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COMMUNICATION

# Design and Evaluation of a New Transdermal Formulation Containing Chlorpheniramine Maleate

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**ABSTRACT**

*The antihistamine chlorpheniramine maleate (CPM) is used for symptomatic relief of hypersensitive reactions and in pruritic skin disorders. The objective of the present study was to develop a topical formulation that contained CPM to increase patient compliance. Compliance was increased by exploiting foams that, given their application methods, avoid direct contact with the afflicted area. The study also aimed to optimize the permeability of the CPM by discerning an adequate carrier, as well as choosing the correct enhancer. The foams were formulated using aqueous solutions. In vitro studies were carried out using Franz cells with the formulations, as well as with the available pharmaceutical product Polarmin Crema®, which contains CPM. These studies showed that the permeability of the CPM in the solutions is increased more then 100 times with respect to the water-in-oil emulsion Polarmin Crema. In particular, the highest permeability was obtained using limonene as an enhancer.*

***Key Words:*** *Chlorpheniramine maleate; Enhancer effect; Foams; Limonene; Transdermal permeability.*

## INTRODUCTION

The antihistaminic chlorpheniramine maleate (CPM) is a typical cationic amphiphilic amine drug characterized by the hydrophobic ring structure of the molecule and the hydrophilic side chain with a charged cationic amino group. CPM is used for topical ointments, especially for skin disorders such as sunburn, urticaria, angioedema, pruritus, and insect bites (1,2); in conventional formulations, there is contact with the afflicted areas of the epi-

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dermis during the spreading phase. For this reason, foams, which avoid contact with the afflicted areas, were developed. This formulation enables enhanced patient compliance.

In recent years, investigators have intensified their interest in the controlled delivery of drugs through the skin. Transdermal ointments have been developed by including in the formulation molecules that would reversibly remove the barrier resistance of the stratum corneum and thus allow the drugs to penetrate.

In this study, the permeation of CPM from topical formulations was optimized by selecting the appropriate carrier and by using two enhancers with a different mechanism of action: limonene and Transcutol®.

Limonene has a terpenic structure. The terpenes increase permeability by means of a disruption of the stratum corneum lipids at physiological temperatures, as confirmed by the changes in differential scanning calorimetry (DSC) thermograms of pretreated human stratum corneum with terpenes compared to the untreated samples (3).

Transcutol is a powerful solubilizer especially used in topical agents. Transcutol did not show any changes in the DSC thermograms of pretreated human stratum corneum, meaning that it does not interact with the stratum corneum and does not modify the structure of intercellular lipids (4). The enhancer effect of Transcutol would seem to be that of increasing the solubility permeants in the stratum corneum, as demonstrated in the case of Griseofulvina (5).

The permeability of CPM in the formulations developed therefore is compared with the commercially available pharmaceutical product Polaramin Crema®.

## FORMULATIONS

Three aqueous solutions of CPM at 1% concentration for use as foams were prepared. The compositions of the solutions are reported in Table 1. The solutions were then conditioned by Coster s.p.a. in protected aluminum canisters using isobutane (3:2) as a propellant.

The permeation of CPM from the solutions was compared to that of Polaramin Crema, a water-in-oil emulsion; its composition is reported in Table 2.

## MATERIALS

The following chemicals were used as received: CPM from Sigma Chemical Company (St. Louis, MO); diethylene glycol monoethyl ether (Transcutol) from Gattefossè; *d*-limonene from Sigma Chemical Company; Tween 80 from Atlas Chemicals; and glycol propylene from Fluka Chemical Company.

***Table 1***

*Compositions of the Prepared Solutions*

| | Solutions (%) | | |
|---|---|---|---|
| Components | A | B | C |
| Chlorpheniramine maleate | 1 | 1 | 1 |
| Limonene | — | 1 | — |
| Transcutol | — | — | 3 |
| Tween 80 | 4 | 10 | 4 |
| Glycol propylene | 4 | 4 | 4 |
| Bidistilled water | 95.5 | 83.5 | 87.5 |

## METHODS

### Tissue Preparation

The porcine skin is largely used for in vitro experiments because it is very similar to the human epidermis, as demonstrated by the fact that the DSC of the porcine and human stratum corneum are very similar and present the same peaks (6). Full-thickness skin with a fair amount of underlying connective tissue was removed surgically from the ears of freshly killed male pigs (30–50 kg), obtained on each study day from a local slaughterhouse (CLAI, Imola, Italy). The skin was placed in ice-cold phosphate buffered saline (PBS), pH 7.4. The connective tissue of the skin was removed carefully using fine-point forceps and surgical scissors. The cleaned membrane was

***Table 2***

*Composition of Polaramin Crema*

| Components | Polaramin Crema (%) |
|---|---|
| Chlorpheniramine maleate | 1 |
| Glyceryl monostearate | 16 |
| Cetyl ester wax | 3.8 |
| Sorbitol 70% | 3 |
| Glycerin | 2 |
| Cetyl alcohol | 1.2 |
| Liquid paraffin | 1 |
| Essence of lavender | 1 |
| Methyl parahydroxybenzoas | 0.1 |
| Water | 69.9 |

then placed in ice-cold PBS until it was mounted in the diffusion cells.

### In Vitro Diffusion Study

The in vitro diffusion studies were carried out in standard Franz diffusion cells having 0.64 $cm^2$ diffusion area (7,8). The receptor compartment had a volume of 4.8 ml and was maintained at 37°C by means of a water bath, circulator, and jacket surrounding the cells. The cells were filled with fresh PBS. The solution in the receptor compartments was stirred continuously at 600 rpm using a Teflon-coated magnetic stirrer. The porcine skin, which was about 1-mm thick, was clamped between the donor and receiving compartments. One ml of the tested formulations was placed in the donor compartment.

The amount of CPM diffused through porcine skin was determined by removing aliquots of 1 ml from the receptor compartments using a syringe and immediately replacing with the same volume of PBS (kept at 37°C).The samples were transferred to volumetric flasks and stored in a refrigerator until they were analyzed. The sampling schedule was 0.5, 1, 2, 4, 8, 12, and 24 hr. All experiments were carried out in triplicate.

### Analyses

The CPM in samples was determined using a high-performance liquid chromatography (HPLC) device (model 305, Gilson) equipped with a variable-wavelength ultraviolet (UV) detector (model Spectra 200, Spectra-Physics). A Nova-Pak C18 (150 × 3.9 mm, 4 μm, Waters) column was used. Elution was carried out at room temperature with a mobile phase consisting of phosphate buffer 0.025 M adjusted to pH 3 with phosphoric acid and acetonitrile (7:3, v/v); the injecting volume was 20 ml. The flow rate was 1 ml/min, and the detection was at 276 nm. In this condition, the retention time of CPM was 7.50 min.

### Data Analysis

For the CPM, absorption is a passive diffusion process and can be described by Fick's second law equation:

$$J_s = dQ_r/Adt \quad (1)$$

where $J_s$ is the steady-state flux in micrograms/square centimeter per hour, $dQ_r$ is the change in quantity of material passing through the membrane into the receptor compartment expressed in micrograms, $A$ is the active diffusion area in square centimeters, and $dt$ is the change in time in hours. The steady-state fluxes of the CPM through the skin were calculated from the slope of the linear portion of the cumulative amount permeated through the membrane per unit area versus time plot.

To determine the permeability coefficient, we used the following equation:

$$K_p = J_s/C_d \quad (2)$$

where $K_p$ is the permeability coefficient, $J_s$ is the flux calculated at the steady time, and $C_d$ is the donor concentration (9).

The effectiveness of each formulation was evaluated using the enhancement ratio *ER* (10), where

$$ER = K_p \text{ of the CPM from a formulation with the enhancer}/K_p \text{ of the CPM from the referring formulation} \quad (3)$$

***Table 3***

*Cumulative Amounts of Permeated CPM from the Solutions and from Polaramin Crema*

| | Cumulative Amount of Permeated CPM (μg) | | | |
|---|---|---|---|---|
| Time (hr) | Solution A | Solution B | Solution C | Polaramin Crema |
| 0.5 | 4.88 ± 1.16 | 7.13 ± 2.45 | 6.20 ± 1.51 | 0.86 ± 0.11 |
| 1 | 6.45 ± 1.85 | 20.10 ± 16.70 | 6.21 ± 0.23 | 0.15 ± 0.25 |
| 2 | 15.81 ± 8.43 | 132.85 ± 16.88 | 22.05 ± 4.62 | 0.18 ± 0.11 |
| 4 | 148.48 ± 37.91 | 344.40 ± 85.39 | 134.15 ± 32.53 | 0.84 ± 0.99 |
| 6 | 254.30 ± 66.42 | 612.47 ± 141.98 | 284.55 ± 68.07 | 2.18 ± 1.16 |
| 8 | 484.57 ± 51.22 | 825.62 ± 217.92 | 431.97 ± 77.44 | 3.43 ± 1.49 |
| 10 | 669.73 ± 64.86 | 1201.76 ± 315.94 | 627.47 ± 110.15 | 4.28 ± 0.99 |
| 24 | 2149.80 ± 31.21 | 2782.16 ± 536.77 | 1764.41 ± 377.94 | 13.10 ± 1.66 |

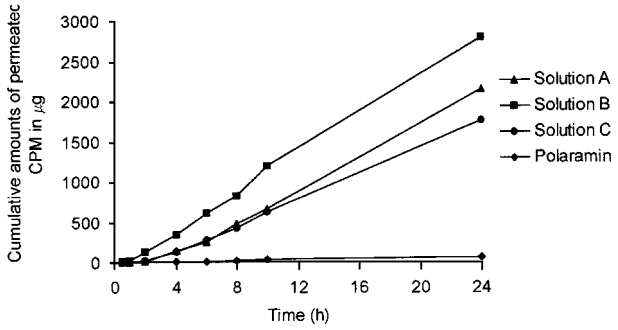


**Figure 1.** Permeation profile of CPM from the tested formulations.

## RESULTS AND DISCUSSION

The cumulative amounts of CPM passing through porcine skin from the solutions and from Polaramin Crema are represented in Table 3. Permeation profiles of CPM from the tested formulations are shown versus time in Fig. 1. The $K_p$ of CPM from the tested formulations, the *ER* of solutions B and C with respect to solution A, and the *ER* of the solutions with respect to Polaramin Crema are represented in Table 4.

From the results it, can be deduced that

- The steady state is established in all of the tested formulations after about 1–2 hr.
- The terpene limonene was an effective accelerant, providing a 1.81-fold increase in the permeability coefficient of CPM with respect to the solution without enhancer, whereas the Transcutol was quite ineffective.
- There was a strong improvement in the CPM permeation across the porcine skin in all the solutions with respect to the Polaramin Crema.

## CONCLUSION

The aqueous solutions containing CPM are good vehicles for the transdermal permeation of CPM compared to the water-in-oil emulsion of Polaramin Crema. In particular, the solution that contains CPM and limonene at a 1% concentration could be a good candidate for a new formulation given its good characteristics of permeability and compliance.

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***Table 4***

$K_p$ *of CPM from the Tested Formulation and the* ER *of Solutions B and C with Respect to Solution A*

| | $K_p$ (cm/hr) | *ER* of Solutions B and C with Respect to Solution A | *ER* of the Solutions with Respect to Polaramin Crema |
|---|---|---|---|
| Solutions | | | |
| A | 9.46 ± 0.64 | 1 | 135.14 |
| B | 16.13 ± 2.73 | 1.81 | 230.43 |
| C | 8.44 ± 0.97 | 0.98 | 120.57 |
| Polaramin Crema | 0.070 ± 0.01 | — | 1 |

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