Ex Vivo Study of Transdermal Permeation of Four Diclofenac Salts from Different Vehicles

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ABSTRACT: The *ex vivo* permeation of diclofenac was studied using four different salts (sodium, potassium, diethylamine, and epolamine) dissolved in four different solvents (water, propylene glycol (PG), Transcutol®, and oleic acid (OA)) as donor phases through a human skin membrane. The four salts show different solubility values and different behavior in the four solvents, which are also permeation enhancers and this fact further is connected to the permeation results. The same order of magnitude of fluxes through the membrane as those previously reported for acidic diclofenac released from buffer solutions of pH >7 were found, taking into account differences originated by different membranes and other parameters tested in the experiments. Saturation concentration for the four salts in different solvents, necessary to calculate permeation coefficients, was critically evaluated; a short discussion made it possible to explain that corrections in the solubility values must be considered, related to the complex behavior in solution of these salts. Statistical processing of the experimental data suggests that differences between the four salts in promoting absorption of the drug is unproven; while differences are evident between the solvents, water is the most effective enhancing vehicle. Aqueous formulations containing diclofenac salt with an organic base appear to be the best combination to promote permeation in topical applications. J Pharm Sci 96:814–823, 2007

Keywords: diclofenac salts; solubility; permeation enhancer vehicles; transdermal permeation; permeability coefficient; counterions

INTRODUCTION

Pharmaceutical salts represent a very common chemical form for the formulations of basic and acidic drugs, such as, for instance, nonsteroidal antiinflammatory drugs (NSAIDs). While a sodium salt is the most frequently used form, mainly due to the physiological presence of sodium, in the case of diclofenac the problem of the chemical form is far from being resolved, since this drug is present in the pharmaceutical market as four different salts; free diclofenac in fact displays a very low water solubility in its unionized form, and a salt form is therefore often preferred in commercial formulations.

However, acidic diclofenac (at 0% ionization) displays a partition parameter about 3000 times higher than that of the ionized (or salt) form, and this ratio was found to be the same when the values of permeability rate constant were considered for the two, unionized and ionized, forms of diclofenac.[1] This agrees with the general results whereby, in the case of ionizable drugs, the chemical form, most suitable candidate for topical application (where permeation occurs), is the unionized one, for its lower polarity and high log P, which means a higher affinity for the horny layer to be crossed for absorption. At the same time, in *in vitro* permeation experiments, in the case of the donor phase containing an acidic drug in buffer at pH >7 or a salt form of

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the drug, a flux, though low, can be measured across membranes. Possibly both chemical forms are involved in this flux: the ionized form because of its high concentration, and the unionized form because it compensates its lower concentration with a higher partition ability.

As a consequence, when administered cutaneously, the salt form of the hydrophobic drug is able to guarantee transdermal absorption, since it is possible that the hydrophobicity of the parent molecule is partly maintained, even when the drug is ionized in the form of a salt.[2] These results support the choice of a salt as chemical form for topical applications and transdermal absorption of diclofenac; and this study, aimed at comparing the absorption ability of counterions in different diclofenac salts through a model membrane, therefore, appears of interest in assessing the best chemical form for this administration route.

Although a variety of counterions have been studied associated with diclofenac anions,[3,4] the salts present in commercial pharmaceutical products contain only sodium, potassium, diethylamine, and *N*-(2-hydroxyethyl) pyrrolidine (epolamine) ions. These salts are considered both for oral and topical administrations, both as semisolid preparations or patches.[5,6] The effect of the counterion on diclofenac transdermal permeation is reported in a limited number of studies,[6–10] mainly in iontophoretic experiments; few studies have been performed through human skin and no author has investigated the permeation of different diclofenac salts in combination with chemical enhancers.

The aim of this study was to compare the effect of different counterions on the percutaneous absorption of diclofenac from saturated solutions of its salts in water and three different solvents: propylene glycol (PG), Transcutol® and oleic acid (OA). The solvents were selected among well-known permeation enhancers, considering their different chemical structures and different mechanisms of action; the penetration enhancer and the solvent of the donor phase are thus the same. The skin permeation experiments were performed using Franz's diffusion cells and human stratum corneum and epidermis (SCE) as a model membrane.

MATERIALS AND METHODS

Materials

Diclofenac sodium (DNa) (Dipharma, Ud), diclofenac diethylamine (DEt) (Calao Srl, Milano, Italy), diclofenac potassium (DK) (Farchemia, Bergamo, Italy), diclofenac epolamine (DEp) (IBSA, Lugano, Switzerland) were gifts of pharmaceutical grade. The purity of each salt was >99%.

Propylene glycol (Carlo Erba Reagenti, Milano, Italy), OA (Polichimica, Bologna, Italy), Transcutol® (di-ethylene glycol mono ethyl ether, TR) (Gattefossé Italia Srl, Milano, Italy) were commercial samples of pharmaceutical grade. All substances were used as received.

Solubility Study

The solubility of the molecules in water and in (each) permeation enhancer was obtained by equilibrating a large excess of the solute and vehicle for 72 h. Each solution was stirred vigorously with a magnetic bar throughout the experiment and the temperature was maintained at $32 \pm 1^{\circ}$C. After equilibration the sample was filtered quickly with a membrane filter. The filtrate was adequately diluted with methanol and analyzed by HPLC, using the method reported below.

Skin Preparation

The skin used in the transdermal permeation studies was obtained from the abdomen of one single female patient who had undergone cosmetic surgery. The full-thickness skin was sealed in evacuated plastic bags and frozen at -20°C within 24 h after removal. Prior to preparation, the skin was thawed to room temperature and the excess fat was carefully removed. The skin sections were cut into squares and, after immersing the skin in water at 60°C for 1 min, the SCE was gently separated from the remaining tissue with forceps and left to dry. The dried samples were wrapped in aluminum foil and sealed in plastic bags. The prepared samples were kept frozen at -20°C until used.

The SCE was thawed prior to experimental use and was carefully inspected visually for any defects before mounting them on the Franz diffusion cells.

Skin Permeation Test

Before use, the dried SCE sample was hydrated at room temperature by immersion in saline solution for 16 h. The SCE was placed carefully on the lower half of the Franz cell with the epidermis facing upwards and the stratum corneum side in