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Effect of iontophoresis and penetration enhancers on transdermal absorption of metopimazine

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Porcine skin;
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Summary

Background: Metopimazine is an antiemetic drug already used by oral and rectal administration. It would be interesting to develop a new formulation for a transdermal administration.
Objective: The objective of this study was to determine the influence of iontophoresis on the metopimazine transdermal absorption and the possible synergistic enhancement with chemical enhancers.
Methods: Transdermal transport of metopimazine was studied *in vitro* in a Franz cell with pig skin according to the following protocol: 1 h of iontophoresis followed by 7 h of passive diffusion. Different current densities were applied: 0, 0.125, 0.25 and 0.5 mA/cm^2. Chemical enhancers used as solvent dilution were ethanol, propylene glycol and isopropyl myristate. Metopimazine was assayed by HPLC. Fourier transform infrared spectroscopy was used to determinate the interaction between chemical enhancers and *stratum corneum*.
Results: The iontophoresis has increased the percutaneous absorption of metopimazine and has decreased the lag time with 3.85 ± 0.90 μg/(cm^2 h) and 1.9 h for 0.5 mA/cm^2 and with 0.27 ± 0.20 μg/(cm^2 h) and >8 h for passive diffusion. Transdermal transport has been increased with current density and with isopropyl myristate and was not modified by ethanol or propylene glycol.
Conclusion: Results indicated that iontophoresis is an effective method for transdermal administration of metopimazine.

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1. Introduction

Metopimazine (MPZ) is a phenothiazine derivative with dopamine D_2-receptor antagonist propriety [1] which presents an antiemetic activity. The MPZ chemical structure is represented in Fig. 1. This drug has a short elimination half-life and requires frequent dosing [2,3]. Oral administration of drugs is generally the route of choice. In this case, oral absorption is often compromised by nausea and vomiting [4]. The transdermal route has a potential interest in those situations in which oral administration may be inadvisable. Calpena et al. have studied the MPZ transdermal absorption in Franz's cells on rat skin. The predicted range of MPZ permeated amounts during the first 24 h was inferior to the theoretical daily transdermal dose and the lag time of MPZ was more important to have an immediate therapeutic effect [5].

Transdermal iontophoresis is an effective technique for facilitating the transport of permeates across the skin using an electromotive force and providing a better control of administrated dose compared to passive diffusion. It was developed for instance to increase the permeability coefficient of many drugs as acyclovir, buprenorphine and fentanyl [6—8]. The drug, in its ionic form, is placed in a reservoir on the skin, under an electrode bearing the same charge as the penetrant. An indifferent counter electrode is positioned elsewhere in the body and a voltage source supplies a small constant electric current, resulting in the repulsion of the active substance from the active electrode. This electrorepulsion mechanism forces the drug into the skin and contributes to its penetration enhancement. For the drug administration iontophoresis is well tolerated. The effects of iontophoresis on human skin are low for current densities of less than 0.5 mA/cm^2 [9—11]. The structural changes are either non-existent or minor and reversible.

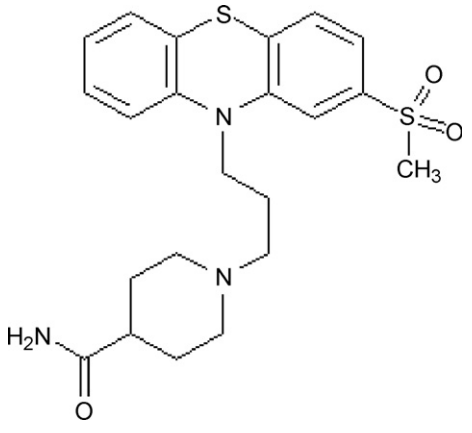

Fig. 1 Molecular structure of metopimazine.

The most frequent side effect would be the emergence of a transitional erythema. Any investigation on MPZ transdermal administration by iontophoresis has been previously published. In this work, we have studied the influence of MPZ concentration and the relationship between current density and flux of MPZ.

Combination of chemical enhancers and iontophoresis can conduct to synergistic enhancement. It was used, in particular, to increase the iontophoresis effect for drug with a very poor percutaneous absorption like insulin, arginin vasopressin or small peptides [12,13]. This combination was also performed since the combining effect of these two methods may permit the use of lower quantities of enhancer and current within the delivery system and potentially circumvent adverse reactions and dermatotoxicity. Chemical enhancers have been used only to promote the drug flux across the skin. Alcohols, polyols are known to increase solubility and to improve partitioning coefficients. Ethanol, may extract lipids, making the stratum corneum more permeable. Propylene glycol or isopropyl myristate have known to disrupt the horny layer intercalating into the structured lipids of the skin, which renders the structure more fluid and increases the diffusion coefficient of the permeant, in particular, that of aspirin and diclofenac [14,15]. Nevertheless, chemical enhancers only used have limitations concerning the delivery of high amounts of ionic molecules, large molecular weight active substances and are known to irritate the skin. To overcome these main drawbacks, transdermal iontophoresis can be used only or associated with chemical enhancer.

The purpose of the present paper was to study the influence of iontophoresis on the MPZ transdermal absorption and the possible synergistic enhancement with ethanol or propylene glycol and isopropyl myristate. The transdermal iontophoresis was tested in Franz's cells on pig skin and the effect of chemical enhancers on skin was investigated with Fourier transform infrared spectroscopy (ATR-FTIR).

2. Materials and methods

2.1. Materials

Schwartz Pharma (Boulogne Billancourt, France) provided the injectable solution of MPZ, Vogalene®. The commercial product is composed of a water solution of MPZ hydrochloride at 10 mg/ml, ascorbic acid at 1 mg/ml, sodium chloride and of sodium citrate with a pH at 5.5. HPLC solvents were from Carlo Erba (Rodano, Italia). All other chemicals were obtained from Acros Organics (Geel, Belgium).