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3

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AMMONIO LATTATO "ATTIVATO" LA RISPOSTA DERMATOLOGICA ALLE IPERCHERATOSI



Ipercheratosi intrinseca



Ipercheratosi estrinseca

"ACTIVATED" AMMONIUM LACTATE THE RIGHT REPLY TO HYPERKERATOSIS



KERATOTAL 1

Emulsione - Ammonio Lattato 14%

KERATOTAL 2

Emulsione - Ammonio Lattato 8%

KERATOTAL SHAMPOO

Ammonio Lattato 7%

KERATOTAL BAGNO

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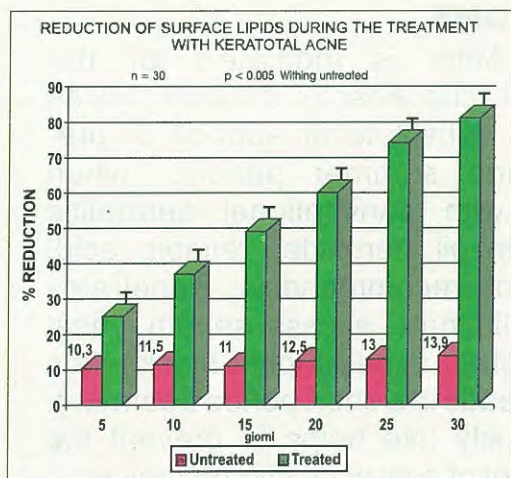
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KERATOTALACNE™

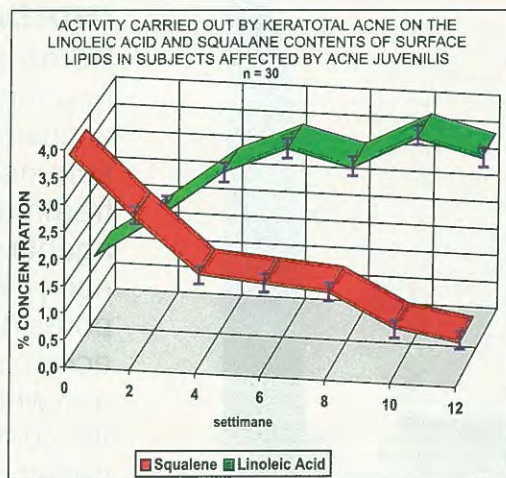
Dermatologically tested

- Effective for initial and maintenance therapy ^(1,2,3)
- Compatible with all the drugs and cosmetics
- Formulated to treat mild-to-moderate inflammatory acne, indispensable for patients with sensitive skin

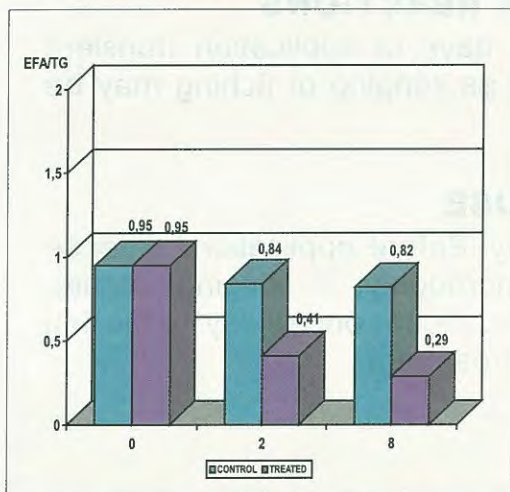
CLINICAL RESULTS ^(1,2,3)



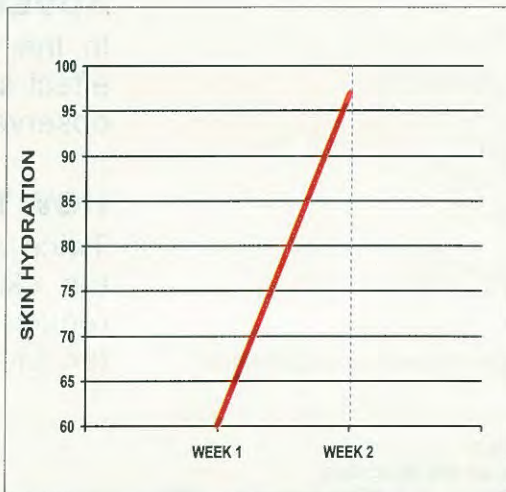
⇒ Decreases the Squalene content of acne affected skin



⇒ Reduces excess lipids



⇒ Significantly reduces EFA/TG ratio



⇒ Increases skin hydration by 97%

BRIEF SUMMARY

KERATOTALACNE™

THE GENTLE ANTIACNE
TREATMENT WITH
NO-DRUG CONTENT



DESCRIPTION

Keratotal Acne is a special fat-free lamellar phosphatidylcholine emulsion developed for the treatment of acne. It is delivered in a special phospholipidic-vehicle linoleic acid rich which contains glycolic acid and salicylic acid partially neutralized by a special patented blend of aminoacids

INDICATIONS

Keratotal Acne is indicated for the treatment of acne. Absolutely necessary as a cosmetic substitute or support in pre-summer and summer periods, when treatment with conventional keratolytic agents (benzoyl peroxide, retinoic acid, ecc.) is not recommended. Penetrates pores to eliminate excess sebum, most acne blemishes, acne pimples, blackheads and whiteheads in a short period treatment. Its continuous use helps to prevent the development of new acne efflorescences

ADVERSE REACTIONS

In the first days of application transient effect such as stinging or itching may be observed

HOW TO USE

Twice a day. Before applications cleanse the skin thoroughly; if stinging occurs, reduce application to once a day for the first ten days of treatment

For more information
call to:

Mavi Sud Srl

V.le dell'Industria 1

04011 Aprilia (Lt)

Italy

Tel. +39.6.92.86.261

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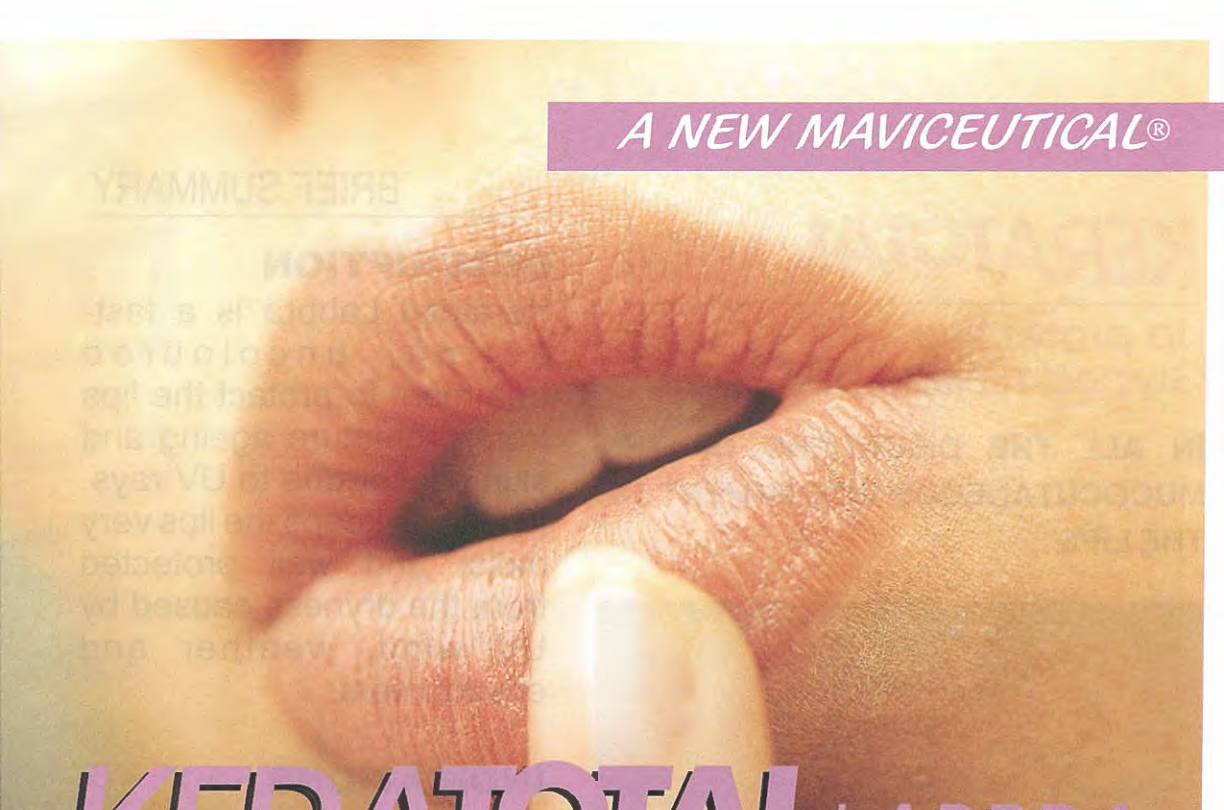
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3 - M. Ghiczy, H.P. Nissen, H. Biltz (1996) The treatment of Acne Vulgaris by phosphatidylcholine from Soybeans, with a high content of linoleic acid. *J. Appl. Cosmetol.* **14**, 137-145



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Lip protective with Glycoaminoacids(*)

INDICATIONS

Cosmetic adjuvant in all the forms of cheilitis and lips dryness caused by:

- | | | |
|----------------------------|-------|--|
| • Retinoids | • • • | Such as Cheilitis or chapped lips |
| • UV rays | • • • | Actinic cheilitis (acute and chronic) |
| • Wind | • • • | Allergic cheilitis |
| • Weather | • • • | Exfoliative cheilitis |
| • Environmental pollutants | • • • | Angular cheilitis |

HOW TO USE

Use day and night as a regular lipstick

(*) partially neutralized by a special patented blend of aminoacids

Please see a brief summary of prescribing information on next page



KERATOTALTM LABBRA

Lip protective with
Glycoaminoacids^(*)

IN ALL THE DISORDERS OF THE
MUCOCUTANEOUS INTEGUMENT OF
THE LIPS



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(*) partially neutralized by a special
patented blend of aminoacids

BRIEF SUMMARY

DESCRIPTION

Keratotal Labbra is a fast-acting, uncoloured treatment to protect the lips from premature ageing and skin cancer due to UV rays. It helps to keep the lips very moist and well protected from the dryness caused by UV, wind, weather and environment.

INDICATIONS

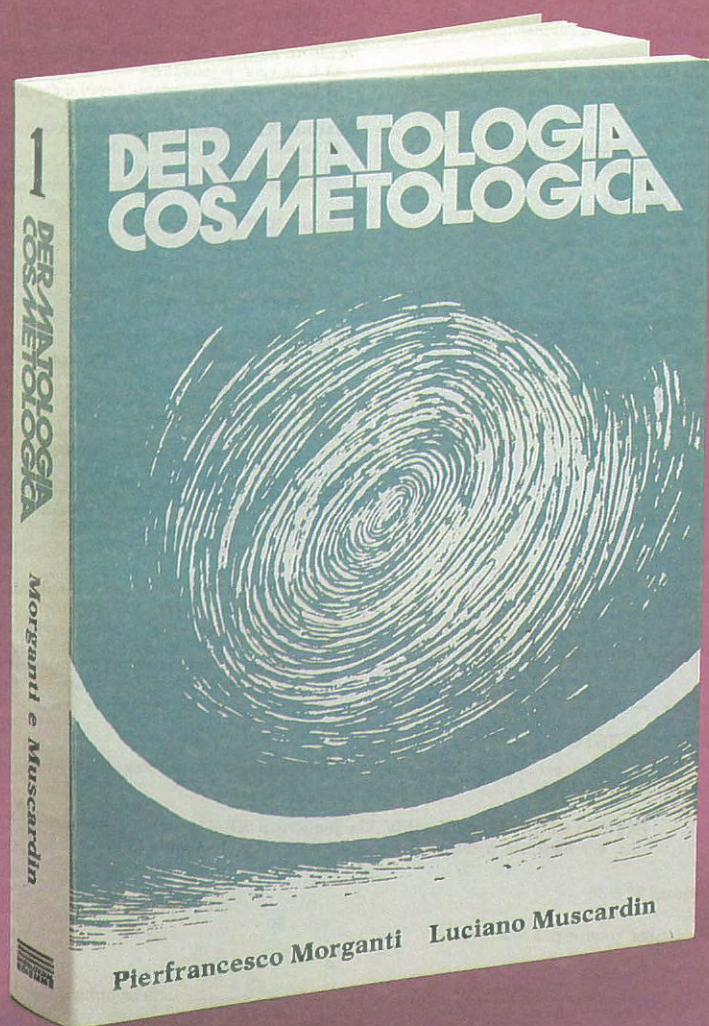
In all forms of dryness caused by the use of retinoids or other drugs, or by environmental pollutants. To avoid the premature lips ageing caused by UV activity.

ADVERSE REACTIONS

No adverse reactions to the use of this product are known.

HOW TO USE

Apply as a regular lipstick. Keratotal Labbra is intended for round-the-clock use.



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DERMATOLOGIA COSMETOLOGICA

A cura di P. Morganti e L. Muscardin
Ed. International Ediemme

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- 2 La bellezza della figura umana

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Trimestrale di Dermatologia Cosmetologica Quarterly Review of Cosmetic Dermatology

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IN-COSMETICS CONFERENCE 1997
"Modern challenges to the cosmetic formulation"
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DECREASING THE STINGING CAPACITY AND IMPROVING THE ANTIAGING ACTIVITY OF AHAs

P. Morganti*, S.D. Randazzo**, G. Fabrizi *** and C. Bruno****

*Department of Dermatology, Dermatologists' Training School, II University of Naples, Italy

** Department of Dermatology, University of Catania, Italy

***Department of Dermatology Catholic University of Rome, Italy

****Physiology Institute, University of Urbino, Italy

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Key words: AHAs, Glycolic Acid, Gelatin-Glycine, Arginine, Stinging Capacity, Antiaging.

Synopsis

The AHAs ability to affect wrinkling, specially increasing the rate of skin cell renewal, seems to be strictly correlated to the plasticization effect and to some degree of irritation. The purpose of this study was to determine whether some aminoacids, used to buffer AHAs, can reduce the stinging and burning sensation caused by the use of Alphahydroxyacid containing formulation, enhancing the skin penetration and maintaining, its antiaging activity.

The obtained results seem to demonstrate that the aminoacids used to buffer glycolic acid (gelatin-glycine enriched with arginine), markedly reduces the irritating side effects of AHAs-containing emulsions potentiating their antiageing activity. Conversely, AHAs depigmenting activity on age-spots, as well as their control on free radicals, are enhanced.

Riassunto

La capacità degli AHAs di agire sulle rughe, soprattutto aumentando il tasso di rinnovamento delle cellule della pelle, sembra essere strettamente correlata all'effetto plastificante e ad un certo livello di irritazione. Lo scopo di questo studio era di determinare se alcuni aminoacidi, usati per tamponare gli AHAs, potessero ridurre la sensazione pungente e di bruciore causata dall'uso di formulazioni contenenti alfa-idrossiacidi, aumentandone la penetrazione attraverso la pelle e mantenendone l'attività anti-invecchiamento. I risultati ottenuti sembrano dimostrare che gli aminoacidi usati per tamponare l'acido glicolico (la gelatina-glicina arricchita con arginina) riducono considerevolmente gli effetti collaterali irritanti delle emulsioni contenenti AHAs, potenziandone l'attività anti-invecchiamento. Viceversa risulta potenziata sia l'azione schiarente degli AHAs nei confronti delle iperpigmentazioni cutanee provocate dall'età, che il loro controllo sui radicali liberi.

Introduction

As well known AHAs when applied topically, have been demonstrated an interesting efficacy in the treatment of conditions predisposing to dry, rough skin, including ichthyosis. Therapeutic benefits have been reported also in the treatment of acne, keratoses, and problems related to aging, such as dyschromia and wrinkling (1-5)

The AHAs ability to affect wrinkling, specially increasing the rate of skin cell renewal, seems to be strictly correlated to the plasticization effect and to some degree of irritation. (6-8) The purpose of this study was to determine whether some aminoacids, used to buffer AHAs, can reduce the stinging and burning sensation caused by the use of Alpha hydroxyacid containing formulations, enhancing the skin penetration and maintaining, its antiaging activity. All the study was carried out during the months of September through December 1995. Each caucasian subject was used, when possible, as her or his own control; the tests and comparative formulations being, on randomized basis, to bilateral symmetrical areas.

Materials and methods

MATERIALS

TREATMENT A

Day cream

Vehicle + glycolic acid, gelatin, glycine, arginine. pH 5.5.

Night cream

Vehicle + glycolic acid, gelatin, glycine, arginine. pH 5.5.

TREATMENT B

Day cream

Vehicle + glycolic acid, gelatin, glycine, lysine. pH 5.5.

Night cream

Vehicle + glycolic acid, gelatin, glycine, lysine. pH 5.5.

TREATMENT C

Day vehicle

Day cream - Water, stearyl heptanoate, cetareth-10, beeswax, cetearyl octanoate, cetyl esters, myristyl alcohol, dimethicone copolyol, mineral oil, isopropyl lanolate, dihydroxycetyl phosphate, isopropyl hydroxycetyl ether, cetearyl alcohol, titanium dioxide, desamidocollagen, glycerin, linoleic acid, linolenic acid, sodium PCA, tocopheryl acetate, allantoin, disodium EDTA, imidazolidinyl urea, methylparaben, fragrance - pH 5.5.

Night vehicle

Night cream - Water, sodium PCA, caprylic/capric triglyceride octyl stearate, cyclomethicone, glycerin, cetyl dimethicone copolyol, isopropyl lanolate, cetearyl octanoate, squalane, linoleic acid, linolenic acid, retinyl palmitate, tocopheryl acetate, magnesium sulfate, BHT, imidazolidinyl urea, methylparaben, propylparaben, fragrance - pH 5.5.

TREATMENT D

Day cream

Vehicle + glycolic acid. pH 5.5.

Night cream

Vehicle + glycolic acid. pH 5.5.

Selection of stingers

We selected 40 women (between age 27/35) with light complexions and personal history of easy sunburning. According to Frosh and Kligman (9) the stinging activity was evaluated using a 5% aqueous solution of lactic acid rubbed briskly over the nasolabial fold and cheek after sweating induced by a 15 minutes steam. Those who experience sharp stinging at least 3 to 5 minutes were identified as stingers.

METHODS

1st. STUDY

Stinging test

The first experimental study was carried out on preselected volunteers individuals (40 women between age 27/35) classified as "stingers" according to Frosh and Kligman methodology. (9)

Stinging test was evaluated out on four groups of 10 stingers.

- 1 group treatment formulation A (day cream) on right nasolabial fold and cheek
vehicle A on left side
- 2 group treatment formulation A (day cream) on left nasolabial fold and cheek
vehicle A on right side
- 3 group treatment formulation B (day cream) on left nasolabial fold and cheek
vehicle B on right side
- 4 group treatment formulation B (day cream) on right side and fold
vehicle B on left side

Each subject placed the face directly into a steam stream (40°C) for at least 10/15 minutes. When sweating was brisk, each cream and vehicle were randomly rubbed over one side of nasolabial fold and cheek (right or left). The other side serving as control. Stinging was evaluated immediately after application of the cream (10 sec) and at 2.5, 5.0 and 8.0 min. on a 4 point scale:

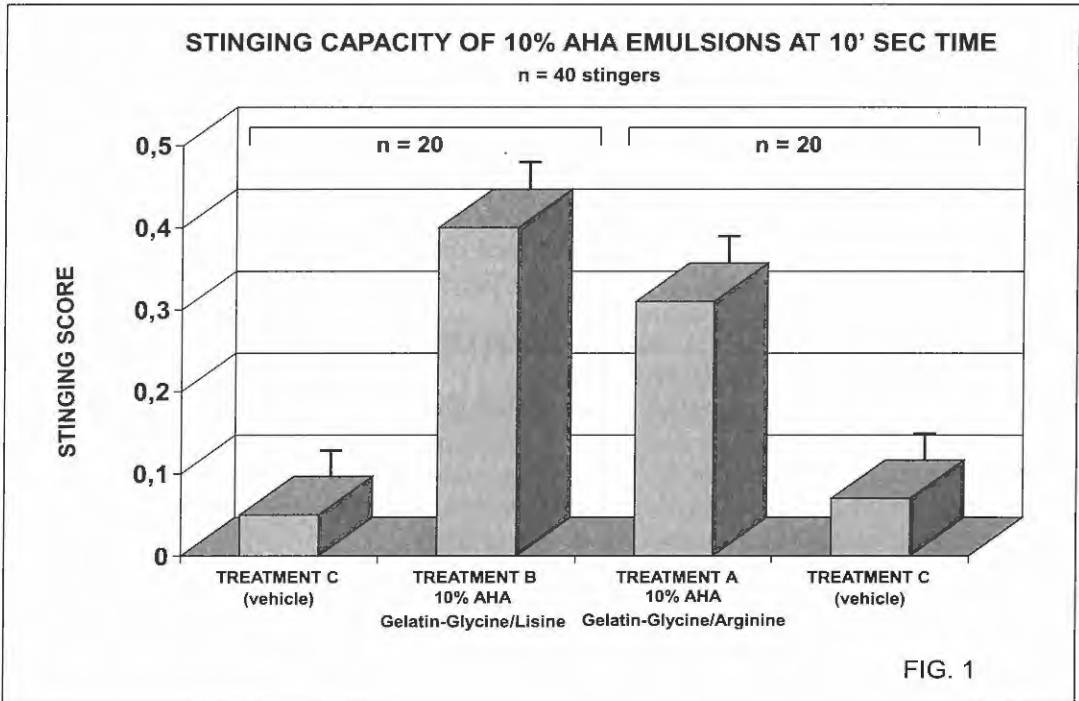
- 0 = no stinging
- 1 = slight stinging
- 2 = moderate stinging
- 3 = severe stinging

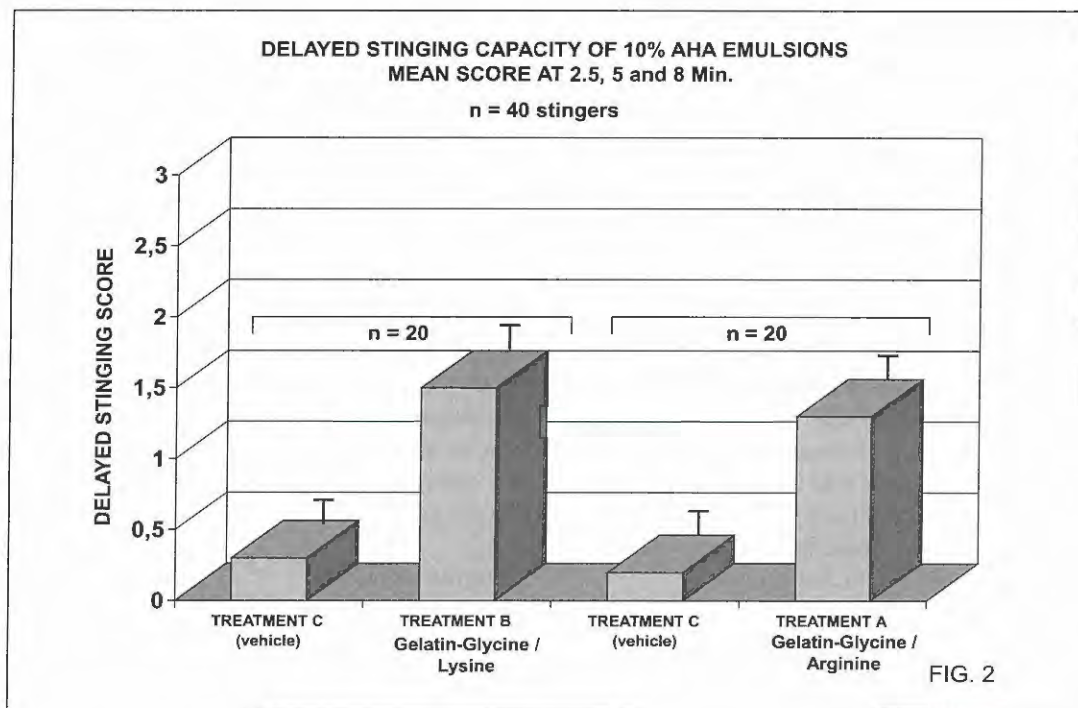
The obtained results are reported at **fig. 1**. The mean of the three readings at 2.5, 5.0 and 8.0 min was considered as "delayed stinging" score.

The obtained results are reported on **fig. 2**.

Stinging capacity

As is known, the topical use of glycolic acid and/or lactic acid based emulsions at concentrations of between 5 and 14% can give rise to transitory forms of erythema and to widespread sense





of burning. By partially neutralising these acids with the gelatin-glycine-lysine or arginine mixtures, the erythemogenous and reddening action is practically eliminated (10). This unpleasant sensation is no longer noted by the user, while the stimulant activity on cell turnover remains unaltered. To better control this in use recovery, erythema was induced by washing forearms of 3 groups of 10 volunteers women (between age 18-25) with a solution of acetone/ether for 15 minutes (day-1). The different tested emulsions (A,B and C/0,8ml each) were applied twice a day (morning/day-cream and evening/night-cream) from day zero on one arm of each group of 10 volunteers, the others, untreated arm, served as control. Immediately after the second application, were evaluated in both the arms the level of redness or skin roughness using a scale:

- 3 intense erythema and extreme skin dryness
- 2 medium intensity erythema and evident dryness

- 1 barely perceptible erythema and very little dryness

- 0 no erythema and skin with normal appearance. The recovery was carried out on the same day before the erythema was provoked (day-1), after provocation of the erythema and after 1,2 and 3 days from application of the emulsions, which were applied on day zero. The results are given in fig. 3.

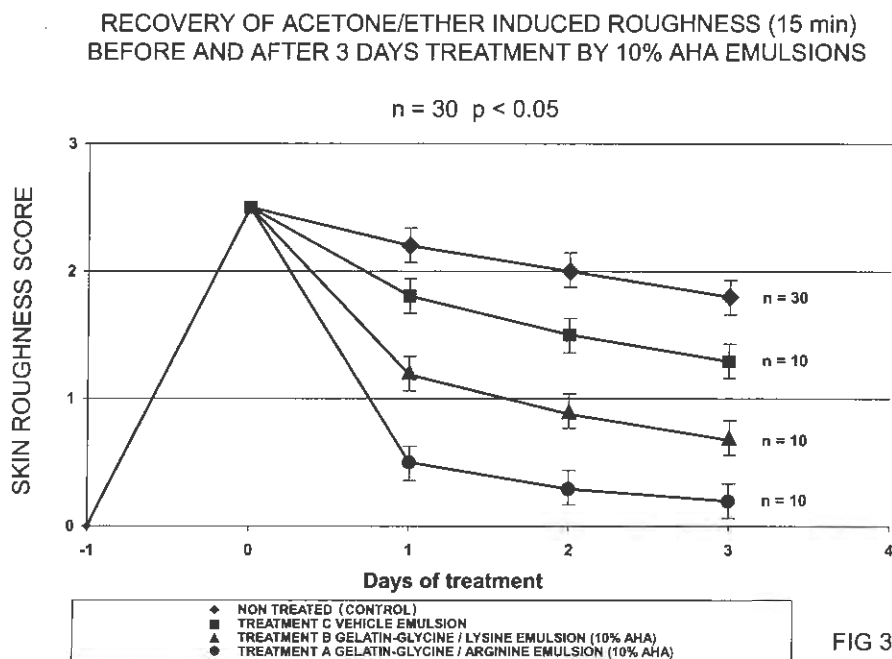
2nd STUDY

Depigmenting Activity

The depigmenting activity is often required for the treatment of some hyperpigmentary disorders such as melasma, lentigo solaris or the so called Age-Spots.

Age-Spots

To control the depigmenting activity of the studied treatment A and B in relation of the treatment D (10% glycolic acid alone), each emulsion was ap-



plied twice daily (day-cream morning and night-cream evening) for 3 months on 3 groups of 10 women (between age 65-68 and selected, from the residents of nursing home for the elderly).

The tested products were applied to the back of one hand of each group affected by hyperpigmented lentigo, (dark skin spots), the other hand served as untreated control.

Other peoples, unaffected by lentigo, served as normal control.

The intensity of the color was measured with a Minolta Chromameter CR 200, that is a light-weight and compact tristimulus color analyzer for measuring reflected object color (11).

Chromameter CR 200 provides practical numerical basis for quantifying the perceived color of the skin's surface. This method assures also good accuracy and reproducibility (measuring error < 1%).

Each parameter L, a and b related to skin colour, were measured, six times, at the beginning and at the end of the treatment period. The statistical

analysis between untreated and treated hands, showed that all the active emulsions (A,B and D) significantly lightened the age spots ($p < 0,005$). The average results obtained are given in **fig.4**. As can be clearly seen from **fig. 4**, positive results were obtained ($p < 0,005$) both using the emulsion based on 10% glycolic acid (treatment D) and using same neutralized with gelatin-glycine/lysine ($p < 0,005$) (treatment B) and gelatin-glycine/arginine ($p < 0,005$) (treatment A). However, the most noticeable depigmentation was obtained using the emulsion based on the use of gelatin-glycine/lysine and gelatin-glycine/arginine, which showed a depigmenting activity almost double that of glycolic acid alone.

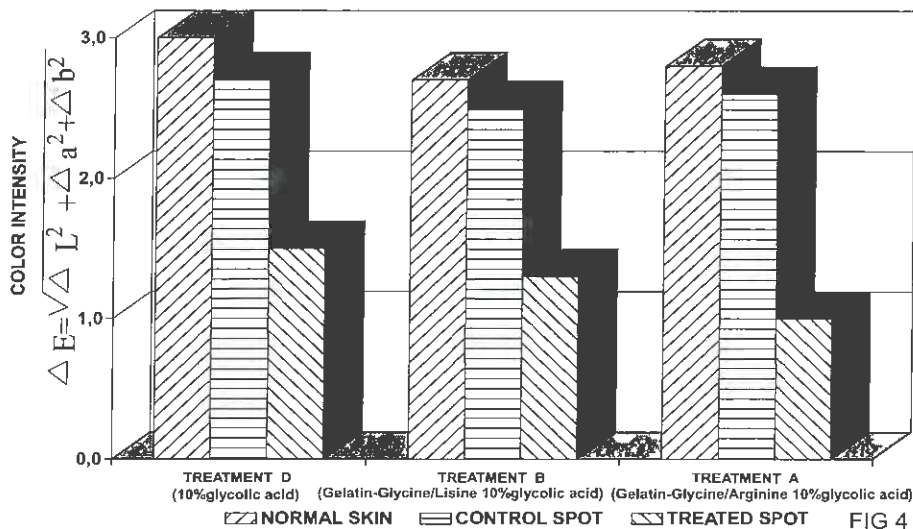
Skin Elastic Properties

The skin firmness was evaluated by the use of the Twistometer (12) after two months treatment twice a day (day cream morning and night cream evening) on 30 volunteer women (between age 65 - 68).

COMPARATIVE EFFICACY OF 10% AHA COSMETIC EMULSIONS TESTED ON THE DEPIGMENTATION OF ACTINIC LENTIGO PLAQUES ON THE HANDS AFTER TWO MONTHS OF TREATMENT

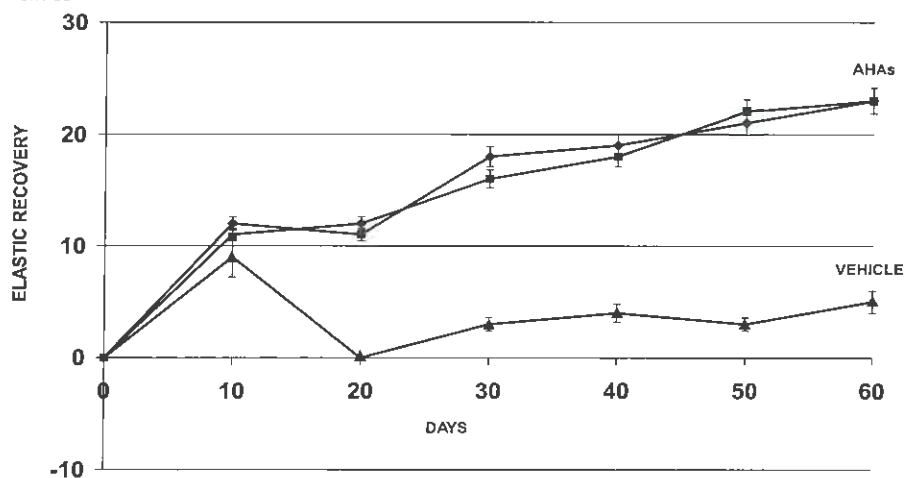
A versus B $p < 0.005$
A versus D $p < 0.005$
B versus D $p < 0.005$

n = 30 (Between age 65-68)



% $\frac{DUR}{UR} / \frac{UE}{UE}$

ELASTIC PROPERTY OF HUMAN SKIN TREATED BY 10% AHA EMULSIONS



Emulsion A (GLY-ARG) versus Emulsion B (GLY-LYS) ns
Vehicle versus Emulsion A $p < 0.001$
Vehicle versus Emulsion B $p < 0.001$

◆ TREATMENT A 10% AHA + (Gelatin Glycine-Lysine)
■ TREATMENT B 10% AHA + (Gelatin Glycine-Arginine)
▲ TREATMENT C VEHICLE

FIG. 5

The tested emulsions were applied for 60 days to one arm the other served as untreated control (only vehicle). The obtained elastic recovery controlled each 10 days is reported on **fig. 5**. The figure shows the results obtained after a continuous treatment twice a day for 60 days relative to the untreated controlateral arm in term of elastic recovery (UR/UE) ($p < 0,001$).

Measurement of skin hydroperoxides

Skin, serving as a barrier against the external attacks, is the potential target organ of environmental oxidative stress, the major cause of skin aging. The greater the amount of peroxides at skin level, the faster the ageing.

A topical treatment which neutralizes peroxides seems, thus, able to perform an antiageing activity.

The tested emulsions (1 mg each for each cm²) were applied twice a day (day cream morning and night cream evening) to one arm (forearm) of 30 volunteers women (between 65-68) the other, treated by the vehicle, served as control. Skin lipids were extracted from the skin by acetone. According to the methodology of Pugliese (13). A glass cylinder measuring 5 cm in diameter was placed on the skin and held snugly, extracting the lipids by two different aliquots of 5 ml portions of acetone.

The two added portions of acetone were dried under a nitrogen stream.

The lipid residue was emulsified with 0,2 ml of 8% sodium dodecyl sulfate, 1,5 ml of 20% acetic acid and 0,5% of thiobarbituric acid solution making up the final volume to 4 ml with water. Finally the concentration of peroxides determined as MDA precursors on supernatant extracted with 4 ml of n-butanol, was read at 531 nm.

The obtained results are reported on **fig 6**.

3rd STUDY

Measurement of skin hydration and trans epidermal water loss (TEWL)

It is known that the electrical properties of the

skin and its hydration are related to the water content of the stratum corneum (SC). SC hydration state may be detected by the capacitance method (14).

It is also known that TEWL provides an assessment of the integrity of the SC rather than its moisture content. A stratum corneum that is damaged, as happened in psoriasis, will result in an high TEWL and low hydration.

TEWL

Quantitative measurements of TEWL were performed using the 3C System DERMOTECH (15). TEWL was expressed as the amount of water evaporated per unit of surface in 1 hour gr/m²/h. The instrument probe has held perpendicular to the skin surface (forearm) and allowed to equilibrate for 20 seconds. The computerized 3C System collects up 10/15 measurements over 25 second sampling period and records the mean value automatically standardizing the environmental conditions.

The study control was made on 30 volunteers patients (15 men and 15 women) aged between 8 and 18 years and suffering from atopic dermatitis. 10 normal volunteers (5 women and 5 men) acted as controls. For this study was used the Treatment A only (gelatin-glycine-arginine) twice a day (day cream morning and night cream evening) for 30 days.

As is known, skin affected by atopic dermatitis has an high TEWL when compared with normal individuals, and low capacitance levels (skin hydration) (**fig.7**). As can be seen from **figures 7** and **8**, after 30 days of twice-a-day treatment (active A), the atopic skin gives TEWL and Capacitance values more or less the same as those found in the skin of normal individuals. The vehicle don't has the same activity.

Hydration activity

The hydration activity was controlled on a group of 30 volunteers women aged between 35 and 48 years suffering from psoriasis on restricted areas of both the forearms, at least 25 cm. apart.

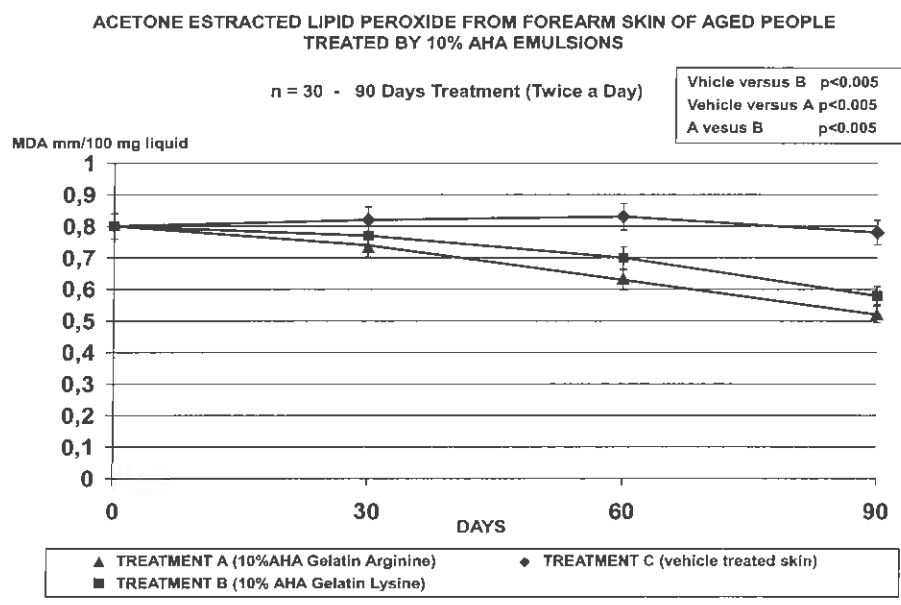


FIG. 6

TRANSEPIDERMAL WATER LOSS (g/m²h) AND CAPACITANCE (arbitrary units) OF UNTREATED ATOPIC SKIN AND UNINVOLVED CONTROL OF THE SAME REGION

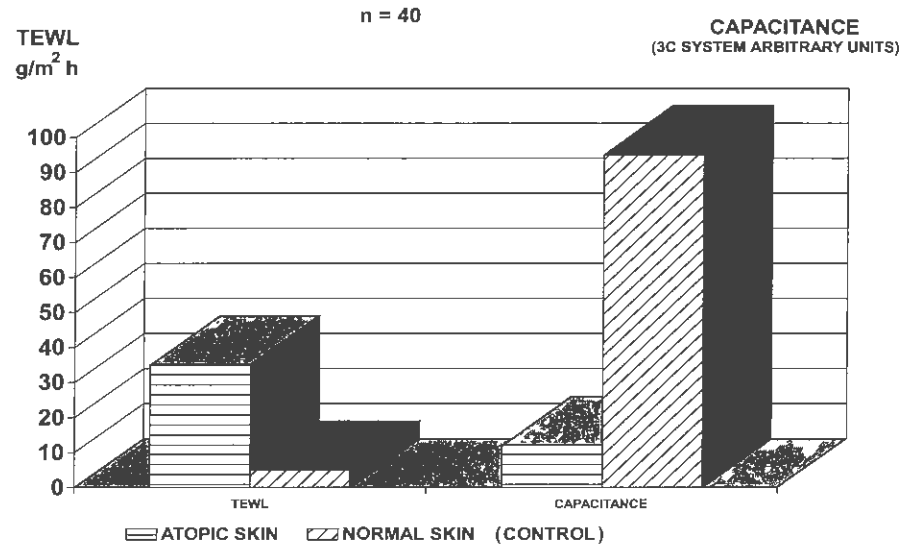
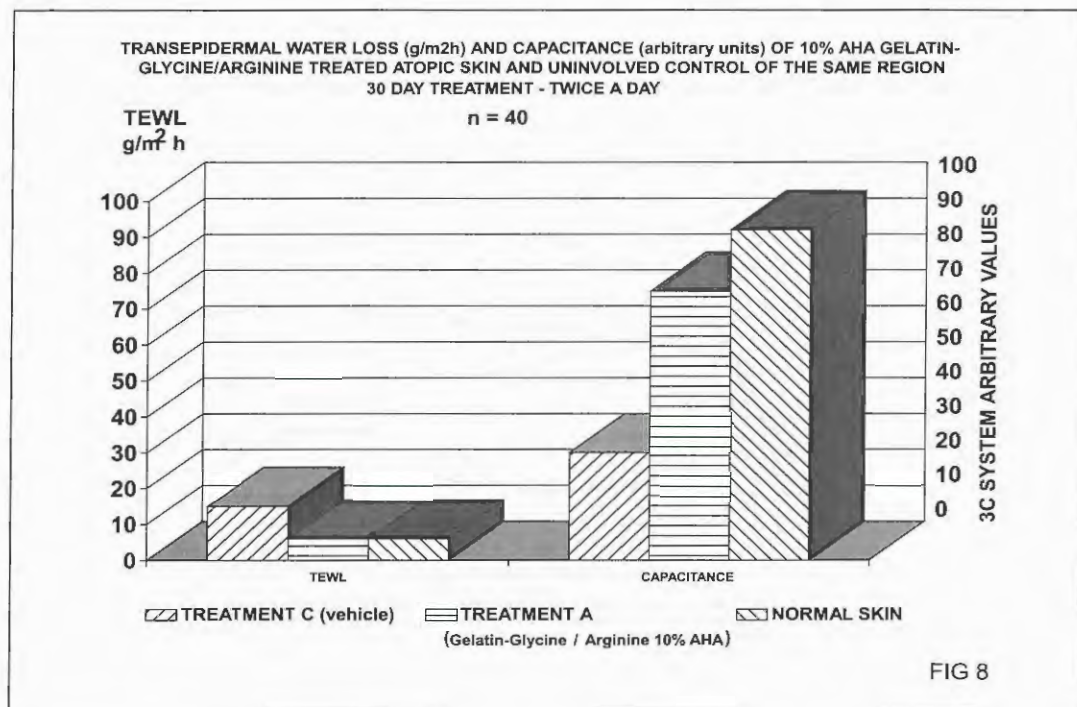


FIG 7



Experimental design

No volunteers had used other topical treatments within two weeks or systemic drugs or dietetics within 4 weeks prior to commencement of the study.

Study products were packaged in identical container (150 ml. tube) identified by study number, women number and side administered (right or left).

The experimental design used a randomized, double-blind and contralateral comparison (vehicle only).

Women were randomly divided into two groups, one of which contained 12 people, who were instructed to use the treatment A and C (right or left forearm); the other contained 13 people who were instructed to use the treatment B and C. 5 people served as untreated control.

After the forearms were washed with a non-medicated soap (MAVIGEN® SAPONE) and patted dry with a soft towel, they applied the assigned product treatment. Depending of the group, one

site on the ventral forearm of each people was treated with treatment A or B (1 ml.) twice a day (day cream morning and night cream evening) for 35 days. The other site, on the ventral forearm, was treated with treatment C.

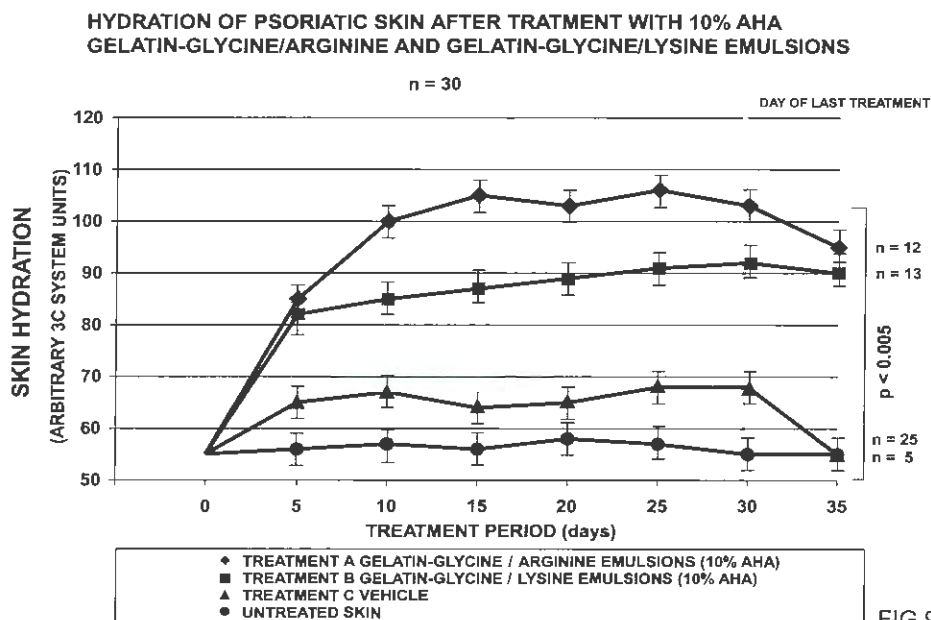
A randomized schedule was used to determinate which was used on which ventral forearm.

The average values recorded, which represent the average of five simultaneous measurements taken on the same area of the skin, are given in fig. 9. Hydration measurements were taken every five days using the 3C SYSTEM DERMOTECH (15).

4th STUDY

Consumer complaints: skin redness

A degree of transitory stinging, burning or moderate irritation is a common side effect of glycolic acid preparation especially at the beginning of the treatment (first 10/15 days). When the cosmetic formulations are buffered at the right way closer to pH 5.5, they are generally, less irritative. Mo-



reover the degree of skin irritation and skin redness seems to be strictly correlate to the buffer-compound and to the kind of vehicle used. By this last study it was recorded the stinging and redness score over the first 2 weeks of product use.

Thirthy women with normal to dry and slightly sensitive skin (between age 20-27) divided in 3 groups of 10 peoples were supplied with two AHAs containing treatments. Each treatment was coded as A,B,C or D including day and night creams. Each product was packaged in 150 ml. tube and labeled left and right, day and night, to avoid panelist confusion.

Therefore each panelist received 4 tubes, A (day and night) + C (day and night); or B (day and night) + C (day and night); or D (day and night) + C (day and night) treatments, which were randomly applied (2 mg./cm²) to the left of right side of their face twice a day (day cream morning and night cream evening).

One week before the study all subjects were re-

frained from using any kind of cosmetics products.

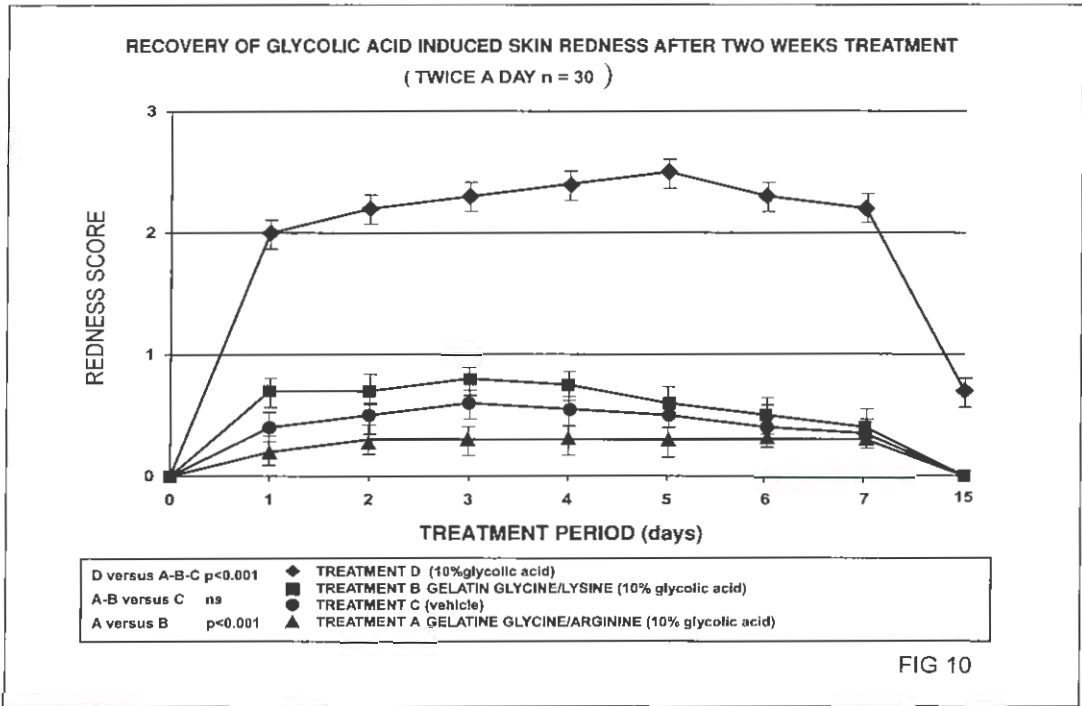
On days 0,1,2,3,4,5,6,7 and again at 15, and 7 all the subjects were controlled by a trained clinician at the Test Center in the morning (prior the day-cream application) to evaluate score redness on a 4 point scale:

- 0 no redness
- 1 slight redness
- 2 moderate redness
- 3 severe redness

The obtained results are reported in **figure 10**.

RESULTS AND COMMENTS

These first experimental data seem to show clearly that some balanced mixtures of aminoacids (gelatin-glycine), especially enriched with lysine and arginine, reduce the stinging and burning sensation which are usually a side-effect of emulsions containing glycolic acid (**Figs. 1, 2 and 10**). In fact, the emulsions containing gelatin-



glycine/lysine and specially gelatin-glycine/arginine noticeably reduce the severity and duration of the stinging effects provoked by glycolic acid (Figs. 1 and 2). Thus, the above aminoacids seem to have not only an anti-irritative activity but also a rehydrating and normalizing effect on the surface lipid film.

The skin delipidized with solvents such as acetone - a well known solvent of ceramides too - rapidly gets back to normal, especially when emulsions are added with these aminoacids (Fig. 3). It is mostly arginine that seems to speed up the hydration and the normalization of the lipids arrangement in the skin, be it healthy (Fig. 3) or affected with diseases including atopic dermatitis (Figs. 7 and 8) and psoriasis (Fig. 9). These two particular diseases are also characterized by markedly reduced ceramide-1 at the level of keratin-filled cells (17) and a greater lack of free fatty acids and cholesterol esters (18) respectively.

As we know, the molecular substitution of one li-

pid with another may alter the structure and functional properties, such as fluidity and water permeability, of the membranes in the stratum corneum. In addition, it may affect the action of non-lipid components.

Upon the re-arrangement of lipids, which are interlocked among keratin-filled cells, both the skin moisture level and TEWL (transepidermal water loss) get back to normal (Figs. 8 and 9). This re-balancing is important to keep and make the skin look younger, as shown also by the marked improvement in skin elasticity and the noticeable depigmentation obtained on hyperpigmented lentigo just after respectively 30 or 60 days continuous treatment (Figs. 4 and 5).

The reason why adding an aminoacid, such as arginine, brings about an increase of water, re-arranging the lipid enriched intercellular skin matrix is still unknown. However, it is possible to propose an hypothesis, without necessarily limiting ourselves to it. It is suggested that arginine, when added to the AHA formulations with gela-

tin/glycine, may turn into urea at skin level and enhance the skin rehydrating activity of gelatin/glycine (18-19).

In fact, urea is known to turn bonded water into free water, thus rehydrating the skin tissue and emilliorating its tone and appearance.

To sum up, we can state that buffering glycolic acid in a balanced way (10) with a mixture of aminoacids, such as gelatin-glycine, especially enriched with arginine, markedly reduces the irritating side effects of AHAs-containing emulsions (**Fig.10**) potencing their antiageing activity. Conversely, AHAs depigmenting action on age-spots (**Fig. 4**), as well as their control on free radicals (**Fig. 6**), are enhanced.

Author address:

P. Morganti, Ph.D.

Via Innocenzo XI, 41,

00165 Rome - Italy

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ABOUT CLAIMS SUBSTANTIATION FOR TOPICAL FORMULATIONS: AN OBJECTIVE APPROACH TO SKIN CARE PRODUCT'S BIOLOGICAL EFFICACY

L. Rodrigues, I. Jaco, M. Melo, R. Silva, L.M. Pereira, N. Catorze, E. Barata, H. Ribeiro and J. Morais
UCTF (Pharmaceutical Sciences and Technology Unit) - Laboratory of Experimental Physiology
Faculdade de Farmácia da Universidade de Lisboa - Av. Forças Armadas 1600 Lisboa - Portugal

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Synopsis

In the recent past years a fast growing interest in skin care products has justified major investments on their global design development, involving new formulations, new molecules and new concepts regarding their use and efficacy. Among the latter, skin cleansing products are nowadays widely used as an effective and at the same time mild way to assure proper skin detergency. These effects are, sometimes difficult to demonstrate in a scientific basis; however, recent technological developments made possible to approach these claims. Present work pretends to contribute to the definition of the "biological efficacy" concept for this range of products, through the evaluation of the most relevant cutaneous variables changes following the application of several equivalent (commercially available) skin cleansing products, to human healthy volunteers. Results showed to be reproducible in the experimental conditions chosen, leading to the confirmation of the generally accepted "mildness" quality of these products. Results also suggest that transitory epidermal changes may result from the use of formulations with extreme values of pH, and that the dynamic water balance established at skin surface may require the complementary use of other products in order to avoid an eventual desiccation effect.

Riassunto

Il crescente interesse di questi ultimi anni nei confronti dei prodotti della pelle, ha giustificato i maggiori investimenti rivolti allo sviluppo di nuove formulazioni, nuove molecole e nuove metodologie di studio sull'efficacia del loro uso. Tra i prodotti cosmetici di grande uso molte attenzioni vengono rivolte ai detergenti che debbono assicurare una profonda pulizia senza, peraltro, risultare aggressivi per la pelle. Il presente lavoro cerca di dimostrare "l'efficacia biologica" di questa categoria di prodotti attraverso la rilevazione dei cambiamenti indotti sulla pelle dei volontari dopo l'uso di alcuni detergenti in commercio. I risultati ottenuti nelle condizioni sperimentali prescelte dimostrano che è giusto ed accettabile definire i prodotti prescelti come "non aggressivi" per la pelle. I risultati ottenuti dimostrano, inoltre, le variazioni comunque indotte sia sul pH cutaneo che sulla dinamica dell'acqua, consigliano l'uso successivo di altri prodotti cosmetici necessari per evitare eventuali fenomeni di disidratazione.

Skin care products are a very important component of the R&D effort of both pharmaceutical and chemical industries, reflecting their current remarkably good acceptance not only by consumers but also by clinical dermatology among which the image of "mildness" is generally accepted, specially when confronted with other classical forms (e.g., soaps) used for skin detergency. In fact, most of the studies performed with this class of products are specially concerned with their safety profile (most often related with surfactants), failing however, to demonstrate their biological effects [3, 6-8].

The recent development of objective methodologies to assess skin most representative variables (Skin Bioengineering) allowed the establishment of new perspectives for all the areas related with such important organ. In fact, a detailed analysis on skin dynamic behaviour (physiological and/or pharmacological) objectively characterising skin's response following topical products application, is now possible, thanks to this novel technological tools. Ultimately, is now possible to rationalise and to define the "efficacy concept" for a wide range of topical products, including cosmetics [4] whose claims, from 1997 on, will have to be substantiated [9]. This implies that, concerning this particular class of products, precise rationale for methods and techniques will have to be defined in order to anticipate the relationship between the proposed instrumental measures and the relevance of the study used for claim support. Facing these entirely new perspectives, the authors tried to contribute to the biological effects definition of Skin Cleansing products, proposing an original methodology to evaluate the (acute) consequences of their application on skin surface. This procedure also intends to contribute for the development of other methodologies which will be fundamental (including for official authorities) to evaluate efficacy claims not only for cosmetics but, eventually, also applicable to a wide range of topical products.

Thirty commercially available cleansing products were selected on the basis of their label designation (Skin Cleansing product) and galenic formulation

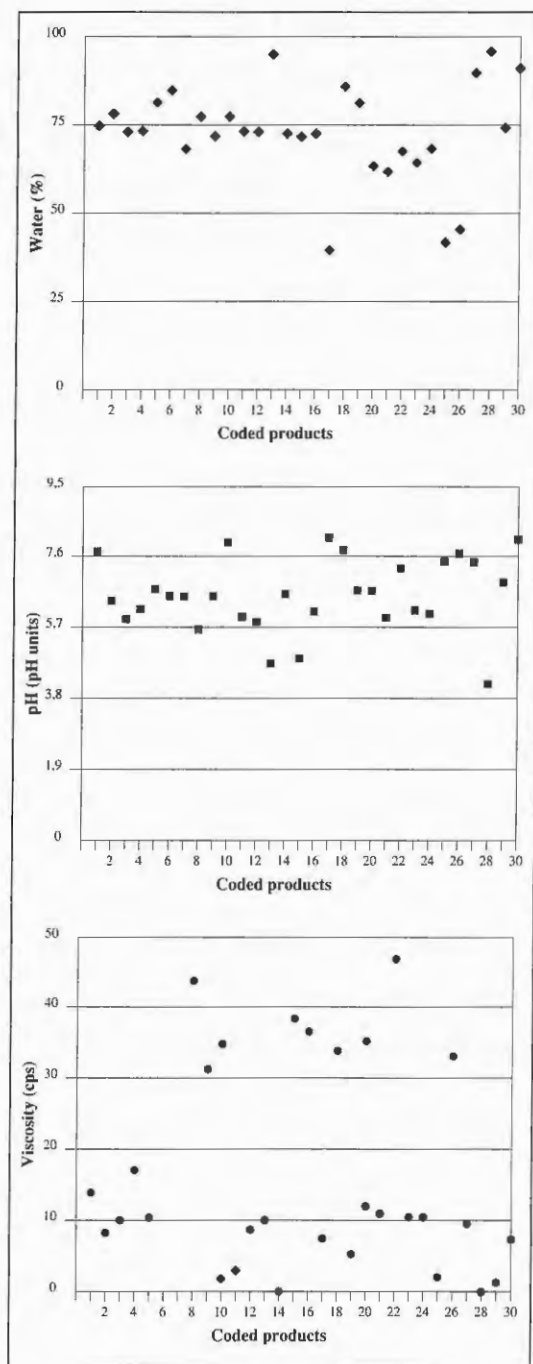


Fig. 1: Physical chemical data obtained from 30 different (coded) skin cleansing products.

(emulsions O/W). Planned as a standard study on their *Biological Efficacy Analysis*, a simple physical and chemical analysis, consisting on the determination of pH (direct potentiometry - *Metron Merisau pH-Meter E516*), Viscosity (*Brookfield LV viscosimeter*), and Water content (IV dissector - *Moisture Analyser Sartorius MA50*) was, nevertheless, performed in order to establish the formulation's proximity.

Biological (in vivo) Efficacy Analysis was carried out on 14 healthy volunteers of either sexes with ages between 19 to 23 years old (mean: $21 \pm 2,83$), chosen after pre-defined inclusion criteria appreciation. All products were applied on all volunteers.

Evaluation of skin most important variables was performed using non invasive techniques such as: Corneometry (Corneometer CM820®) as a direct measure of skin hydration; Sebumetry (Sebumeter SM810®) to evaluate total epidermal lipid content; Trans Epidermal Water Loss -TEWL (Evaporimetry - Tewameter TM210/TM215®) an indicator of skin barrier function; and Potenciometry (Skin pH-Meter PH900®) for the assessment of skin pH changes. All devices were manufactured by *Courage+Khazaka electronics, Germany*. Room temperature and humidity were fully controlled in order to implement a complete standardisation of product application and removal routines (according with the manufacturer specification) and measurement.

Lipid Removal Capacity (forehead), *Acute Epidermal Water Dynamics* and *Cutaneous pH* changes (volar forearm) were evaluated after 15min following the application and removal of the cleansing products. These results were compared with the corresponding values for each variable obtained immediately before the protocol execution (basal line values). Significance was considered based on the exclusion of the 100% value from 95% confidence intervals around the mean.

In spite of all products exhibited the same general classification on their labels, data from elementary physical-chemical analysis showed clear qualitative

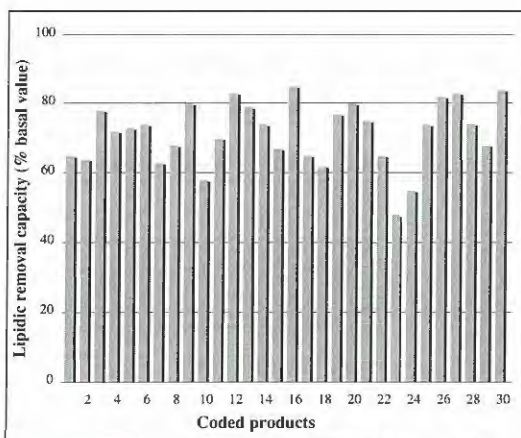
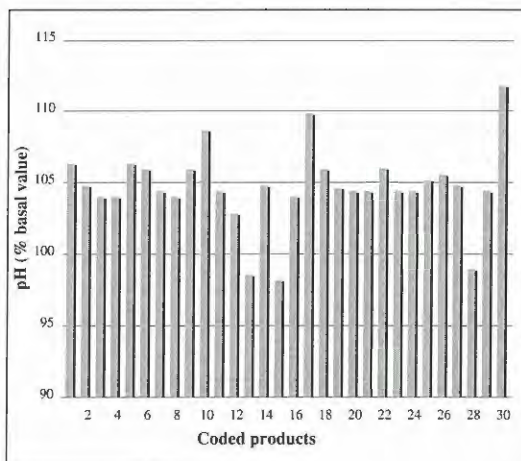


Fig. 2a: Graphic representation of Lipidic removal Capacity determined for each cleansing product;

Fig. 2b: Graphic representation of epidermal pH changes following the use of each cleansing product.

In both cases, values were obtained 15 min (reference time) after removal of each product (standardized routines). Results are expressed as a percentage variation of basal values.



and quantitative differences regarding pH, viscosity and water content (**Fig. 1**). This fact, apart from reflecting the lack of the information supplied from the manufacturer, cannot be ignored in terms of the final evaluation of each product efficacy, no matter the claim involved. Thus, fundamental question was, to test the capacity of the proposed methodology, in discriminating different levels of efficacy for each product in terms of the biological

Table 1

	Trans-epidermal Water Loss (TEWL) (%)						Epidermal Hydration (%)					
	1'			15'			1'			15'		
	Mean	SD	Sign.	Mean	SD	Sign.	Mean	SD	Sign.	Mean	SD	Sign.
Cp 1	593,8	191,7	*	160,8	35,2	n.s.	124,2	6,9	*	122,9	7,6	*
Cp 2	681,3	189,6	*	140,0	15,5	*	124,2	9,8	*	108,8	4,0	*
Cp 3	748,8	188,1	*	189,7	15,1	*	125,3	17,0	n.s.	101,3	4,2	n.s.
Cp 4	525,9	99,0	*	173,0	13,9	*	132,9	14,2	*	116,7	5,8	*
Cp 5	740,5	115,2	*	140,4	20,0	*	122,3	11,0	*	103,8	4,6	n.s.
Cp 6	770,0	117,5	*	134,7	15,9	*	117,1	7,4	*	100,8	2,4	n.s.
Cp 7	639,4	163,8	*	121,2	14,9	n.s.	126,9	8,2	*	119,9	6,4	*
Cp 8	702,8	176,2	*	127,6	13,4	*	106,7	4,7	n.s.	101,4	3,1	n.s.
Cp 9	699,5	168,3	*	158,0	21,5	*	119,3	9,2	*	105,1	4,6	n.s.
Cp 10	628,7	146,9	*	150,6	14,3	*	125,5	9,4	*	101,6	1,4	n.s.
Cp 11	603,0	93,9	*	111,4	13,6	n.s.	118,8	10,3	*	113,3	8,8	n.s.
Cp 12	419,1	157,3	*	109,0	6,9	n.s.	106,4	4,5	n.s.	101,0	1,2	n.s.
Cp 13	898,5	116,1	*	254,6	107,4	n.s.	121,2	6,6	*	110,4	4,1	*
Cp 14	541,8	95,6	*	123,6	12,8	*	120,5	10,6	*	113,2	9,6	n.s.
Cp 15	557,8	144,7	*	125,0	18,2	n.s.	115,0	8,8	n.s.	101,4	2,3	n.s.
Cp 16	419,4	76,3	*	113,1	8,7	n.s.	115,1	6,2	*	109,6	8,1	n.s.
Cp 17	328,5	74,5	*	105,8	9,9	n.s.	114,1	5,6	*	110,5	8,6	n.s.
Cp 18	697,0	147,6	*	150,8	16,5	*	128,1	8,1	*	110,4	5,2	*
Cp 19	681,3	108,1	*	127,6	13,4	*	112,3	9,0	n.s.	101,7	4,0	n.s.
Cp 20	565,4	142,1	*	118,4	10,1	*	109,9	5,0	*	108,6	2,6	*
Cp 21	524,3	121,9	*	116,7	8,7	*	111,3	4,5	*	105,1	6,0	n.s.
Cp 22	661,7	119,8	*	119,7	11,0	*	115,4	5,2	*	103,7	4,4	n.s.
Cp 23	408,1	52,7	*	112,3	6,7	*	112,8	3,8	*	110,0	4,8	*
Cp 24	425,7	58,2	*	115,1	6,1	*	113,0	3,3	*	111,5	5,4	*
Cp 25	498,0	114,0	*	114,1	8,2	n.s.	118,1	6,7	*	109,8	4,1	*
Cp 26	481,9	88,4	*	112,3	7,1	n.s.	115,8	5,9	*	109,8	4,1	n.s.
Cp 27	598,0	130,8	*	136,4	22,8	n.s.	121,4	6,5	*	105,7	7,3	n.s.
Cp 28	615,0	132,3	*	137,7	23,4	n.s.	124,7	7,7	*	99,4	6,0	n.s.
Cp 29	564,6	78,1	*	127,1	8,8	*	111,3	4,3	*	105,2	4,6	n.s.
Cp 30	564,6	123,7	*	132,1	15,5	*	123,8	6,5	*	101,5	7,2	n.s.

* = significantly n.s. = not significantly different from baseline ($\alpha = 0,05$)

Table 1: Trans-epidermal water loss (TEWL) and Corneometric (Hydration) Changes obtained after one application (and removal) of several cleansing products (Cp 1 to Cp 30). Results (from 14 healthy volunteers) were obtained at the 1st and 15th minutes, and expressed as a percent variation from basal values (see text).

assess chosen. In this view, particular care was put on the experimental development following a variance analysis, specially regarding the application and removal routines (on skin surface) and data collecting. As shown in Fig. 2, different Cleansing potencies are detected, in spite of no cleansing product, in the analysis group, has been capable of a

total removal of the forehead epidermal lipid component. In our view, these results contribute to reinforce the general mildness characteristics attributed to this class of products, specially if one admits that the process itself (application and removal) may also contribute to the epidermal penetration of some lipid fraction, as it was already descri-

bed in the literature ^[1,2,5]. Regarding skin surface pH changes induced by the use of this products, the obtained results (**Fig. 2**) allowed to demonstrate that formulations with extreme values of pH may, in fact, alter the basal value for each individual, although this effect is clearly transitory (not significant after 15min) and seeming not to affect other variables. Finally, concerning changes detected on epidermal water balance after the use of cleansing products (**Table 1**) the results suggest the existence of a variable “desiccation effect” on epidermal surface as a primary consequence of the fast evaporation of the aqueous fraction of the disrupted emulsion ^[1,4]. This results also suggest that, at least where lipids represent a major component of the epidermal hydro-lipidic film, cleansing products exhibiting a strong Lipid Removal Capacity will predictably exert a stronger effect on *Stratum corneum* desiccation and exposure, underlining the need for complementary care (e.g., moisturisers) after cleansing the skin, no matter the cutaneous situation (physiological or pathological) involved.

The proposed methodology showed to be reproducible in the present experimental conditions, allowing a clear definition and characterisation of biological effects for skin cleansing products. This methodology also shows an interesting potential value in further development since it can be used to test different biological capacities for different surfactants or detergent mixtures used in this class of formulations and, eventually, lead to development of “Efficacy Indexes” which may contribute to a better understanding and full characterisation of cosmetics and other topical products efficacy.

Corresponding Author :

Prof. Dr. Luis A.M. Rodrigues
Fac. Farmácia da Universidade de Lisboa,
1600 Lisboa PORTUGAL
Tell/Fax: +(351-1) 793 30 64

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TRANSDERMAL DRUG DELIVERY BY IONTOPHORESIS. II. TECHNIQUES AND *IN VITRO*-*IN VIVO* MODELS

Rosario Pignatello¹, Massimo Fresta¹ and Giovanni Puglisi^{1,2}

¹ Dipartimento di Scienze Farmaceutiche, Facoltà di Farmacia, Università degli Studi di Catania,
Via Andrea Doria, 6 - 95125 Catania (Italy)

² Istituto di Scienza del Farmaco, Università "G. D'Annunzio", Chieti (Italy)

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Synopsis

The recognised validity of iontophoresis in promoting the dermal or transdermal transport of biologically active compounds, mainly ionized species, to gain a systemic effect, is related to an accurately and controlled choice of materials and devices, as well as of the operative conditions used for its realization. Extensive work has been done with *in vitro* experimental models to better define the different factors which can influence the effectiveness and reliability of iontophoresis. In this paper, we took into considerations such parameters, illustrating also the *in vitro* and *in vivo* models and devices, developed during last years.

Riassunto

La iontoforesi rappresenta ormai una tecnica ampiamente considerata per la sua efficacia nel favorire la penetrazione dermica o transdermica di sostanze farmaceutiche ad azione sistemica, altrimenti difficilmente somministrabili per questa via. Comunque, la riproducibilità e l'efficienza di questa metodica è strettamente dipendente da un attento controllo di diversi parametri operativi e dalla scelta dei dispositivi più adatti alle sostanze da somministrare. In questo lavoro, a proseguimento di una precedente rivisitazione dei principi teorici sui quali la iontoforesi si basa, vengono presi in esame alcuni di questi fattori, dei quali è ben nota l'influenza sul trasporto iontoforetico dei farmaci, nonché i diversi modelli sperimentali, *in vitro* e *in vivo*, sviluppati nel corso degli ultimi anni.

Introduction

In a previous part of this review (1), we have described the theoretical considerations governing the technique of iontophoresis. It is defined as the procedure of releasing a drug through the intact skin for an intradermal or a systemic effect, by means of a suitable electric current applied on the skin itself. Transdermal delivery of drugs has a number of advantages over other routes of administration and conventional dermatological systems, in particular that one of increasing the skin penetration of ionized or charged molecules.

After the initial papers which described a number of experimental approaches for optimizing the iontophoresis as a drug delivery device, clinical and therapeutical applications have been referred by many Authors, and iontophoresis is, to date, a valid alternative to the systemic administration of many drugs and biologically active species.

Such a number of works have well evidenced the various factors, whose exact knowledge and definition can influence the effectiveness and reproducibility of this technique. However, many studies are also in progress in such a field and a continuous improvement of materials and operative conditions is expected during next years.

Thus, in this second part of our review on iontophoresis, we have described some of these factors whose effect on iontophoresis are well known; moreover, the *in vitro* and *in vivo* experimental models and devices developed during these years are also reviewed.

Experimental variables affecting iontophoresis

The efficiency of drug delivery by an iontophoretic application depends upon many physico-chemical and technical variables, apart from the same factors which regulate the skin permeation of a drug during its passive diffusion (2). Table I reports a list of factors which can affect iontophoretic transport efficiency and whose contribution is briefly discussed in the following section.

Table 1

PRINCIPAL FACTORS INFLUENCING IONTOPHORETIC TRANSPORT OF DRUGS

1. Physico-chemical properties of drugs:

- a) Charge
- b) Molecular size and weight
- c) Solubility and concentration in the donor solution
- d) Rate of ionization (also dependent on pH in the donor solution)
- e) Hydro-lipophilicity
- f) Electro-chemical stability

2. Experimental variables:

- a) Density of current applied
- b) Nature of electrodes used
- c) Duration of treatment
- d) Nature of current (constant or pulsatile)
- e) Presence of competing ions (i.e. buffer ingredients) (cfr. 15, 21, 37)

3. Physiological factors:

- a) site of application (density of appendages)
- b) individual variables (sex, age, race)
- c) Rate of hydration of skin
- d) Integrity of skin surface
- e) Utilization of permeation enhancers or delipidizing solvents

Type of iontophoretic devices and electrodes

The quality and nature of the instrument may have a great influence on the resulting iontophoretic flux, in terms of both efficiency and predictability-reproducibility. Basic systems have been reviewed by Tyle (3); in particular, they can be chosen under the light of safety, economical convenience and pa-

tient compliance considerations.

Portable 9-V battery-operated devices which can be easily transported by the patient have been realized. The electrodes are fixed by an adhesive pad or membrane at few centimeters from each other on the skin surface and a continuous delivery of the active agent is ensured while the patient can attend his common daily activity. An example of such a device is the Phoreser of Motion Control Inc. (Salt Lake City, U.S.A.) (4). A control system is of great importance to ensure that a constant current (5-50 mA) is supplied to the patient during time. In some cases, it is also possible to choose the polarity of electrodes, in order to achieve the best delivery of a cationic or anionic molecule (1). The drugs are usually placed as an aqueous solution in a refillable plastic chamber limited by a diffusion polymeric membrane, or simply absorbed on a gauze pad. In other systems, the drug-loaded patch consisted of a hydrogel matrix, fitted with a metallic wire or lamina to serve as the donor electrode. The hydrogel reservoir is usually contained in a circular plastic holder.

A pencil-shaped iontophoretic systems has been described by Groning for the transdermal administration of antihistamine agents, in the localized treatment of acute skin irritations, such as insect bites (5). Deeper informations on the *in vivo* iontophoretic delivery devices commercially produced, mainly in the U.S.A., can be found in the review work of Singh and Singh (2).

The type of electrodes can, in turn, deeply modify the transport rate of ionic drugs. Two kinds of electrodes are usually used, inert and reversible ones (6). Inert electrodes, made of platinum, tin, some stainless steels or nickel, do not participate to the electrochemical reaction and then are not consumed during it; however, they induce a bubbling of gas into the solution and a large electrolysis of water into H^+ and OH^- ions, which are responsible for the changes in the pH of the skin surface underneath the electrodes. Apart from the possible consequences for skin integrity (1), modifications in the ionization rate of drugs, and hence in their electrical mobility can result. Risks of

burns can be prevented by covering the electrode with a cellophane or plastic pad or sponge, which in the meantime avoids the direct contact with the body and possess a flexible conformation enough for adaptation to irregular skin surfaces. A further adhesive coating (e.g., medical silicon) allows a better permanence of the electrode to the site of application. To avoid pH variations during the treatment a buffered solution can be used as the drug donor and receptor solutions; however, the presence of extraneous ions in the buffer, basing on their specific conductivity (1) and charge (they can be co-ions or counter-ions with respect to the drug), could deeply influence (both by competing or assisting) the transdermal flux of the ionic species to be delivered (7).

Among reversible electrodes, silver/silver chloride ones are the most diffused. They are prepared electrochemically: for example, Oh and Guy (8) used a 3 cm silver wire (1 mm diameter) which was accurately washed and cleaned with a warmed 1 M HCl solution. After rinsing with water, the Ag wire was anodically plated with AgCl (using a platinum cathode) by placing it in 0.5 M KCl and passing a 0.1 mA current for 20 min (sensing electrodes) or 5 h (signal electrodes). Oldenburg et al. (9) prepared a cathode electrode by placing a 0.1 mm diameter Ag wire in 0.1 M HCl and passing a charge of 18-20 coulombs for 18-24 h. The redox potential for the Ag/AgCl system (1.22 V) is lower than the oxidation potential of water, thus avoiding the degradation of the latter. The occurring reactions at the cathode and anode are, respectively, the dissociation of solid silver chloride ($AgCl + e^- \rightarrow Ag + Cl^-$) and the association of chloride ions with silver ($Ag + Cl^- \rightarrow AgCl + e^-$). This kind of electrodes has a particular advantage when the drug to be iontophoresized is a hydrohalide salt, e.g., lidocaine hydrochloride (6). In solution, these salts dissociate into the drug cation and the halide counterion, thus directly providing one of the species needed for the above electrode reaction. Moreover, the product of the reaction, AgCl, is insoluble and precipitates on the anode, without generation of other ions which could compete with the drug for the

current flux. The most evident limitation to the use of Ag/AgCl electrodes, is their precipitation effect on proteins and peptides (10).

To reduce the consumption of the AgCl electrode during the work of the system, a periodically switch of the polarity between the two electrodes has been proposed (11,12): e.g., in the experiment of Su et al. (11), the patch containing the Ag electrode was initially settled as the anode while the other patch containing Ag/AgCl was the cathode. After the first 6 h and then periodically every 4 h, the polarity was reversed. This switching allows to regenerate the Ag/AgCl electrodes during the reverse cycle and to reduce the pH changes. Moreover, the drug (tetraethylammonium bromide) was delivered alternatively from both patches (the one acting as the anode at that time), thus reducing the depletion of solute from a patch.

Influence of pH

The degree of ionization of a weak electrolyte is known to depend upon pH. Thereby, changes of pH of the fluid under the releasing electrode have been indicated as responsible for significant variations in iontophoretic transport of some drugs: e.g., lignocaine (13), sulfamidics (14), verapamil (15), thyrotropin-releasing hormone (16), and other solutes (17). As pH determines the charge of the drug ions, it can modify the fractional contribution of these species to the total current, namely their transport number (1). Noteworthy, the pH range of solutions that can be applied to the skin is usually between 3 and 8, since at outer values skin damage and irritation may compare (18). This implies that for most acidic drugs, with low pK_a values, which are in a neutral form or carry negative charge(s) at most experimental pHs, the iontophoretic flux will be quite negligible. Of course, for peptides, proteins and other substances which show an isoelectric point, the pH of the vehicle or in the donor solution is of extremely great importance, since it will determine the charge of solutes.

The pH variations at the releasing electrode can

also induce a rapid depletion of the drug from the donor compartment (11, 12). Sanderson et al. (19) have paid their attention on the possibility of limiting pH variations in the subcutaneous layer during iontophoresis. Their objective was that to optimize the delivery of cationic drugs which request a treatment for extended periods of time (also for 24 hs), so that to minimize the effects (i.e., skin trauma) of the large amount of current required to delivery the drug.

Four approaches have then been described to control skin pH changes near to the electrodes: i) to use a salt of the (cationic) drug with a weak acid (e.g., acetate or succinate), instead of the hydrochloride. This would result in a reduction of pH lowering at skin surface under the donor electrode; ii) to change the drug with a charged form of it (e.g., a quaternary ammonium salt for the corresponding free base); iii) to increase the concentration of the drug in the donor solution or, even better, to enhance its solubility by choosing a suitable solvent (e.g., by replacing aqueous buffer solutions with an ethanol-water mixture); iv) finally, these investigators suggested to reduce the permselectivity of the skin to cations by reducing the presence of anions in the receptor compartment, i.e., by using a polyacrylic acid solution instead of Cl⁻-containing saline, or by a skin pretreatment with a surfactant, like sodium lauryl sulfate, which neutralizes the fixed positive charges on the skin surface and enhances the iontophoretic flux of cationic species. Apart from the practical utility of such approaches, the Authors demonstrated the possibility of a real enhancement of drug delivery, by reducing the amount of current required and thus its side effects on the skin (19).

Duration and intensity of the current applied

From Faraday's law, it is clear that in an electrolytic solution the amount of electricity conducted depends on the strength of the current applied and the duration of its passage:

$$M_D = \frac{i_D}{Z_D} \frac{t}{F}$$

where M_D is the moles of the ionic drug and Z_D is its valence (number of charge per drug molecule), t is the time (in seconds), i_D is the current carried by the drug, and F is a proportionality factor (Faraday's constant).

A linear relationship between the flux of many drugs and current density has been reported under different experimental conditions, both for cathodal and anodal iontophoresis (16, 20-33). For example, studies on a model peptide (TRH) (23) showed that flux is proportional to the applied electric field and this linearity was observed both at pH 4 and 8, that is, either when the drug was in a neutral or charged state in the donor solution. Such a behaviour can obviously be related to the appearance of an electroosmotic flow from the anode to the cathode, involved in the transdermal transport of large molecules with a different charge than positive one (1).

The positive effect of increasing applied current densities on drug flux, is mainly related to the parallel reduction of skin resistance (34). However, for application to human, the used current can not be extremely high, and an optimal intensity between 40 μ A and 10 mA, a limit which was found to not cause perceptible physical discomfort or pain (35), has been individuated; it corresponds to a maximum current density of 500 μ A/cm² (36) [a current of one ampere (A) corresponds to one coulomb per mole (C/mol)]. At higher densities or/and for exposure times longer than 10-30 min, an irreversible modification of skin conductivity could begin, as a consequence of serious histological alterations of the skin itself (1).

Chemical structure of solutes

Yoshida and Roberts (37) have extensively described the relationships existing between the molecular size and structure of many drugs and their iontophoretic behaviour. In general, it has been de-

monstrated that the logarithm of iontophoretic flux is inversely proportional to solute molecular weight (27, 38, 39). Two different theories have been advocated to explain such results: the 'free volume' theory predicts that a molecule diffuses only when a hole or free volume into which it can move is present near to it (Fig. 1a) (40); this approach better fits with the assumption that solutes move through the lipid domains of the SC. According to that theory, the enhancement of iontophoretic flux sometimes observed by using a penetration "enhancer" (e.g., ethanol, DMSO, DMA) (37) can be explained by considering that these solvents dissolve some lipids from the stratum corneum matrix, thus allowing more "void" volumes to become available for the diffusion of solutes through the epidermis.

The second model is based on the hypothesis that when a compound has to pass through skin pores, dimensions of these latter lead to the exclusion of molecules with too large sizes (Fig. 1b) (41). Scheuplein (42) suggested that in human skin the radii of outer and inner sweat ducts are 7 and 2.35

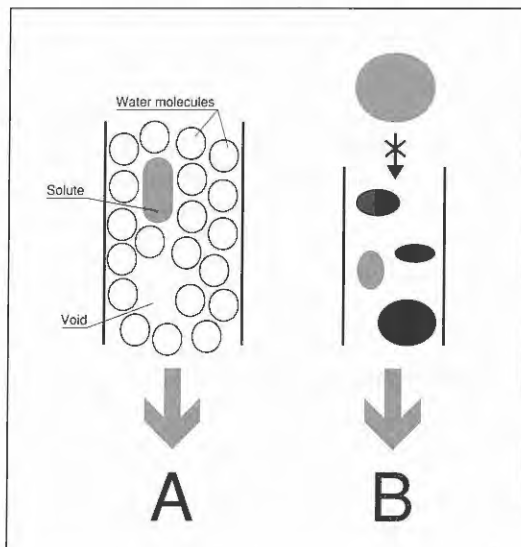


Fig. 1: Schematic representation of the "free volume" model (A) (40) and "size exclusion" theory (B) (41) to explain the influence of solute molecule size on its transport through skin pores (adapted from ref. 37)

μm , respectively, and those of surface opening of sweat ducts and hair follicles of about $35\ \mu\text{m}$. Lower values ($0.675\text{--}2.7\ \text{nm}$) were reported for hairless mouse skin pores (43). Moreover, the movement of the solute within skin pores is also affected by its friction with pore walls. However, at present none of the two models seems to completely explain the experimental data collected.

Oldenburg et al. (9) have studied the effects of composition of some oligonucleotides on their iontophoretic transport efficiency. Working with 15-mer homopolymers, they concluded that the base composition can strongly influence the flux of compounds; in particular, bases that can form more hydrogen bonds, as pyrimidine ones, may better interact with skin structures and therefore slow the transdermal migration of oligomers.

Drug concentration

Increased concentrations of the ionic drug to be released in the donor electrode generally are related to an enhancement of drug flux across the skin. Findings in such direction have been reported for benzoates (21), verapamil (22), morphine hydrochloride (24), and many other inorganic salts and ionic drugs (28).

However, the positive effect of such a parameter on a drug iontophoretic flux is limited by the solubility of the drug itself in the donor medium (water or buffer solution), along with the possible variation of solubility linked to the eventually occurring pH variations during iontophoresis (see above).

In vitro models

The simplest apparatus for *in vitro* iontophoresis studies is illustrated in Fig. 2. It basically consists of a source of electric power (a battery) connected to a couple of electrodes immersed in the donor and receptor compartments; they acts as the anode and the cathode and operates by transforming the electron current to ionic current. The donor reservoir (i.e., skin surface) is an aqueous (or buffered)

solution of the ionic drug; however, a drug-containing gel formulation can be used, e.g., when the experiment has to be carried out on a living animal. The receptor compartment commonly is an isotonic solution of sodium chloride (normal saline), which simulates the dermis. The driving system maintains the current field constant during the operating time.

A diffusion membrane, either natural (human or animal) or artificial (cellophane or cellulose) separates the two compartments. Human skin samples generally derive from plastic surgery or from cadavers (44). For permeation studies, either full skin (excised or dermatomed) or its isolated layers are employed. Intact epidermis is obtained by bathing the skin in water at 60°C for 1–2 min, then peeling the epidermis from the other tissues, while full thickness skin was prepared by removal of the subcutaneous fat. Stripped skin can be obtained by removing the stratum corneum by repeated stripping (25–30 times) with an adhesive tape. Finally, isolated stratum corneum can be prepared by one of the known methods, as the heat separation described by Kligman and Cristophers (45).

However, the uneasy availability of good samples, generally makes the animal models more suitable for basic studies, both from hairless (mouse, nude rat, guinea pig) and furry animals (mouse, rat, rhesus monkey) (46). Hairless mouse skin (47) or shed snake skin [the latter completely lacking of any appendageal structure (47, 48)], have been particularly proposed as models for human skin in the *in vitro* assessment of transdermal iontophoretic drug delivery.

A comparison of the electrokinetic behaviour affecting the iontophoretic transport of drugs between excised human skin and hairless mouse skin has been reported by Pikal (49). While many of the flux characteristics [e.g., the different effects of cathodal or anodal delivery of neutral or charged compounds (1) as well as skin damage effects] after iontophoresis are similar between the two skin models, however human skin showed a worse correlation between the calculated electroosmotic flow and the permeability (flux) measured for neu-

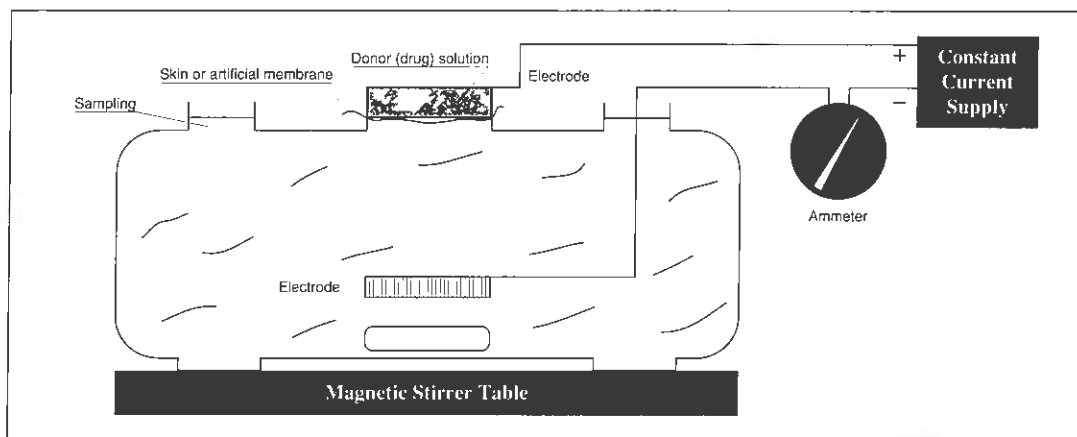


Fig. 2: A basic experimental device for *in vitro* iontophoretic investigations.

tral species, in particular when low current densities are used.

More recently, Hager et al. (50) have described a cultured skin system, obtained from cultures of human cells and matrix normally present in the skin and known as "living skin equivalent" (LES). It well simulates the human skin, showing differentiated stratum corneum, epidermis and dermis layers, and lack the typical skin appendages (hair follicles, glands), thus allowing to better define the permeability properties of the skin. Studies on LSE indicated that such a membrane is an accurate model for *in vitro* experiments on iontophoretic transport through the skin and permeation results of different model drugs are in good agreement with those obtained by using guinea pig skin (50).

When skin was used as the diffusion membrane, the stratum corneum is obviously oriented toward the donor compartment. Normally, subcutaneous fat layer was removed before experiments: in fact, it is generally not involved in permeation and absorption phenomena through the skin, since it is placed under the blood circulation within the dermis.

To study the particular influence of iontophoresis on cutaneous penetration of model or drug molecules, modified skin or isolated skin layers are often used. For example, isolated epidermis can be obtained by placing the full skin in water at 60°C

for about 90 sec (51) and then peeling off the epidermis. In the model of "stripped skin", stratum corneum was removed by means of an adhesive tape applied on the skin; when these samples are used, they are mounted vertically in the diffusion cell with the dermal side bathing the receptor fluid. This latter can be constituted by an isotonic buffer, like pH 7.4 phosphate-buffered saline.

Masada et al. (52) have described a four-electrode system for a two-chamber diffusion cell. In such a system, a couple of reference electrodes are placed close to the two sides of the diffusion membrane, while a constant voltage difference is maintained between them by a potentiostat. Another couple of counter electrodes are placed into the donor and receiver-containing cell, respectively, in order to maintain the required current flow through the cell itself. The main advantage of such a system, is the possibility to know and measure simultaneously the voltage difference and the current across the membrane.

To develop a cathodal iontophoresis (i.e., the release of negatively charged species) (1), the cathode electrode was placed in the donor compartment (an aqueous solution of the drug to be administered) and the anode in the receiver compartment. Their position is reversed in the case of an anodal iontophoresis (with cationic drugs or ions).

Generally, a constant current was applied across

the skin sample (with a current density between 100 and 500 $\mu\text{A}/\text{cm}^2$) for the wished period of time (up to 12 h for permeation studies). Samples from the receptor compartment were withdrawn periodically and analysed by a suitable method (HPLC, UV, radiolabeling, etc.).

Comparison of *in vivo* studies with *in vitro* findings

The main aim of all the iontophoretic experimental models, is to predict as better as possible the results which will be obtained when *in vivo* delivery is performed.

Different Authors have reported interesting observations of very good correlations between the *in vivo* iontophoretic behaviour of drugs and findings drawn by experimental models. Sage and Riviere (6) found that the human skin flap is the best model in predicting the *in vivo* delivery of lidocaine. Riviere et al. (53) used an isolated perfused porcine skin flap (IPPSF) model, which correlated well with the *in vivo* iontophoretic permeation of arbutamine. Such a model of skin has the advantage of possessing anatomical and functional properties similar to the viable skin, like a microcirculation system (54).

Metoclopramide (7) and hydromorphone (55) were also studied *in vivo*. Interestingly, results indicated that a better *in vitro* simulation of the *in vivo* flux of many charged drugs can be obtained by using a hypotonic (0.08-0.09 M) NaCl solution, instead of a normal saline (0.15 M) in the receiver compartment, i.e., the conditions probably existing in the epidermis (7).

Conclusions

Studies on the current-assisted delivery of drugs and other compounds to the body through the intact skin, would obviously need to use the ultimate model: humans *in vivo*. In the practice, investigators have described many interesting experimental models, both using synthetic (e.g., permselective, ion-change resins, etc.) or natural skin (human or

animal) as the diffusion membranes. As well, ever more efficient *in vitro* devices have been realized to gain a better prediction of the behaviour of a drug under *in vivo* iontophoresis.

However, both types of studies need a deep knowledge and description of the different operative and formulative variables which can influence the results. Apart from the intrinsic properties of the drug to be delivered, many factors can be suitably standardized to obtain an effective and reproducible output of the treatment.

Correspondence: Prof. Giovanni Puglisi
Dipartimento di Scienze Farmaceutiche
Città Universitaria,
Viale A. Doria, 6 - 95125 Catania (Italy)
Tel.: +39 95 222 215 - Fax: +39 95 222 239

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THE SCOPE OF MINERAL OIL IN PERSONAL CARE PRODUCTS AND ITS ROLE IN COSMETIC FORMULATION

David S. Morrison,* Jürgen Schmidt[°] and Ricardo Paulli[§]

* Penreco Division of Pennzoil Products Co., The Woodlands, Texas 77380, USA

[°] DEA Mineraloel AG, 22297 Hamburg, Germany

[§] Giuseppe Cambiaghi SpA, 20131 Milano, Italy

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Synopsis

White mineral oil is a commonly used ingredient in nearly all types of personal care products, from emulsions to anhydrous cosmetics. It provides many benefits to personal care formulations, including moisturization and emolliency, and is safe and effective for topical use. Interestingly, the purification process of mineral oil permits it to be considered "natural" when compared with the purification of other natural ingredients.

Riassunto

Ultima classe di principi attivi di uso cosmetico, gli alfaidrossiacidi sono al centro di molte ricerche e di molte attese. Ne viene descritta la composizione chimica, il probabile meccanismo d'azione e le varie possibilità di impiego nella Dermatologia Cosmetologica.

Introduction

White mineral oil has long been recognized as an important part of many cosmetic formulations. Its unique feel, ready availability, and low cost have enabled it to be used in a variety of health and beauty aid products, from bath oils to hair care products, to skin care cosmetics. Today, I will review the role of mineral oil in cosmetic preparations, with emphasis on its beneficial characteristics.

The mineral oil used in personal care (white mineral oil) is a highly purified material obtained from the refining of crude oil. It consists of a complex mixture of straight- and branched-chain saturated hydrocarbons and cyclic saturated hydrocarbons. The concentrations of these constituents, as well as their molecular weights, determine the physical characteristics of the oil, such as viscosity, boiling range, and carbon number distribution.

Before discussing the applications of mineral oil, I would first like to give a little background on the processing and purity of white mineral oil and where this material fits relative to the current trend of "natural" cosmetics.

Processing, purity and nature

While the source of mineral oil (crude oil) often leads to criticism of its use, one must remember that the great majority of consumer products used worldwide, from plastic bottles and ink pens to automobile tires, telephones, and fabrics are prepared from petrochemicals. The white mineral oil used in cosmetic products is essentially extracted and purified from the crude oil mixture, not unlike the extraction and purification of vegetable oils. Whereas vegetable oils are often obtained from solid materials, white mineral oil is obtained from a liquid source. The purification of mineral oil involves distillation, hydrogenation, and extraction. What remains is a hydrocarbon liquid of sufficient purity which enables it to be topically applied to the skin of an infant with no dilution by other ingredients. The purity of white mineral oil also is

evident from its allowed use in the United States as an over-the-counter orally administered laxative. Needless to say, its taste leaves something to be desired. White mineral oil is a pharmacopeia-recognized ingredient, and it also should be noted that, unlike some plant-derived oils, the consistency of mineral oil does not vary from season to season or from year to year.

The purification of white mineral oil also relates to the "natural movement" which has been gaining more and more prominence within cosmetics during the past several years. While the focus on natural goods has been evident in several other industries for many years, only recently has such a high level of concern been seen in the personal care industry. The popularity of The Body Shop and similar stores is evidence of the focus on natural products. Many cosmetic product manufacturers stress the natural aspect of their products, even when the products are distributed by others.

Often, the debate between natural and synthetic arises within the cosmetic community, with the general feeling that "natural" products must be better since they have not been adulterated by chemical processing. For example, such a debate was presented at a 1993 Cosmetic, Toiletry, and Fragrance Association meeting in the United States, between Dante Rutstrom of Eastman Chemical Company and Alban Muller of Alban Muller International. The natural issue also is being cited in many journals and trade magazines. An article in the January 1993 issue of *Cosmetic Dermatology* addressed what was called the misperception of natural cosmetics.¹ The October/November 1994 issue of *Cosmetics & Toiletries Manufacturers & Suppliers* contained an article on consumers and the "natural" labels in skin care products.² And the list goes on and on.

In the midst of these emotionally-charged discussions, few people have been able to decide where mineral oil belongs. How is "natural" defined? Some people insist that it means that no animal products have been used or that no animal testing has been done. But this really doesn't address what is natural. Pharmaceuticals which are 100% synthetic

contain no animal products, but no one would consider them “natural”. Some people imply that natural can only mean plant-derived, but if this is true, then naturally-occurring inorganic materials such as talc, titanium dioxide, and mica are relegated to the “synthetic” category.

While it is likely that no definitive answer exists to the question, “What is natural?”, a reasonable definition of “natural” would be one which describes a material as being essentially unchanged from its naturally occurring state. That is, a natural material is one whose bulk chemical structure has not been significantly changed through synthetic chemical processes. Using this definition, many products which are undoubtedly natural (such as titanium dioxide) are retained in the “natural” category.

Since no one has yet invented the infamous Philosopher’s Stone of alchemical lore to permit transmutation of lead into gold, an assumption which most everyone would agree is valid is that gold is natural. Interestingly, when gold ore is removed from the earth, it often contains as little as 0.04 ounces of gold per ton of ore. A separation and refining process is needed to make the gold fit for use, yet the resulting gold is not synthetic -- it is still natural.

Similarly, the white mineral oil used in cosmetics is only a small fraction of the entire crude oil. A separation and refining process is needed to make the white mineral oil suitable for its intended use, and again, since the mineral oil has not been synthesized from other ingredients, it is indeed considered natural.

How does this apply to cosmetic formulation? Often a bias exists for incorporating natural materials in a cosmetic product, or for using only ingredients which are known to be present in human skin. The utilization of ceramides in skin creams is one example of adding compounds present in skin to a particular cosmetic formulation. Professor Stig Friberg of Clarkson University reported in 1994 that straight-chain hydrocarbons like those found in mineral oil are naturally-occurring materials in a variety of living organisms.³ These hydrocarbons

have been detected in red ants, in shark livers, and in pig livers. Plants also produce hydrocarbons, with up to 27% being found in the cuticular waxes of plant leaves. The human spleen forms straight-chain hydrocarbons at up to 6% in certain instances.

The types of hydrocarbons which are found in both plants and animals indicate that they are produced *in vivo*. Hydrocarbons also are naturally present in human stratum corneum, which is comprised of many types of lipids, with hydrocarbons making up about 3 to 4%. Thus, the use of mineral oil in skin care cosmetics is another example of incorporating natural materials, especially those which occur naturally in healthy skin.

Mineral Oil Applications in Cosmetics

The types of cosmetics in which mineral oil is found are almost as numerous as the cosmetic products which are marketed today. White mineral oil finds use in all areas of personal care, even in the most unexpected applications.

We all are aware of its incorporation in general skin care cosmetics, where mineral oil is used at levels ranging from less than 1% to almost 100%. This is true for baby products, such as baby creams, lotions, diaper rash ointments, and baby oils. Hand and body care cosmetics also include mineral oil at a wide variety of percentages.

Hair care products, especially ethnic products such as pomades, brilliantines, and relaxers, typically contain high levels of mineral oil. However, it may be surprising to note that white mineral oil is occasionally formulated into conditioners and shampoos as well, albeit at much lower levels. Makeup products, including pressed powders, mascara, eyeliner, and foundations, all can contain significant amounts of mineral oil, even up to 60%. Eye makeup remover often contains very high levels of mineral oil, or it may even be essentially 100% white mineral oil. This very useful hydrocarbon material can be found in shaving creams and lotions at up to 50%, as well as in the non-stinging

emulsion-type after shave lotions.

While shampoos and conditioners were mentioned previously, other bath products also incorporate mineral oil. Likely the most frequent use of white mineral oil in bath products is in bath oils, which often contain close to 100% mineral oil. Interestingly enough, some soaps even contain mineral oil, but only in very small amounts.

Other topical applications of mineral oils include lip products, such as lip balm and lipstick. Due to the reason for applying the lip product, mineral oil typically is found at higher concentrations in lip balms than in lipsticks. Epilation waxes and depilatory products also may contain mineral oil at moderate levels. Depending on the method of application, deodorants and antiperspirants may include white mineral oil, generally from 1 to 50%.

Lastly, white mineral oil is used in sun products, from the very high concentrations found in tanning oils (nearly 100% mineral oil), to the more moderate amounts normally used in sunscreens, sunblocks, and after sun products (about 1 to 40%).

Moisturization

Probably the most common function that mineral oil plays in cosmetics is one of moisturization. While mineral oil adds other important properties to a cosmetic formulation, moisturizing the skin is usually its primary purpose, with its other functions being strictly secondary.

Excluding color cosmetics and what we'll define as "specialized" products such as antiperspirants, deodorants, and sunscreens, moisturization, for most people, is the main reason why they purchase a general skin care cosmetic product. The need for a product to combat dry skin and its associated itchiness, redness, and irritation leads the typical consumer to look for an emulsion cream or lotion which has a good skinfeel. It has been known for decades that efforts to overcome dry skin usually involve applying a moisture barrier to the skin surface which will retard the loss of water from the stratum corneum through evaporation. The reduction of this transepidermal water loss is what is

meant by the term "moisturization", even though no water is actually added to the skin. Kligman has defined a moisturizer as "a topically applied substance or product that overcomes the signs and symptoms of dry skin."⁴

Bath oils are the simplest and one of the most effective methods for treating general skin dryness. In 1961 and 1963, Taylor reported his attempts to quantify the deposition of mineral oil onto human skin, and determined that bath oils based on mineral oil adhere to skin better than similar products formulated with vegetable oils.^{5,6} The importance and efficacy of mineral oil as a moisturizer is clearly evident when it is used in this manner. In fact, because of this effectiveness in reducing water loss from skin and because of its economy, availability, and safety, white mineral oil is likely the most widely used oil in bath oil products.

A large portion of the cosmetic market is controlled by leave-on skin care products which are typically emulsions. Depending on the purpose of the product and the regional culture to which it is being marketed, the emulsions will be either water-in-oil or oil-in-water. The oil-in-water emulsions are generally preferred because of their dry, non-oily feel upon application to the skin. Water-in-oil emulsions are more difficult to stabilize, and low-viscosity water-in-oil emulsions frequently prove troublesome to prepare. Despite these drawbacks, water-in-oil emulsions are sometimes favored for sunscreens due to their resistance to washoff, and in dermatological creams and lotions since a higher percentage of oil-phase, barrier-forming ingredients are usually present in the formulation. In the case of oil-in-water emulsions, the water evaporates not long after application, and the actual "moisturizing" is performed by the remaining oil-phase ingredients.

Contrary to common belief, esters and silicones are not very good moisturizers, especially when compared to mineral oil. When mineral oil is an ingredient in the oil phase of an emulsion, the moisturizing benefits come from the mineral oil, not from any other oil phase ingredients like esters or silicones. In 1993, Frömder and Lippold showed that,

after application, mineral oil reduces *in vitro* transepidermal water loss to a significantly greater extent than silicone and certain esters which are commonly used in skin care cosmetics.⁷ The esters evaluated were caprylic/capric triglyceride, dibutyl sebacate, and cetearyl octanoate. The silicone was dimethicone with a viscosity of 100 cSt. Mineral oil reduced transepidermal water loss to 86% of the original state, whereas the other ingredients lowered it to only 91-98% of the value prior to lipid application.

In another 1993 article, Strüßmann and coworkers at Akzo verified the low water vapor permeability of mineral oil relative to 14 esters, thus revealing mineral oil's moisturizing properties.⁸ These selected esters included isopropyl myristate, isopropyl palmitate, octyl palmitate, and oleyl oleate. The water vapor permeability of oleyl oleate was 4 times higher than that for mineral oil, and isopropyl myristate allowed a moisture penetration *ten times* higher than mineral oil.

While these studies were performed on pure ingredients, Blanken and coworkers reported in the journal *Contact Dermatitis* that emulsions based on mineral oil reduce skin vapor loss much better than emulsions containing linoleic acid-based oils.⁹ In fact, the higher the content of linoleic acid in the emulsion, the greater the skin vapor loss. It was stated that, for the mineral oil-containing emulsion, the reduction of skin vapor loss probably occurs with a concomitant increase in the hydration state of the stratum corneum, again showing that mineral oil acts as a "moisturizer" to the skin.

These results indicate what consumers have long known: that mineral oil is one of the best moisturizers available, and probably the most popular one in the world. In the United States, many of the top-selling skin care products in the low-priced market contain mineral oil as a moisture barrier, and a top-selling product in the high-priced market also contains mineral oil as the primary moisture barrier. Not only is mineral oil one of the world's most common moisturizers (that is, an emulsion's primary barrier ingredient), it is also one of the most commonly used emollients.

Emolliency

Emolliency is a very difficult concept to describe. It is related to other skinfeel terms and seems to affect moisturization. Emolliency can be described as the overall skinfeel of a cosmetic product as it is spread onto the skin, from initial application through the entire rub-in process. It is related to moisturization to the degree that soft, supple skin is evidence of a well-hydrated stratum corneum. A good emollient will confer a smooth, pleasant feel to the skin, both initially and for a period of time after application. Some scientists relate emolliency so closely to moisturization that emollients have been described as bland, fatty substances that render skin softer and more pliable.

Many skinfeel characteristics of a cosmetic product have been used in attempts to quantify (or at least estimate) emolliency. Such variables include slip, texture, spreadability, absorption time, stickiness, smoothness, friction, and oiliness. Evaluation of mineral oil alone gives predictable skinfeel characteristics. For example, it has very low stickiness and excellent slip. Its spreadability is high, but so is its oiliness. It has low friction, high absorption time, and good smoothness. Mineral oil is used very often as an emollient in many cosmetic products, not just skin care formulas, because it has many desirable skinfeel properties and reducing its drawbacks is not a difficult task. As mentioned before, cost, safety, and availability also play a role in a scientist's choice of ingredients. These factors are no less important when it comes to decisions regarding emollients.

An interesting feature of mineral oil is the relation between its spreadability and its moisturizing abilities. Materials with low surface tensions are substances which have high spreadability. However, these ingredients normally provide poor moisture barriers on skin. Examples of these substances are isopropyl myristate, caprylic/capric triglyceride, and octyl palmitate. Typically, oil-phase ingredients which produce good moisture barriers are heavy, waxy materials which spread poorly. White mineral oil strikes a nice balance between spreadability and moisturization which is not common

in esters or other lipophilic materials. Its spreadability is similar to many esters used in cosmetics, but its moisturizing properties are unsurpassed by other hydrophobic liquids. Additionally, mineral oil can be obtained in a variety of viscosities, so its spreadability can be tailored to the cosmetic being formulated while retaining the benefits of moisturization.

While no one ingredient is ideal for every application, mineral oil is often used as a primary building block for cosmetic skin care emulsion formulations due to the pleasant feel it leaves on the skin. Its natural oiliness, which provides moisturization, is easily minimized or eliminated by incorporation of the mineral oil in a well-designed emulsion, without affecting its moisture barrier advantages. When added to an emulsion, mineral oil also enhances the product's smoothness, lowers its friction during application, and can reduce the stickiness of certain formulations.

Slip, Shine and Safety

As mentioned earlier, white mineral oil is a useful ingredient for adding "slip" to cosmetic products. Very often, a certain formula containing desired ingredients may be too tacky on the skin, or drag during application. Several ingredients exist which add slip, with silicones being some of the more well known ones. However, mineral oil can add the necessary characteristic of lowered friction at a fraction of the cost of silicones. Its oiliness and natural lubricating properties are the very qualities which are needed in order to add "slip" to a cosmetic formula.

White mineral oil is often used as part of cleansing creams, primarily as the lipophilic agent which carries away dirt and oils from the skin's surface. In this application, slip is very important to give the consumer a proper skinfeel during the cleansing process. A soft, moisturized-feeling skin is desired after using cleansing creams. Tautness and dryness are not desired when using these products, so mineral oil is the ideal ingredient for such use. It also is used to carry ingredients toward the skin in

many nonprescription topical pharmaceutical ointments. Again, low friction (that is, "slip") during use of the product is desired in order to provide good skinfeel and ease of application.

The "slipperiness" of white mineral oil enhances its spreadability as well. When used in hair dressings, mineral oil reduces friction during application. The same is true for anhydrous products such as tanning oils and baby oils. The ease of application of the cosmetic product (its slip) is one reason why white mineral oil is often used in these products.

Quite often, consumers of hair dressings, in particular ethnic consumers, want a long-lasting shine in their hair. Mineral oil has long been a commonly-used ingredient in ethnic hair dressings for many reasons. Moisturization and slip have been mentioned, but shine also is important. Of course, the prevailing fashions determine how much shine is desired, but very few, if any, other cosmetic ingredients can provide long-lasting shine along with moisturization and slip to a hair care product.

The safety of white mineral oil is often called into question, particularly of late. However, in topical use, the safety of mineral oil is quite clear. During the last 50 years, millions of people have safely used mineral oil in topical products. In fact, a 1994 white paper published in the U.S. by the CTFA stated that "topical use of white mineral oils does not represent a local or systemic toxicity risk to humans."

White mineral oil has been tested and shown to be noncomedogenic in both the rabbit ear assay,¹⁰⁻¹² a common method for determining comedogenicity, and in humans¹³ (the true test of comedogenicity). It has been recommended as a moisturizer for acne-prone skin,¹⁰ and has been reported as being nonacnegenic.¹³ In fact, attendees of an American Academy of Dermatology Invitational Symposium on Comedogenicity concluded that "neither the consumer nor the physician can assess whether the formulation will be acnegenic by simple inspection of the product or by examining the list of ingredients. Furthermore, the product's physical characteristics, such as oiliness or viscosity, are not in

themselves predictors of an acnegenic response.”¹³ Mineral oil also has found widespread use as a carrier for anhydrous ingredients and products in human patch tests, which also attests to its safety. The structure of the molecules in mineral oil also play a role in its safety in cosmetic formulations. Thermal decomposition of the product rates as a concern during cosmetic formulation and preparation. A more obvious safety concern is poor preservation and subsequent contamination of the product by microorganisms while in use by the consumer. The inertness of white mineral oil allows cosmetics containing this material to be formulated with a minimum of preservatives. Due to the lack of unsaturation in its hydrocarbon constituents, mineral oil is quite stable and very resistant to thermal and oxidative degradation. In addition, the lack of heteroatoms in mineral oil makes it less supportive of bacterial growth than more reactive species such as synthetic esters and vegetable oils. One final note about the safety of mineral oil should be mentioned. Baby oil, consisting of mineral oil and less than 0.02 percent fragrance, has been used as an extremely safe and effective agent for removing hot bitumen tar from human skin, including the face.¹⁴ Other removal agents which are used, such as acetone, alcohol, and kerosene, are highly toxic in large quantities and act harshly on the injured skin. Removal of bitumen with these agents is laborious and time-consuming, often taking up to 48 hours in some cases. In one example of using baby oil, a worker had boiling bitumen tar splatter on his face, forearm, and hand, for a total of 4 percent of total body surface area. Baby oil was used to remove the bitumen by applying it to the bitumen surface. Once dissolved, it was washed with soap and water, all within an hour and a half. The patient was discharged just 24 hours after admission.

Conclusion

White mineral oil has been shown to be a highly effective material for adding moisturization and other beneficial characteristics to skin when used

in cosmetic products. Its low cost and safety are important, particularly when today's consumer is looking for a good value in personal care products. Every type of skin care emulsion, from cleansing creams to lotions to sunscreens, can use mineral oil, and its use in anhydrous liquid cosmetic products such as baby oils is unrivaled. White mineral oil has been used successfully for decades and likely will be used for many years to come, as more cosmetic scientists rediscover the benefits it provides.

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TECHNIQUES OF SKIN CORRECTION USING BOVINE COLLAGEN: IS IT POSSIBLE UNDER ANALGESIA?

G. Sito* MD, L. Sorrentino MD

* ASL NA5. Department of Surgery, Naples.

* II University of Naples, Department of Human Anatomy.

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Synopsis

Authors split up the means to improve skin ageing damages into "surface" and "filling" techniques. Among the former they focus on glycolic acid peeling along with related indications and action mechanism; among the latter they analyze bovine collagen expounding its physical, chemical and biological characteristics as well as its action mechanism, indications and infiltration techniques.

They propose the use of a topic anaesthetic in cream form, consisting in a mixing of lidocaine and prilocaine so as to perform collagen implanting in absolute analgesia. Related characteristics and range of applications are also described.

Finally, the authors set out the "Protocollo Sito" which provides for the contemporary use of bovine collagen and glycolic acid peeling in progressive steps. Both substances are able to stimulate endogen collagen synthesis and, according to the authors, their effects may be combined and strengthened by this procedure. The initial hypothesis seems to be validated by the histological and clinical results of the testing in progress.

Riassunto

Gli autori suddividono i mezzi per migliorare i danni prodotti dall'invecchiamento cutaneo in tecniche di "superficie" e tecniche di "riempimento". Prendono quindi brevemente in esame tra le prime, il peeling con acido glicolico, le sue indicazioni ed il meccanismo d'azione; tra le seconde il collagene bovino purificato esponendone le sue caratteristiche fisiche chimiche, biologiche, il meccanismo d'azione, le indicazioni, le tecniche d'infiltrazione. Propongono l'utilizzo di un'anestetico da contatto in crema, costituito da una miscela di lidocaina e prilocaina, per effettuare gli impianti di collagene in assoluta analgesia. Sono prese in esame le sue caratteristiche e gli altri possibili e svariati campi di utilizzazioni. Infine gli Autori espongono il "Protocollo Sito" che prevede l'utilizzazione contemporanea in steps successivi, di collagene ed acido glicolico. Ciò determinerebbe secondo gli Autori, un potenziamento degli effetti delle due sostanze, che stimolano entrambe la sintesi di collagene endogeno. I risultati istologici e clinici dello studio in corso per verificare l'efficacia di tale protocollo, sembrano avvalorare tale ipotesi iniziale.

It is a well-known fact that skin-ageing can be subdivided into three categories: chemical, extracellular and intracellular ageing.

Ageing involves changes in the epidermis and dermis which can be explained as changes in the thickness and orientation of the bundles of collagen and elastic fibres, atrophy of the dermis due to a reduction in the number of fibroblasts, blood vessels and mastocytes, and a resulting flattening of the dermo-epidermal junction. Changes to the melanocytes are also observed (1,2).

Clinically, there is a loss of skin elasticity, an increase in dryness, discoloration, sagging and wrinkling. The authors split the various techniques used to improve the damage induced by photoaging and/or other skin pathologies into two main categories: surface treatment techniques and filling techniques. These take advantage of the numerous substances available at present - one of which is bovine collagen which is the most common and relatively easy to manage.

This substance is extracted from the dermis of highly-selected bovine strains, it is biocompatible and only marginally immunogenic.

Nevertheless as it is a heterogeneous protein, it is necessary to perform a tolerance test. This is done by injecting 0.1 ml Zyderm intradermally in the inner region of one forearm. Hypersensitivity reactions which may be observed include rash, swelling, hardness, local pain, with or without itching. These signs may appear either within hours of the injection or up to 72 hours post-injection (70%). Systemic hypersensitivity is extremely rare.

The patient must be kept under control for a period of four weeks; if at the end of this period, the intradermal reaction is still negative, the operator can proceed with the implant.

30% of the positive reactions normally appear during the four-week observation period (3-6). In exceptional cases, allergic phenomena have been observed even if the test has resulted negative (0.6%). In the event of dubious results and in those subjects with a history of allergy, it is always advisable to repeat the test on the other forearm after a further two weeks. (3-9).



Fig. 1: Sprague Dawley Rat, on the right a collagen implant only and on the left a collagen implant plus glycolic acid.

A positive reaction after the first and/or second test is an absolute contraindication to collagen implants as is a history of multiple severe allergies, hypersensitivity to suture materials or haemostatic swabs, autoimmune diseases (10,11). Collagen implants are also not advisable in the event of inflammations such as acne or other skin diseases and infections.

The first type of collagen, Zyderm, has been on the market since 1981. Zyderm II, Zyplast and Zyderm Fine Line were subsequently added to the range. Zyplast differs in that there are interchain bonds obtained through glutaraldehyde treatment. This structure gives the molecule greater stability and resistance to collagenase; as a result, the implant lasts longer with a lower immunogenic reaction. This product is mainly used for correcting scarring caused by acne, chicken-pox or similar



Fig. 2: EMLA with occlusive gressing.

atrophy of the dermis, filling of the naso-mental and frontal wrinkles (7,8,12-17).

The needles used to inject the collagen are 30G or 32G for the above mentioned regions i.e. they are very fine. Nevertheless, they may be the root of anxiety and discomfort for the patient.

This can be avoided by applying a 1:1 eutectic mixture of lidocaine and prilocaine (EMLA) to the treatment area. This creamy emulsion anaesthetises the surface and does not affect the normal anatomical relationships in the implantation area, a common occurrence with normal local anaesthetics.

Trials relative to the preparation of an anaesthetic with these properties have been underway since 1957, the year that Monash demonstrated the topical effect on skin of some anaesthetics; however, none of these preparations was of clinical value (18). The mixture, for example, based on ametho-

caine and dimethylsulphoxide (DMSO) was effectively anaesthetic but also brought about a severe toxic reaction (19). This was the main problem - often due to the high concentration of the anaesthetic substance used. The ideal formulation, on the other hand, should be efficacious with a lower concentration of the active base and a lower affinity for the vehicle compared to the keratin strata. Overall, hydrophilic formulations are considered best (20).

In 1981, Broberg and Evers discovered that a 1:1 ration of lidocaine and prilocaine created a eutectic mixture where two solids interacted producing a phase change from solid to liquid but no chemical change.

Such a eutectic mixture was then produced as an oil/water emulsion (21). It was observed that the efficacy, the depth and the duration of the anaes-

Table 1

**Indications for EMLA Paediatrics
and paediatric surgery**
**Superficial surgery of the skin
and the mucosa**
Anaesthesiology

Vein puncture
Venous catheterism
Pre-anaesthesia
Oncology and haemodialysis
Day-hospital surgery

Plastic surgery and Dermatology

Removal of moles, verrucas, keratosis
Skin biopsies
Skin auto-grafting
Dermo-abrasion (peeling)
Laser treatments

esthesia induced by EMLA (Eutectic Mixture Local Anaesthetic) had regional variations. The onset of the analgesic effect was faster on the back and in decreasing order, on the forehead, cheek and back of the hand (22), the latter having a thicker epidermis.

The duration of the analgesic effect is inversely proportional to the density of the blood vessel network, least on the forehead, and in decreasing order the cheeks, the back and the hand (23). The duration of total blockage to sensitivity is, nevertheless, on average 120-140 minutes, comparable to that observed after eight minutes of intradermal infiltration time of EMLA. In general, one hour is recommended for unbroken skin and 15 minutes for the mucosa. The average duration of analgesia ranges from 1-3 hours in the former case and about 30 minutes in the latter for the same reasons as mentioned earlier relative to the greater/lesser epidermal thickness (absent in the mucosa) and the difference in the degree of vascularisation (20,21). The application of EMLA can be extended to up to four hours but the efficacy drops markedly after

three hours. This is due to the fact that the micelles of EMLA in contact with the skin begin to lose some of their anesthetic properties (24). In this case, the cream should be applied using a suitable occlusive dressing and in the event of prolonged applications, the residual EMLA should be massaged into the skin in order to distribute the substance better and to bring the remaining active micelles into contact with the skin (20,21). The onset of anaesthesia is faster on the mucosa. The mean plasma concentration of lidocaine and prilocaine is well-below the toxic threshold - which lies at about 6,000 mg/ml.

Undesired side effects are rare; however, the following may occur:

a) localised vasomotor effects

- localised pallor
- rash
- swelling

b) methaemoglobinemia

The vasomotor effects can be explained through the vasoconstrictor effects of low concentration lidocaine and prilocaine (pallor), and the vasodilator effects of higher concentrations (rash). The rash is

temporary and is due to an accumulation of the anaesthetic in the keratin layers which increases the concentration in the dermis (20,21,25).

Contraindications are:

- hypersensitivity to any starch-like local anaesthetic;
- congenital or idiopathic methaemoglobinemia;
- atopic dermatitis;
- psoriasis. (20)

Considering the ductility and ease of handling of EMLA, it is easy to see that it is viable in a wide range of applications (Tab I) (20,21).

Implant techniques

The quality of the results obviously depends on the accuracy of the technique, and on how suitable it is for the type of defect to be corrected.

Zyderm and Zyderm II infiltrations are made at deep papillary dermis level. The first time it is ne-

cessary to overcorrect the defect, as after 24 hours the liquid in excess is absorbed, and after one or two weeks, the injected collagen decreases. Instead, Zyplast is normally injected in the reticular dermis, that is at the junction between the dermis and the subcutaneous tissue. No overcorrections are needed (8,13).

In the subsequent 6 to 18 months, touch-ups are needed in order to maintain the level of correction desired. The highest amount of collagen that can be injected yearly is 30 ml as for Zyderm, 15 ml as for Zyderm II and 30 ml as for Zyplast (26-30). The treatment site must be thoroughly cleansed, preferably with ether, and disinfected. It is also advisable to use a dermatographic pencil to draw the lines for injection.

The needle must penetrate at a 30 to 60 degree angle into the skin's surface with the bevel facing downwards (26-30).

There are six basic techniques:

- a) serial puncture technique
- b) tunnelling technique
- c) deep layering technique
- d) overlapping techniques
- e) Paris Lip technique
- f) Fine Line technique.

a) Serial puncture technique

The line to be treated must be held tightly between two fingers in order to make the skin smoother and the collagen injection easier. The implant is realized through multiple surface punctures made only few millimeters far from one another and ring-shaped, i.e. similar to the olympic circles. The injected area must be introduced evenly and at the useful place the index finger and the thumb of the controlateral hand so as to create a barrier and better define the limits or funnel the material while injecting (7).

b) Tunnelling technique

The treatment site is stretched with two fingers to make the area smoother. The entire needle is introduced at subcutaneous level along the line. A slow tunnelling operation is now performed

without removing the needle. After 2 or 3 tunnelling operations, the collagen is slowly injected while withdrawing the needle. The treatment area will show the typical blanch. Tunnelling can be painful for the patient, but the relatively slight red-dening is inferior to the previous technique.

c) Deep layering technique

The treatment site must be held between two fingers to better highlight the borders of the area to be injected. The needle must be introduced under the skin, with its bevel facing downwards. It has to slowly penetrate for a few millimeters - deeper than in the other techniques.

As a matter of fact, this method is used mainly for Zyplast implants.

The collagen injection takes place while pulling out the needle, without any tunnelling operations. Given the greater depth, no blanch is visible, but only whit. The following injections are performed likewise, at the same depth and crossing each other in order to obtain an even surface. In the end, it is advisable to massage the area slightly to blend the material into the surrounding skin.

d) Overlapping techniques

When it is necessary to simultaneously inject Zyderm and Zyplast, the serial puncture technique and the deep layering technique can be used together, performing one on top of the other.

e) Paris Lip technique

This technique was conceived by Thierry Besins in 1991 and is used to fill lips with Zyplast. Collagen is introduced through multiple injections starting from the lateral third of the vermilion border of the upper lip and moving towards the center, both on the right and on the left. "Cupid's bow" is then filled in order to create a V-shaped arch right above the vermilion border. The third phase consists of elevating the crest of the lip by injecting collagen from the end of the vermilion border to the columella. The fourth and last phase consists of filling the border of the lower lip starting from the lateral third towards the center.

f) Fine Line technique

This technique is employed exclusively to correct the finest lines surrounding eyes and lips. The treatment site is pulled, as usual, between two fingers. The needle is introduced parallel to the length of the line at a depth of 2 or 3 millimeters, i.e. just under the surface.

Zyderm Fine Line is then injected while withdrawing the needle.

Tolerability profiles

Just after the implant, the patient can develop reactions such as slight reddening, edema, pruritus. In spite of a negative response to the test, hypersensitivity reactions can take place in approximately 1 - 1.5 % of the patients; they consist of localized reactions (erythema, swelling and induration of the treatment site) and/or systemic reactions (skin rash, arthralgia, pruritus, dyspnea, fever).

These reactions are not related to the number of treatments carried out, nor to the dosages used. In most cases, they disappear spontaneously after 4-6 months and do not require a specific therapy.

Zyplast turned out to be less immunogenic than Zyderm (31,32).

Long term results

Zyplast tends to remain longer in situ. Focal areas of Zyplast implants can be detected, at histological level, up to 9 months afterwards, whereas as early as 3 months later there are no more traces of Zyderm left (15-33-35).

Depth histological studies have definitely ascertained that collagen implants stimulate the synthesis of new collagen in the host tissue - which is higher for Zyplast (15-33-35). A remarkable inflammatory reaction - more intense than for Zyderm - was actually observed at histological level. Fibroblasts migrate into the implant and colonize it within about 60 days, producing new collagen. After 9 months, the local areas of implant present neovascularization and complete replacement by new collagen (15-33-35). Also glycolic acid brings

about these effects, causing an inflammatory response and stimulating fibroblasts to synthesize and deposit new collagen, elastic fibres and glycosaminoglycans (36-38).

On the basis of these remarks, the authors decided to evaluate the efficacy of the combined use of collagen and glycolic acid. So, they developed the "Protocollo Sito" and studied its efficacy both at clinical level with accurately selected patients, and at laboratory level with female Sprague Dawley Rats. The preliminary results obtained until now are extremely positive, as they are confirming the initial hypothesis.

Author address:

Dr. Giuseppe Sito

Via Cavallerizza, 14 - 80121 Naples, Italy.

Telephone (+ 39) 81 402042

Fax (+ 39) 81 412168

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IV. INTERNATIONAL DERMATOLOGY SYMPOSION BERLIN



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FIRST ANNOUNCEMENT

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Docent Dr. Ch. C. Zouboulis

Scientific Secretariat:

Department of Dermatology - University Medical Center Benjamin Franklin
The Free University of Berlin - Hindenburgdamm 20, D-12200 Berlin - Germany
Tel. (49) 30 - 8445 2808 - Fax (49) 30 - 8445 4262



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IN-COSMETICS Conference 1997

“MODERN CHALLENGES TO THE COSMETIC FORMULATION”

In cooperation with :

**Colipa (The European Cosmetic, Toiletry and Perfumery Association),
ISCD (International Society of Cosmetic Dermatology)
IASC (International Aloe Science Council)**

Sponsored by SÖFW Journal

The 1997 IN-COSMETICS Conference in Düsseldorf, 5-7 May promises to be the highlight of the cosmetic year.

DAY 1. The Colipa speakers will concentrate on the challenges of cosmetic regulations. They will discuss the work of SCAAT, Colipa's steering committee on Alternatives to Animal Testing. Also the reality of ingredient labelling in the EU will be highlighted. What are the facts about BSE and Cosmetics? If you want to know May 5 in Düsseldorf will show. New sunscreens regulations and the role of Colipa's cosmetic ingredient Committee round out this most interesting day. In a poster session Colipa will also introduce its inventory CD.

Simoultaneously the IASC will hold its scientific workshop on Aloe vera. "What quality standards exist?", "How can Aloe successfully improve formulations etc.", "What is the efficacy of Aloe vera and how can it be tested?". For all who are interested in this unique raw material the IASC work shop offers many interesting features.

DAY 2 of the IN-COSMETICS Conference 1997 is the ISCD Day. The ISCD is a multidisciplinary association of dermatologists, pharmacologists, cosmetic biologists and chemists. Founded in 1986 the goal of ISCD is to encourage a more continuous and stable exchange between the medical community, dermatologists, and cosmetic chemists, pharmacologists, physiologists, toxicologists and experts of all other disciplines related to Cosmetic Dermatology. It provides a forum for the exchange of ideas and methodologies pertinent to the related disciplines and Cosmetic Dermatology.

The themes of the ISCD Day are:

**The Dossier - Quality & Safety Aspects
Scientific Backgrounds
and
Evaluation of cosmetic formulations**

Experimental and dermatological approaches

Scientific topics sponsored by ISCD are the following:

- **Basic requirements**
- **Uv Filters as skin protectors**
- **Hair growth**
- **Allergic reactions to cosmetics**
- **Natural products**
- **Environmental impacts**
- **Activity evaluation of raw materials**
- **Activity evaluation of finished products**
- **Cosmetic approaches in pigmentary disorders**
- **Alternatives to animal experiments.**

DAY 3 is devoted to "Green actives for cosmetics" and "Modern formulation concepts". Leading Research & Development specialists explain the latest developments in new raw materials and formulation concepts.

The IN-COSMETICS Conference 1997 is a must for all involved in cosmetic, pharmacologic and dermatologic science. Some of the most important issues of the industry are discussed. With a visit you will be able to converse with leading scientists and your individual questions and problems could be answered. At the same time a visit of the IN-COSMETICS Exhibition in Düsseldorf gives you the unparalleled opportunity to see and speak to leading manufacturers and suppliers of raw materials and ingredients.

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In close cooperation with IN-COSMETICS



International Society of
Cosmetic Dermatology

THE I.S.C.D. DAY Düsseldorf - 6 May 1997

*President: Prof. Dr. Rodolfo Paoletti,
President of European Federation of Pharmacologists (EPHAR)*

FIRST ANNOUNCEMENT

THE DOSSIER - Quality & Safety Aspects Scientific Backgrounds

Chairs: P. Morganti, C.E. Orfanos

Lecturers:

Prof. Dr. Mercedes **DE SOLA** (Belgium); Prof. Dr. Hans **SCHAEFER** (France);
Prof. Dr. Nicola **LOPRIENO** (Italy)

EVALUATION OF COSMETIC FORMULATION - Experimental and Dermatological Approaches -

Chairs: B. Giannotti, C.E. Jacobson, F. Kemper, H. Schaefer

Lecturers:

Dr. Jochen **SPENGLER** (Germany); Prof. Dr. Helmut **IPPEN** (Germany);
Prof. Dr. Constantin E. **ORFANOS** (Germany);
Prof. Dr. Pierfrancesco **MORGANTI** (Italy); Prof. Dr. Fritz H. **KEMPER** (Germany);
Prof. Luis **RODRIGUES** (Portugal); Prof. Coleman **JACOBSON** and Prof. Brodie **JAMES** (USA).

CALL FOR POSTERS

Organizing secretariat:

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I.S.C.D. Day

President: Prof. Dr. Rodolfo Paoletti

THE DOSSIER - Quality & Safety Aspects Scientific Backgrounds

Chairs: P. Morganti, C.E. Orfanos

- 8,30 Prof. Dr. Rodolfo PAOLETTI, *Italy*
Introductory remarks
- 9,00 Prof. Dr. Mercedes DE SOLA, *EU Brussels*
Scientific demand of the Dossier - VI Amendment
- 9,20 Prof. Dr. Hans SCHAEFER, *France*
Skin barrier
- 9,40 Prof. Dr. Nicola LOPRIENO, *Italy*
Alternatives to Animal Experiments
- 10,00 - 10,30 *Coffee Break*

EVALUATION OF COSMETIC FORMULATION - Experimental and Dermatological Approaches -

Chairs: C.E. Jacobson, F. Kemper

- 10,30 Dr. Jochen SPENGLER, *Germany*
Basic requirements
- 10,50 Prof. Dr. Helmut IPPEN, *Germany*
UV Filters as skin protectors
- 11,10 Prof. Dr. Benvenuto GIANNOTTI, *Italy*
Cosmetic approaches in pigmentary disorders

11,30 Prof. Dr. Constantine E. KOUSKOUKIS, *Greece*
Allergic reactions to cosmetics

11,50 - 13,00 *Lunch*

Chairs: B. Giannotti, H. Schaefer

13,00 Prof. Dr. Constantin E. ORFANOS, *Germany*
Hair growth

13,20 Prof. Dr. Pierfrancesco MORGANTI, *Italy*
Natural products

13,40 Prof. Dr. Fritz H. KEMPER, *Germany*
Enviromental impacts

14,00 Prof. Luis RODRIGUES, *Portugal*
Activity evaluation of raw materials

14,20 Prof. Coleman JACOBSON and Prof. Broadie JAMES, *USA*
Products for skin aging: activity evaluation

14,40 - 15,50 General discussion and poster-discussion

16,00 **End of ISCD Day**

CALL FOR POSTERS

Organizing secretariat:

Mr Robert Fischer - P. Morganti, Ph.D.

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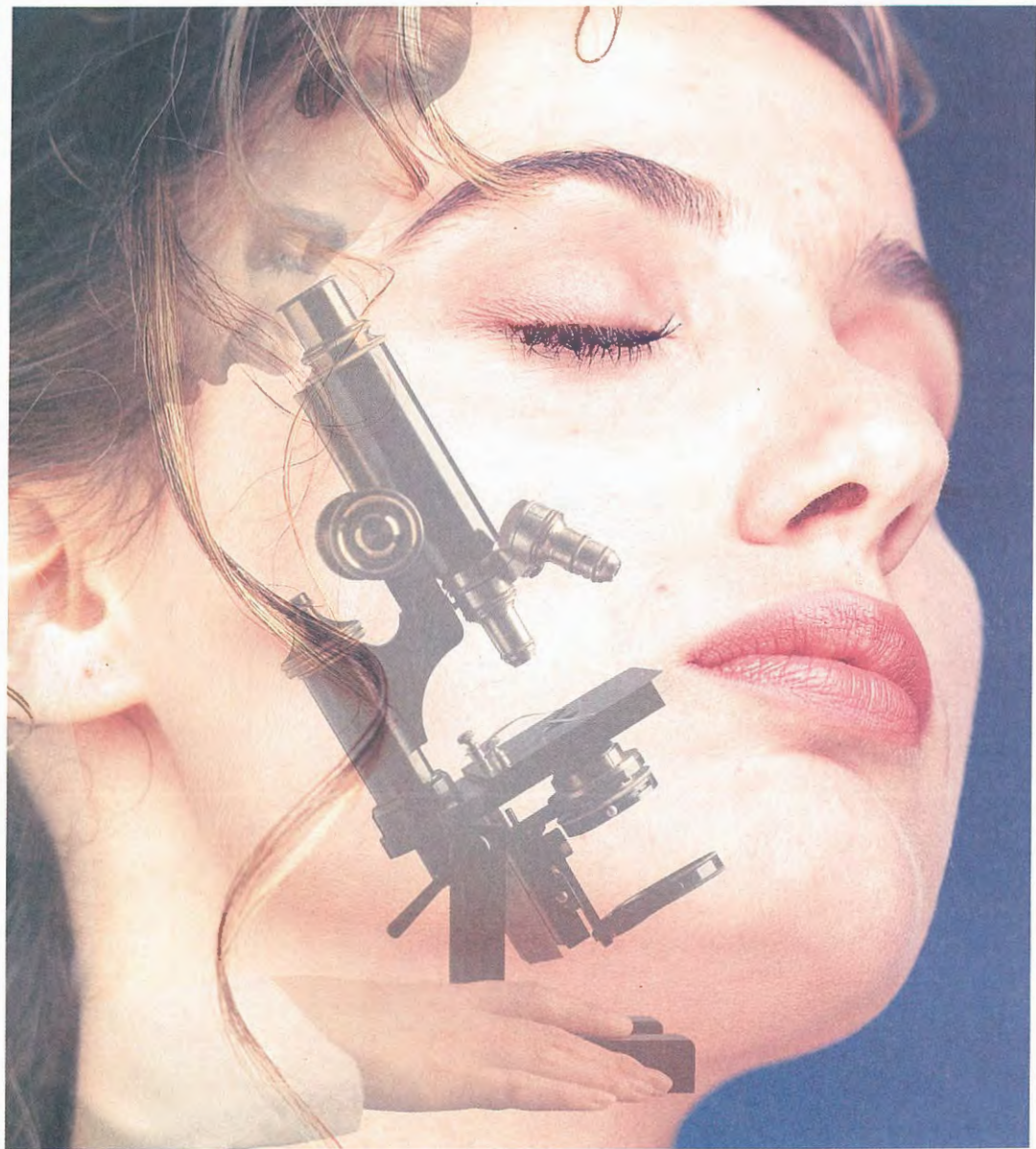


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