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Formulation of diclofenac for dermal delivery

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ABSTRACT

Diclofenac (DF) was first synthesized in the 1960's and is currently available as ophthalmic, oral, parenteral, rectal and skin preparations. This review focuses on the administration of DF to the skin. As a member of the non-steroidal anti-inflammatory (NSAID) group of drugs the primary indications of DF are for the management of inflammation and pain but it is also used to treat actinic keratosis. The specific aims of this paper are to: (i) provide an overview of the pharmacokinetics and metabolism of DF following oral and topical administration; (ii) examine critically the various formulation approaches which have been investigated to enhance dermal delivery of DF; and (iii) identify new formulation strategies for enhanced DF skin penetration.

1. Introduction

Diclofenac (DF), a member of the aryl alkanoic group of non-steroidal anti-inflammatory drugs (NSAIDs), was synthesized by Ciba-Geigy in the 1960's and the sodium salt (DF Na) was launched as an oral formulation in 1973. Development of pharmaceutical compositions of DF for application to the skin was subsequently progressed, and a variety of commercial preparations are currently available today (Table 1). The chemical name of diclofenac is (2-(2-[(2,6-dichlorophenyl) amino]phenyl) acetic acid) and it contains a phenylacetic acid group, a secondary amino group and a phenyl ring, with chlorine atoms at the two ortho positions (Fig. 1). Maximal torsion of the phenyl ring is conferred by the position of the two chlorine atoms (Sallmann, 1986) which contributes to the more potent nature of DF compared with ibuprofen, ketoprofen and naproxen. With a molecular weight of 296.2, DF has a melting point of 156–158 °C, a log $P_{(octanol/water)}$ value of 4.5, and a pK_a value of 4.2 (Moffat et al., 2004).

DF is available as the following salts for administration to the skin; DF Na, DF diethylamine (DEA), and DF Epolamine (EPA). Researchers have also investigated the skin permeability of the potassium salt of DF (DF K) which is also administered orally (see Section 2). These salts (Fig. 1) have higher aqueous solubilities than the free acid which is reported to have a solubility of 60 μM in water at 25 °C (Chiarini et al., 1984) and an intrinsic solubility value of 1.03 ± 0.7 μg/mL, determined using a potentiometric acid–base titration (Llinàs et al., 2007). Reported aqueous solubilities for the salts, determined at 32 °C, are as follows: DF Na – 37 μg/mL, DF DEA – 19 μg/mL, DF EPA – 557 μg/mL, DF K – 218 μg/mL (Minghetti et al., 2007).

DF exerts anti-inflammatory, analgesic and anti-pyretic actions via inhibition of cyclooxygenase enzyme I (COX 1) and cyclooxygenase II (COX II) with a four-fold higher selectivity for the latter (Warner et al., 1999). More recent research also indicates that DF may inhibit the thromboxane-prostanoid receptor thus affecting arachidonic acid release and uptake; other mechanisms of action which have been proposed include inhibition of lipoxygenase enzymes and activation of the nitric oxide-cyclic guanosine monophosphate pathway (Gan, 2010).

Cordero et al. (1997, 2001) determined a topical efficiency ranking of DF and other NSAIDs based on in vitro skin permeation data and IC_{50} values of COX II inhibition. DF had the highest value and was proposed by the authors as a good candidate for topical delivery compared with a number of the other NSAIDs studied. In addition to its indications for use as an anti-inflammatory and analgesic agent, DF is also used topically in the treatment of actinic keratosis (AK), a condition where areas of abnormal growths develop in areas of the skin exposed to sun damage. Proposed mechanisms of action of DF in clearing AK lesions are COX II inhibition as well as apoptosis (cell death) upregulation (Nelson, 2011). The aims of this paper are: (i) to review the pharmacokinetics and metabolism of DF following oral and topical administration; (ii) to evaluate the different formulation approaches which have been pursued for DF topical delivery; and (iii) to consider new and emerging methods for enhanced skin permeation of DF. The

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Table 1
Compositions of selected commercial diclofenac formulations.

Formulation	Composition
Voltarol Emulgel™ (Novartis)	Diclofenac diethylammonium 1.16% w/w,diethylamine, Carbomer, macrogol cetostearyl ether, cocyl caprylocaprate, isopropyl alcohol, liquid paraffin heavy, perfume creme 45, propylene glycol dist., water.
Voltarol 12 h Emulgel™ (Novartis)	Diclofenac diethylammonium 2.32% w/w, butylhydroxytoluene, Carbomers, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, Macrogol cetostearyl ether, oleyl alcohol, propylene glycol, perfume eucalyptus sting, purified water.
Voltaren Gel™ (Endo)[a]	Diclofenac sodium 1% w/w, Carbomer Homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, strong ammonia solution.
Flector Patch™	Diclofenac epolamine 13 mg/g of adhesive, 1,3-butylene glycol, dihydroxyaluminum aminoacetate, disodium edetate, D-sorbitol, fragrance (Dalin PH), gelatin, kaolin, methylparaben, polysorbate 80, povidone, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, purified water.
Voltarol Active 4% Cutaneous Spray™ (Novartis)	Diclofenac sodium 4% w/w, isopropyl alcohol, soybean lecithin, ethanol, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, disodium edetate, propylene glycol, peppermint oil (contains menthol and cineole), ascorbyl palmitate, hydrochloric acid, sodium hydroxide, purified water.
Pennsaid Topical Solution™ (Mallinckrodt Inc.)[b]	Diclofenac sodium 2% w/w, dimethyl sulphoxide, ethanol, purified water, propylene glycol, hydroxypropyl methyl cellulose.
Pennsaid Topical Solution™ (Mallinckrodt Inc.)[b]	Diclofenac sodium 1.5% w/w, dimethyl sulphoxide, ethanol, purified water, glycerine, propylene glycol.
Solaraze™ Gel (Almirall Limited)	Diclofenac sodium 3% w/w, sodium hyaluronate, benzyl alcohol, macrogol monomethyl ether 350 and purified water.

[a] Licensed to Endo in the US by Novartis.
[b] Licensed to Mallinckrodt in the US by Nuvo Research.

emphasis is on studies conducted with porcine and human models or subjects since studies conducted with other animal species are not predictive of skin delivery in man.

1.1. Oral and percutaneous pharmacokinetics and metabolism of DF

After oral administration of DF Na in man a bioavailability of ~90% has been reported. Following administration of doses of 50 mg enteric coated tablets plasma levels of 1.0 μg/mL are achieved after 2 h. The metabolites of DF are primarily hydroxylated forms of the drug (4′-hydroxydiclofenac, 5-hydroxydiclofenac, 3′-hydroxydiclofenac, and 4′,5-dihydroxydiclofenac) which are excreted as glucuronide and sulphate conjugates (Riess et al., 1978). The 4′-hydroxydiclofenac is the major metabolite and is also therapeutically active. The extent of binding of DF to plasma protein is >99% (Chan et al., 1987). DF was detected in the synovial fluid (SF) (0.1–0.6 mg/L) 2 h after oral administration of DF Na to patients with rheumatoid arthritis; values in SF exceeded those in plasma after 4 h (Fowler et al., 1983). Plasma half-life, SF half-life, volume of distribution and clearance values are reported as 1–2 h, 3–6 h, 0.17 L/kg, and 4 mL/min/kg, respectively (Moffat et al., 2004).

Kadowaki et al. (1984) determined DF plasma levels to be 1.3 ng/mL in one human subject 2 h after application of 2.5 g of Voltaren™ Cream (1% DF Na) to the back covering an area of 250–300 cm^2. Application of the cream was continued three times daily for 10 days with steady state plasma levels reported as 6–10 ng/mL; plasma levels of 0.4 ng/mL were detected 98 h after the last application. Riess et al. (1986) investigated the plasma levels of DF following application of Voltaren Emulgel™ (1.16% DF DEA) and Voltaren™ cream (1% DF Na). The dose of Voltaren Emulgel™ applied was 5 mg/cm^2 to unoccluded skin and the dose of the cream was 10 mg/cm^2, applied three times daily. The percentage dose absorbed for the gel formulation was reported as 6% and steady state values of 20–40 nmol/L were reported for the cream.

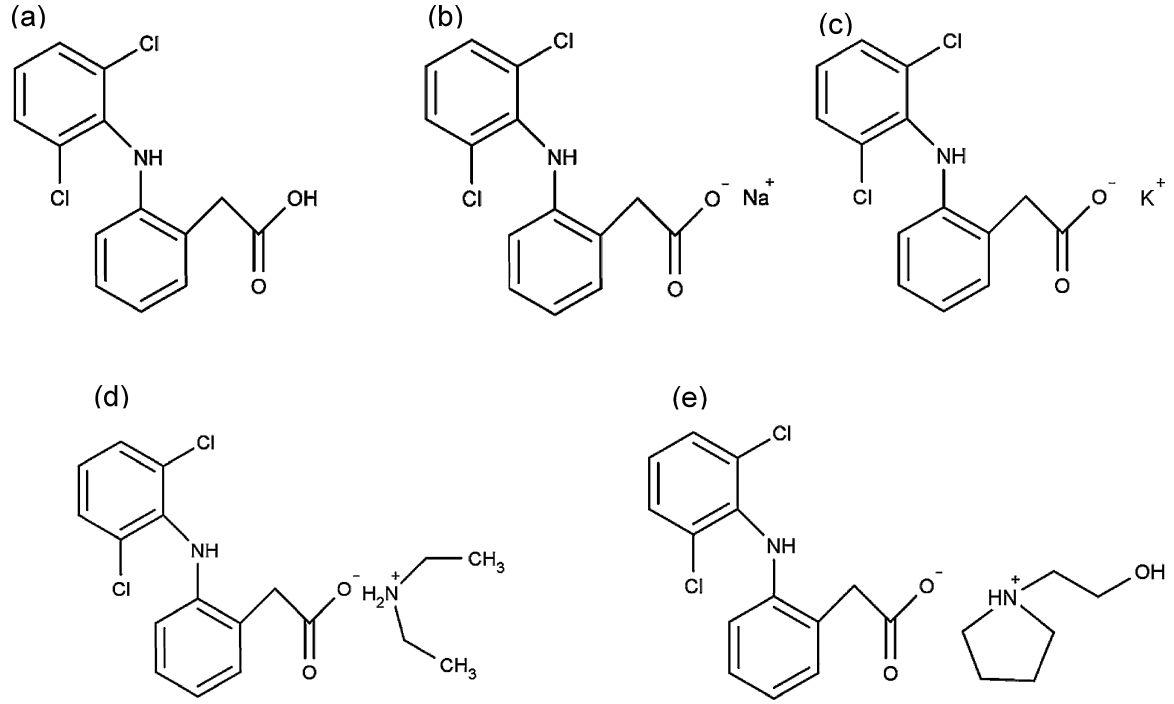

Fig. 1. Chemical structure of (a) diclofenac (DF) and its salts: (b) sodium (DFNa), (c) potassium (DFK), (d) diethylamine (DFDEA) and (e) epolamine (DFE).