. Utilising permeation enhancers like propylene glycol, which is exclusively present in the diclofenac DEA 1.16% emulsion; When combined with additional excipients (see Table 1), skin penetration may increase. Emollients like paraffin and cocoyl caprylocaprate, which are both present in the diclofenac DEA 1.16% emulsion, can also increase skin hydration levels by occluding the skin, which promotes drug absorption

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

	Diclofenac DEA 1.16% emulsion	**Diclofenac Na 5% gel**
Gelling agent	Carbomer	Hypromellose
Emulsifier	Macrogol cetostearylic ether	Macrogol glyceryl cocoate
Emollient(s)	Liquid paraffin, cocoyl caprilocaprate	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.

To understand why the diclofenac DEA 1.16% emulsion was observed to have greater skin penetration, a physical characterization of both diclofenac products was carried out. Despite being semi-solids, both products have physical characteristics that could influence how well the drug is absorbed.

The diclofenac DEA 1.16% emulsion's carbomer and the diclofenac Na 5% gel's hypromellose exhibit distinct behaviours, as demonstrated by rheological measurements between the formulations. When compared to diclofenac DEA 1.16% emulsion, diclofenac Na 5% gel exhibits a higher viscosity at 10 s−1. Drug retention and release may vary depending on the properties of the polymeric network formed in gelified formulations, which can be characterised by factors like viscosity, concentration, and molecular weight of the polymer.35 Interestingly, hypromellose appears to form a denser polymeric network in the formulation; based on the data generated, this may limit the drug's release. Additionally, it appears that the gelling agent and the pharmaceutical dosage form (gel versus emulsion) affect how the drug releases in the various formulations.29

The kinetics and delivery of the drug may also be impacted by the pharmaceutical dosage form.29, 36, 37 Before a drug formulated in a biphasic formulation (such as an emulsion, cream, or ointment) reaches the skin's surface, it usually needs to partition out of the internal phase through the external phase. Stahl et al. have verified this observation, noting that gel releases drugs more quickly than biphasic pharmaceutical forms (such as cream). According to our flux data, this is probably the case. This study found that, in terms of drug delivery through the skin at 24 hours, emulsions exhibited higher drug permeation than gels. The gel product's dense polymeric network, which hypromellose created, may provide one explanation.

We have already covered the possible impacts of physicochemical characteristics, physical characteristics, and product composition (such as excipients) on drug absorption. However, since they will all work together to affect the drug's absorption, physiological factors and the interactions of several ingredients must also be considered.

V. CONCLUSION

We found that, in comparison to a product with a lower concentration of the active ingredient but different properties, a product with a higher concentration of diclofenac does not always result in greater skin absorption.

Even though topical diclofenac was the focus of our investigation, other medications may benefit from the insights we gained about the formulation's impact. As such, these results corroborate earlier research that suggested factors other than drug concentration, like formulation composition, should be considered when developing a topical pain relief product. As previously mentioned, these crucial factors may affect an NSAID's capacity to effectively permeate the stratum corneum and then the skin's lower layers, where it can then exert its local action at the level of soft tissues and/or joints.

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