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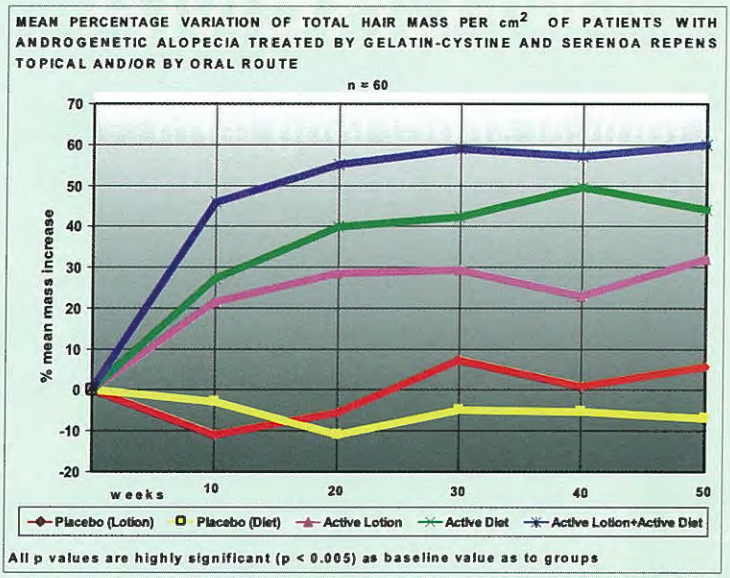

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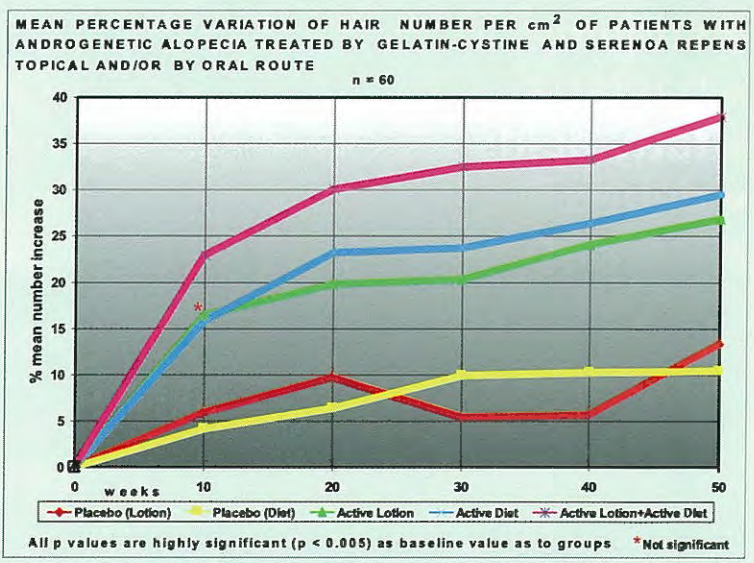

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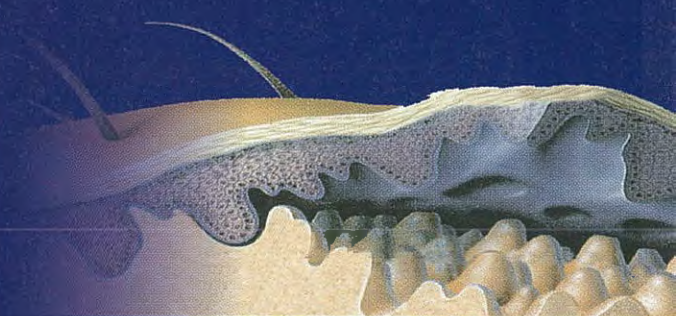

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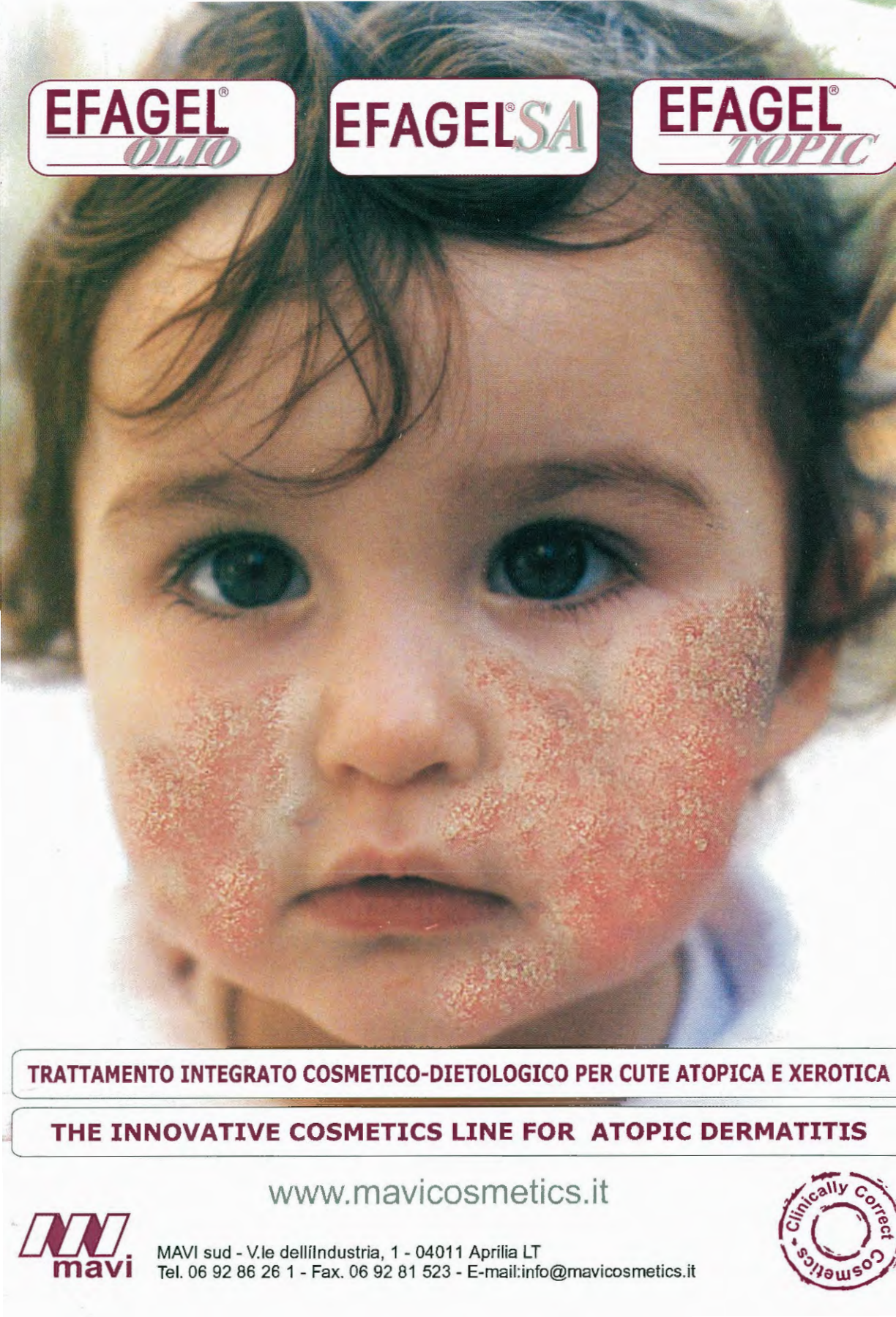
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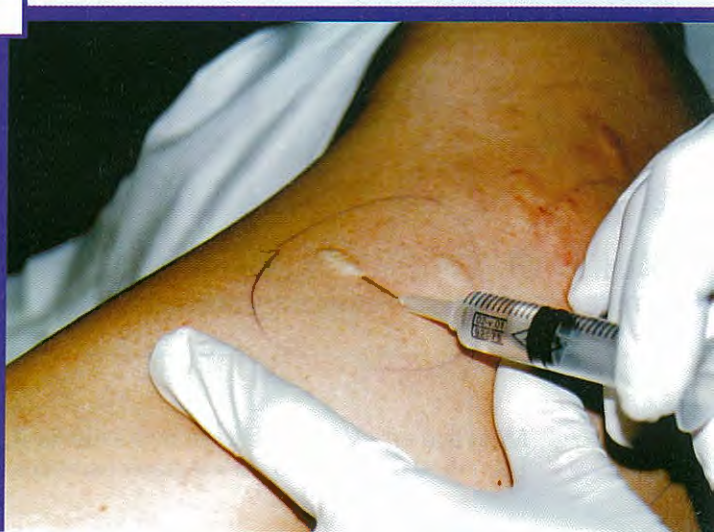

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Contents

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THE DEVELOPMENT OF SILICONE CHEMISTRY: II. HYDROPHILIC SILICONES

Mª A. Ruiz, A. Hernández, J.M. Llácer and V. Gallardo
Dept. of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Univ. of Granada, Spain

Received: *May 2003*

Key words: *Hydrophilic Silicones; Silicone Surfactants; Classification; Chemistry;*

Summary

In this paper the bibliography of hydrophilic silicones chemistry is reviewed. These compounds have an important play role in the development of technology pharmaceutical, because their knowledge is a key factor influencing the technological and economic development of pharmaceutical formulations. In this group are included the silicone surfactants than can be used to prepare emulsions at room temperature, and yields stable W/S and S/W emulsions with excellent appearance and optimum hydrating and protective properties.

Riassunto

In questo lavoro vengono riportati gli ultimi dati tecnici riguardanti la chimica dei siliconi idrofili. Questi composti giocano un importante ruolo formulistico sia per i preparati cosmetici che farmaceutici essendo utilizzati anche come tensioattivi per emulsioni A/S (Acqua/Silicone) e S/A (Silicone/Acqua).
Tali emulsioni svolgono un eccellente attività protettivo-idratante.

INTRODUCTION

This work, a continuation of two previous articles on silicones (1, 2), is dedicated to the study of hydrophillic silicones.

CLASSIFICATION

Attempts were made to modify PDMS by the incorporation of other organic groups so that they would be more compatible with water and/or other organic media. The syntheses carried out have led to a whole series of modified organo-polysiloxanes with a wide range of products and applications. Development has been spectacular due to the interesting properties for application obtained. Below we summarize all the derivatives of silicone known to date that have been obtained by the incorporation of organic groups via direct esterification reaction, hydrolyzed transesterification, or other subsequent reaction phases that may be ionic or non-ionic (cationic, anphoter or anionic) (3). The figure below aids in understanding these new silicones, taking into account their hydrosolubility.

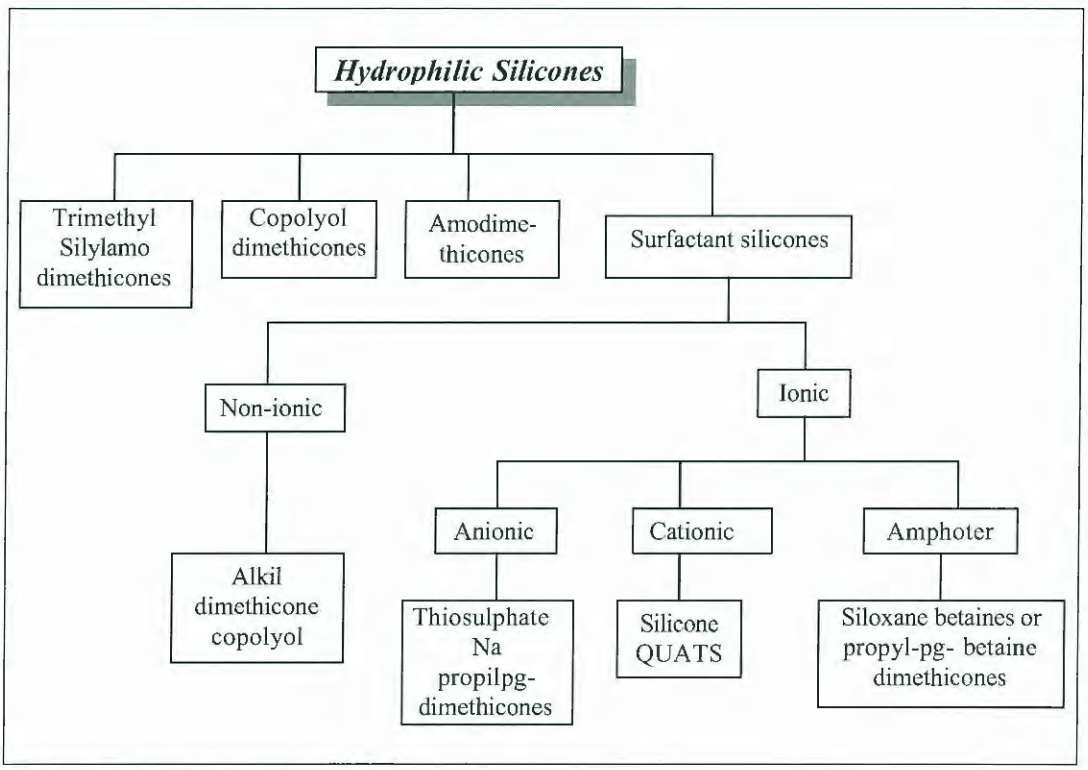

Fig.1 *Classification of hydrophilic silicones*

COPOLYOL DIMETHICONES

The physical properties and usefulness of dimethicone in applications for personal care have been extensively recognized and applied. As the use of silicones has increased in the last 40 years, the limitations of silicones, such as their characteristic lack of reactivity, low compatibility and low solubility both in polar and apolar solvents, have been progressively solved (4).

One of the methods used to develop new silicones has consisted in modifying the basic structure of the dimethicone with organic groups possessing the desired solubility or reactivity, that satisfy special formulation requirements, maintain the high aesthetic and textural properties of silicone oils and, frequently, that also confer particular synergic properties (5).

One aim was to find silicone substitutes that would increase its solubility in water and other polar media. The most common method to modify the insolubility of silicones in water has been to change the structure of dimethicone with polyoxialkalized substitutes that are highly soluble in water. That is, the dimethicone polymers are substituted by methyl groups fixed to the siloxane chain by polyether side-chains (6).

These side-chains are polymers of ethylene oxide or propylene oxide, or copolymers of ethylene oxide and propylene (7). The addition of polyoxiethylened substitutes considerably increases the solubility of the silicones in water. Normally, the amount of subunits of polyoxialkaline needed to reach solubility in water ranges from a 2 to 4 ratio with dimethylsiloxane monomer units.

Copolyol dimethicones are soluble in ethanol and water, with the result that they are employed in non-substantive formulations for skin care, to which they confer the necessary properties of silicones and can then be washed free (4). Polyoxialkalene substitutes in highly water-soluble dimethicone copolyols provide them with a solubility ratio inversely proportional to the temperature. That is, as the temperature increases, their solubility in water decreases (8). This reaction is due to the fact that, at low temperatures, the polyether groups are hydrated and therefore the molecule dissolves. At higher temperatures, the polyether group hydrogen bonds break, the surfactant becomes insoluble and turbidity results.

This property can be used during the manufacture of cosmetics as, above the turbidity point, these products act as anti-foaming agents, while below it, they act as foaming agents. This circumstance is well documented with regard to propylene glycols, in which, at a given concentration, the temperatures of phase separation drop as the molecular weight increases. Polyethyleneglycols, in contrast, do not possess this inverse relationship between solubility and temperature, although it does occur in all the water-soluble dimethicone copolyols (9). Whatever the polyoxialkalene substituted, polyethilene glycols solidify at room temperature when their molecular weight exceeds 600. The addition of polyethilene glycol to a PDMS results in a viscous fluid (400 cP) at room temperature. This effect is obtained by incorporating the polyethileneglycol as various smaller subunits in a polymeric silicone structure (10). This basic PDMS structure is characterized by its exceptional mobility, which makes it remain fluid at high molecular weights (11).

Nonetheless, there is a wide range of possible copolyol dimethicone molecules spanning from fluids like water to waxy-looking solids at room temperature, basically depending on the molecular weight of the polysiloxane chain and on the degree of substitution of the polyoxiethilened chains. Moreover, other properties such as surface tension, solubility, turbidity point, foaming action and the general properties of silicones given by their basic structure, are determi-

ned by the indices of the n, m, x or y polymers (see figure). The combination of these parameters allows us to obtain distinct properties for a whole range of copolyol dimethicones, where the ratio of OE/OP will also influence the hydrophillic/lipophillic properties of the dimethicone copolyol (12). The higher the percentage of propylene oxide in the polyether group, the better its compatibility with oils. In contrast, the higher the proportion of ethylene oxide in the polyether group, the more hydrophillic the dimethicone copolyol. The combination of hydrophillic and hydrophobic properties in siliconglycols is a requirement for obtaining surfactant properties.

Although aqueous solutions of copolyol PDMS produce abundant foam, the height and quality of the foam are insufficient for them to be considered as primary surfactants in dermocosmetic applications. They can be used as transitory defoaming agents for products that, for example, foam when cold and are packaged hot to avoid the problem of foaming during packaging, particularly if it is under pressure.

These organo-modified silicone derivatives have been shown to diminish eye irritation caused by anionic surfactants. The compound is a nonionic surfactant. The relative affinities of the molecules can be established in order to form anything from emulsions of water in oil or water in silicone, to certain tactile properties for a non-greasy, soft feel, to emulsions of oil in water. Copolyol dimethicones can also act as resin modifiers in formulations of hair sprays, as hair sprays incorporate sticky resins that become fragile and inflexible, with no means of eliminating the stickiness and improving the plasticizer level.

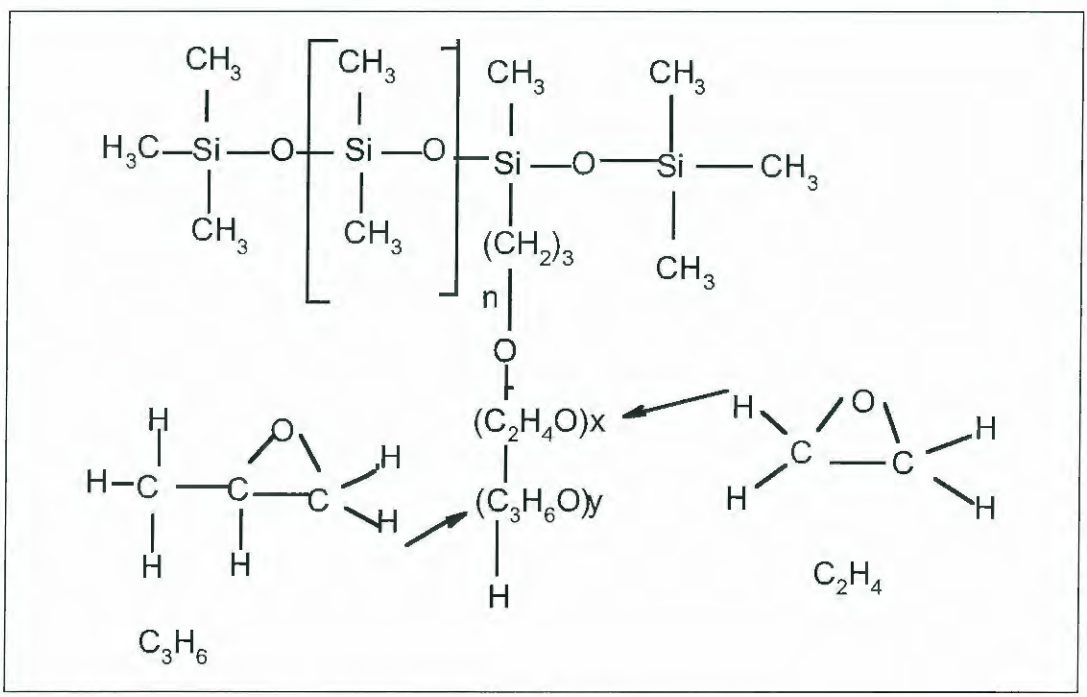

Fig.2 Chemical structure of dimethicone copolyol with ethylene oxide and propylene oxide

Two areas of increasing use are anti-perspirants (together with cyclomethicones) and creams and lotions for skin care. Nonetheless, the potential of copolyol dimethicones as anti-irritants could extend beyond personal care products to include such products as shampoos and soaps. These versatile silicones can also be incorporated in mild or strong liquid detergents, general-use cleaners, floor-cleaning products, liquids for car-washing and products for general cleaning. The anti-irritant properties of these silicones is currently spurring research to solve serious irritant problems caused by cationic substances, perfumes, sunscreens, anti-perspirant salts, a myriad of acids and bases, topical medecines, and other chemical products producing adverse reactions in contact with the human body (13).
Finally, there is another class of copolyol dimethicone that acts as a highly effective non-ionic surfactant at low concentrations. The hydrophobic part of these short-chain, low-viscosity silicones is a dimethyl/trimethyl siloxane of low molecular weight that is a poor lipophillic. The result is moisturizing without the solubilization of lipids.

HYDROPHILIC AMINOSILICONES

These products appeared from the substitution of methyl groups by organic aminofunctional units. There are two types of aminofunctional silicones, according to whether the alpha and omega positions of the linear PDMS have alcoholic groups (amodimethicone) or methyl groups (trimethylsililamodimethicone). These silicones form an emulsion with a neutral or slightly acid pH, where the polar aminic groups have a strong effect on the fixing properties of these organically modified siloxanes, particularly on protein surfaces such as the hair.

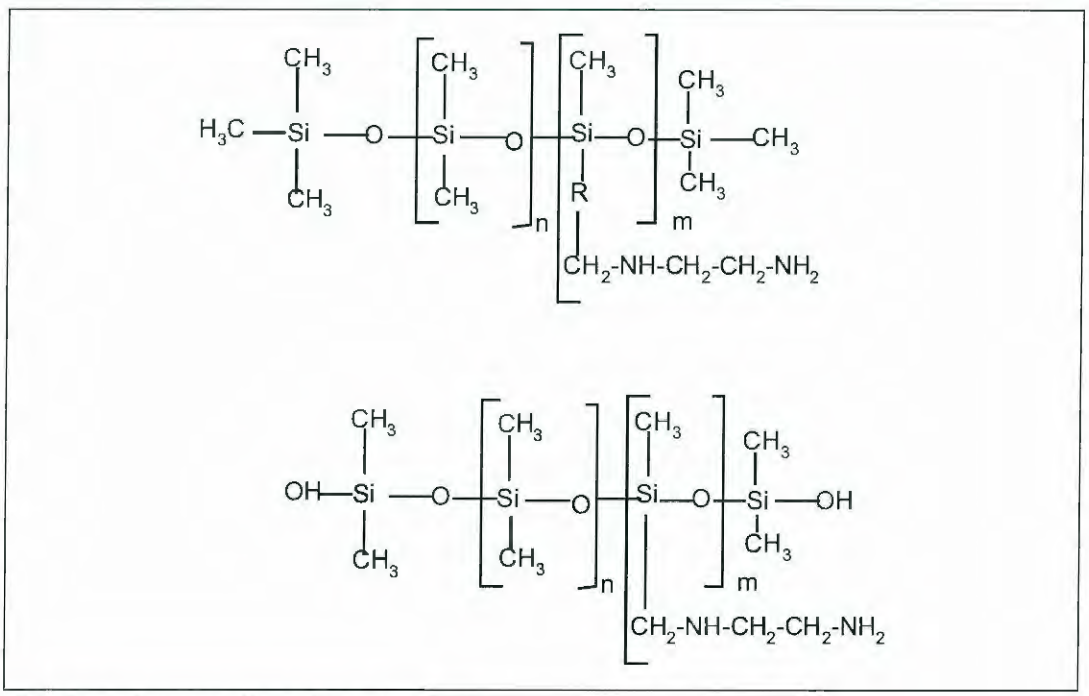

Fig.3 *Chemical structure of hydrophilic aminosilicones*

The durability, substantiveness, and resistance to wash-off of the aminofunctional silicone polymer varies according to the percentage of amina in the molecule and to the degree of polymerization. Certain studies report that, the higher the polymerization compared to the number of aminic groups, the greater the substantive and fixing properties on the hair, with no accumulation phenomena. Although the two types of silicones have a similar degree of capillary fixing, their styling and permanence effects are distinct. Thus, amodimethicones, or reactive PDMS-aminics, have greater capillary spreading due to the hydroxyl radical, which is very reactive. In emulsion they are very stable, but when the emulsion is broken on the surface of the hair, the silanol groups interact to form the siloxane structure:

These long, spiral chains provide a long-lasting film resistant to washing, even more so than the homologous aminic silicone. As described above, both silicones are provided and studied as non-ionic emulsions. Given the basic nature of the amino groups in these aminofunctional silicones, the polymers develop a positive charge (which in theory is what bonds itself to negatively charged particles of the capillary keratin), which has a neutral or slightly acidic pH (14). Therefore, in most cases they are incompatible with the use of anionic surfactants, but very effective or synergic with cationic or non-ionic elements. The conditioning functions of the two silicones are influenced by the different groups in the alpha and omega positions, which also determine other characteristics. Trimethylsililamodimethicones (TSA), for instance, are less reactive and therefore more compatible with a wide variety of formulations. On the other hand, the droplet size is smaller in amodimethicone emulsions, making them more stable in certain formulations.

Since these silicones are ever more important as additives is hair-care products, many tests have been carried out on their safety and environmental impact.

SURFACTANT SILICONES

Modern techniques of manufacturing silicones and organo-modified derivatives of silicones open up new vistas of potential applications for these W/O formulations (15-18). Thus, new ionic, non-ionic and anphoter silicone surfactants have appeared, all applicable in both hair-care, capillary products and sunscreens. They can be classified as follows:

NON-IONIC SURFACTANTS

A certain portion of alkilic radicals have been added to polyether-polysiloxane (copolyol dimethicone), leading to the production of excellent W/O surfactants. The most outstanding characteristic of these copolymers are the hydrophillic and lipophillic side groups fixed to the siloxane backbone via a Si-C bond. The result is a siliconic derivative generically termed a copolymer-polyalkil-polysiloxane or alkildimethiconecopolyol. In the W/O interface of an emulsion with an external oil phase, these polyalkil-polyether-polysiloxanes seem to place themselves such that the hydrophillic groups of polyether are dissolved in the water phase and the alkilic groups in the oil phase. The siloxane units lie between them, as at a particular length they are neither hydrosoluble nor liposoluble. In fact, we could speak of a triphase system: water/silicone/oil. This type of emulsion produces W/O or W/Si emulsions with different viscosities, depending on the percentage and type of the oil phase (19, 20).

These copolymers are generally soluble in oil and have low HLB values, which makes them particularly suitable as surfactants for emulsions with an external oil phase or as secondary or co-surfactants in W/O emulsions. Emulsions pre-

pared with alkil-dimethicone-copolyol have a lighter, less greasy and non-waxy feel in comparison with conventional W/O systems (21). Appropriately formulated, these products neither separate nor lose viscosity. Emulsions formulated with these surfactants are white and shiny, but lack a waxy appearance (22).

These emulsions can be economical thanks to their high water content and the possibility of manufacturing them at room temperature when there are no solid elements requiring prior melting (23). A small amount of electrolyte in the aqueous phase is needed for these emulsions to increase thermostability. This addition is common in all W/O formulations in order to stabilize them (24-25). Vegetable oils can be used in proportions of around 5% or at concentrations that do not vary or affect the physical stability of the emulsion. Co-surfactants such as gliceryl-sorbitan-isostearate must usually be added in order to incorporate vegetable oils.

IONIC SURFACTANTS

PDMS are generally considered to be chemically inert compounds, so that the simple substitution of the methyl groups bonded to the silica, for example via oily alcohols or polyesthers in the sense of a nucleophyllic reaction, is not feasible. For the synthesis of modified organic PDMS, it is necessary to use reactive siloxanes containing halogen atoms, alcoxy groups, or hydrogen atoms with a silica bond beside the methyl groups. These siliconic derivatives are obtained from epoxy siloxanes (reactive compounds) and by the reaction with appropriate nucleophiles (26).

Anionic siloxanes can be obtained by the chemical transformation of epoxy siloxanes with sodium sulphidrate or sodium thiosulphate. Although the corresponding sulfonates have not found an application in cosmetic preparations as yet, silicone thiosulphate are extremely important in the most recent tests on application techniques in capillary treatments. The synthesis of cationic and anphoter siloxanes is obtained from secondary amines and via reaction with epoxy siloxanes (reactive). The intermediate terciary aminosiloxanes obtained can, in turn, be chemically transformed into silicone betains with sodium chloroacetate. In the presence of acids such as acetic acid, the terciary amines break the epoxydic circle, generating the silicone quats.

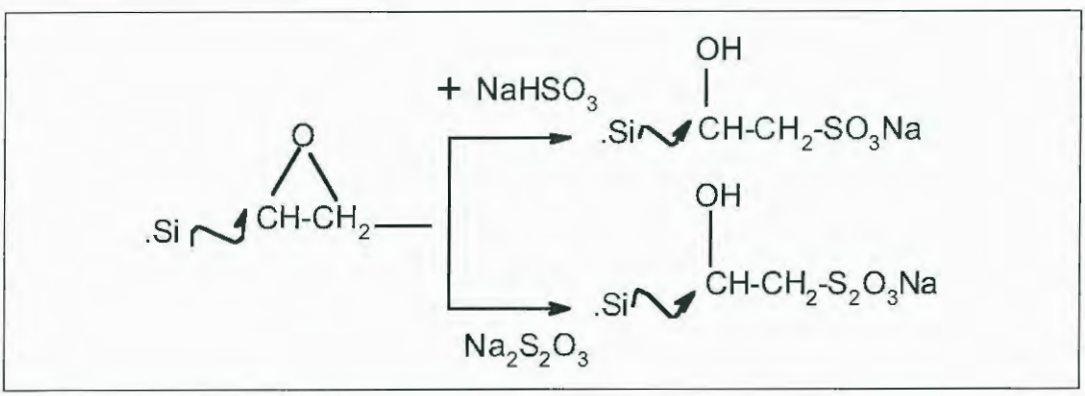

Fig.4 Chemical structure of anionic siloxanes

ANIONIC SURFACTANTS

Anionic surfactants are obtained via the substitution of thiosulphate-sodium alylglicidilether for a methyl from the siloxane unit. This substitution can be made in the methyl and/or or in the side methyl position of the polymer chain, producing linear silicone or comblike thiosulphate, respectively. These silicone salts be-

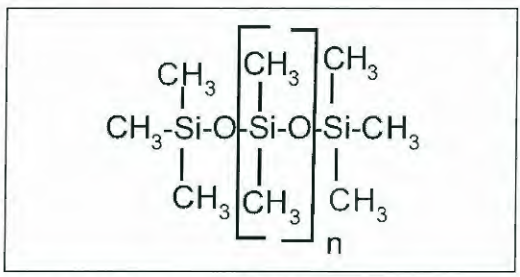

Fig.5 Chemical structure of PDMS

long to the group commonly known as "Bunte salts". This polyorgano-thiosulphate-polysiloxane can be dispersed in water, forming translucid dispersions in which the amount of siloxane monomers with respect to the tiosulfates determines the degree of transparency of the solution. In addition, it can be dispersed in isopropyl myristate and liquid paraffin, and is soluble in propylenglycol and glycerine.

CATIONIC SURFACTANTS

Cationic surfactants are also known as silicone QUATS or Polyquaternium. These surfactants have two drawbacks: 1) their low solubility in water, which limits their use to formulations in sprays or with a high alcohol and/or oil content; and 2) their cationic nature makes them incompatible with anionic surfactants.

The first drawback can be solved using a copolyol dimethicone as the siloxane backbone, to which the cationic radical is incorporated. It can also be solved by decreasing the molecular weight of the siloxane polymer with respect to the alkilic radical of the cationic part, taking advantage of the low surface tension of polydimethylsiloxanes that makes them easily dispersible in water. The second drawback is solved by using diquaternary aminas or iminas.

Amphoter surfactants

Amphoter surfactants are termed siloxane betaines or propyl-pg-betaine dimethicones. The reaction of PDMS with secondary amines gives rise to terciary amine siloxanes that can be made to react with Cl-CH2-CO2-Na amphoter surfactants, producing amphoter surfactants with a siloxane lipophilic chain. These organo-modi-

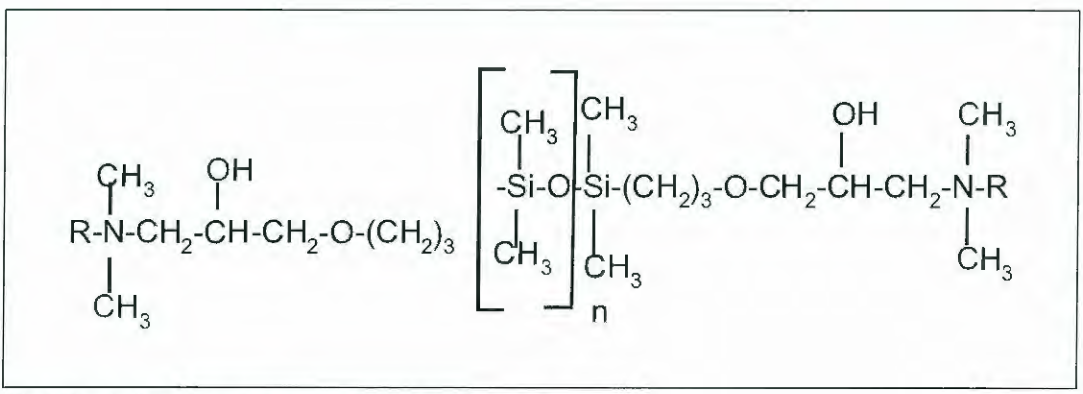

Fig.6 Chemical structure of silicone quats or polyquaternarium 80

fied derivatives are soluble in water up to 10% and therefore cause no problems on being incorporated to the distinct formulations they are used in (27-29).

The world of silicones is so wide and changeable that it is constantly evolving, and so the classification of these organo-modified polymers cannot be considered to be definitively closed (30).

Almost everyday new products of the PDMS group appear in the market. It can be said they are the compounds of the future.

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Author Address:

M.A. Ruiz
Dept. of Pharmacy and Pharmaceutical Technology
Faculty of Pharmacy, University of Granada
Campus de Cartuja,
E-18071 GRANADA, Spain
Tel +34-58-243904
fax +34-58-248958
e-mail: adolfina@ugr.es

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PABA-ALGINATE COMPLEX AS SUNSCREEN AGENT

V. Iannuccelli, N. Sala, L. Costantino, G. Coppi
Dept. of Pharmaceutical Sciences, University of Modena and Reggio Emilia, Italy

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Key words: *PABA; Alginate; Complexation; UV exposure; Photodegradation;*

Summary

In order to improve the photostability of p-aminobenzoic acid as UV-B sunscreen agent, an electrostatic complex with sodium alginate was formed. The occurring of the complex formation was demonstrated by rheological analysis and by difference spectrophotometry. Photodegradation of PABA and PABA-alginate complex, resulting from irradiation by sunlamp, was examined by UV spectrophotometry. The complex showed a greater UV absorbance capacity and nearly overlapped photodecomposition rate in comparison with the original sunscreen agent.

Riassunto

Per migliorare la fotostabilità dell'acido para-aminobenzoico (PABA) utilizzato come filtro UV-B, è stato preparato un complesso di natura elettrostatica con il sodio alginato. La formazione del complesso è stata dimostrata mediante misure di reologia e di spettrofotometria differenziale. La fotodegradazione del PABA e del complesso PABA-alginato, dovuta all'esposizione a raggi ultravioletti, è stata valutata mediante misure spettrofotometriche UV. Il complesso ha mostrato una aumentata capacità filtrante pur mantenendo una velocità di fotodecomposizione paragonabile a quella del composto come tale.

INTRODUCTION

The knowledge of sun exposure side-effects led recently to a growing interest in cosmetic products containing sunscreen agents. However, UV absorbance involving the sunscreen photodegradation (1) might have consequences in terms of photoprotection or phototoxicity (irritation, allergic or photoallergic contact dermatitis, carcinogenic risk).

One of the first and widely used UV-B absorbers is p-aminobenzoic acid (PABA). Published papers have reported that PABA decomposes by sun exposure and potentially harmful metabolites are formed, with also possible changes in screening efficiency. Nevertheless, there is some discrepancy between the reports (2-6).

Since the photochemical modification of PABA involves the amino group (6), the present work attempts to improve PABA photostability by forming a complex with alginate, a polyanionic polysaccharide. Alginates form gels by interacting with polyvalent cations and cationic compounds for which mannuronic residues are mainly involved (7-9).

Therefore, the occurring of the complex formation between PABA and sodium alginate as well as the photodegradation after UV irradiation were tested by monitoring the rheological and UV spectral changes.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used without further purification. Sodium alginate Manucol DM (Mr about 147000, extracted from Laminaria digitata, containing 62% mannuronic acid and 38% guluronic acid) was kindly supplied by Kelco International (Bagnolet Cedex, France). Para-aminobenzoic acid (PABA) was purchased from Fluka Chemie (Buchs, Switzerland).

Rheological analysis

Rheological measurements were carried out on 0.5% (w/v) solutions (water and acetic buffer solution at pH 3.5) of both sodium alginate alone and in the presence of increasing amounts of PABA such as to produce true solutions, i.e. without precipitate. After 24 h, the rheological behaviour of the solutions was determined at 25°C in a coaxial cylinder rheometer (Rotovisco RV 12, Haake, Karlsruhe, Germany) by measuring the shear stress as a function of the shear rate. The reported data represent the average of three determinations.

Difference Spectrophotometry

Difference Spectrophotometry (DS, UV-Vis Lambda 16, Perkin-Elmer, Norlwalk, CT, USA) was performed by the Herskovit's double cell compensation technique (10). The baseline was set to zero with water and sodium alginate water solution (0.136 μM), in double cells in both reference and sample beams. Difference spectra were recorded after addition of the same amount of PABA to water in the reference compartment and to sodium alginate water solution in the sample compartment obtaining increasing PABA concentrations up to 118 μM. The absorbance of PABA in water (118 μM, pH 5.9) and in alginate solution (0.136 μM, pH 6.5) did not change.

Molar extinction coefficient determination

To evaluate the role of the complexation on PABA screening efficiency, the molar extinction coefficient was calculated on the absorbance values, at the maximum absorbance wavelength, of PABA water solutions with water as referen-

ce and of PABA-alginate water solutions with sodium alginate water solution as reference. The data represent the average of three differently concentrated solutions.

Evaluation of photodegradation

Solutions of 0.1 % (w/v) PABA in water and in 0.5 % (w/v) sodium alginate water solution were placed in standard quartz cuvettes (1 x 1 x 4 cm). The cuvettes were exposed to the radiation by a light source from 280 to 400 nm (HP 3115, Philips, Eindhoven, The Netherland) at a distance of 25 cm and a temperature of 30°C by an air flow. After dilution to 29 μM PABA concentration, UV spectra were recorded (Lambda 3B, Perkin-Elmer) every 15 min for 2 h with water or 0.5% w/v sodium alginate water solution as references.

RESULTS AND DISCUSSION

PABA-alginate complex evaluation

PABA-alginate complex formation was investigated by means rheological analysis and Difference Spectrophotometry.

Rheological analysis. Unlike uncharged polymers, dilute solutions of polyelectrolytes show an "electroviscous effect" which leads to increased viscosities. This results from a spatial expansion of the hydrodynamic volume of the molecules due to electrostatic repulsions between charged segments subsequent to the dilution of the counter ion layer surrounding the molecules (11). A 0.5% (w/v) solution of sodium alginate is considered a dilute polyelectrolyte solution having an expanded configuration (12). In such conditions, the addition of a compound having a cationic group and able to interact with the polyanionic alginate decreases the intramolecular repulsion leading to a tighter configuration and, consequently, to a reduced viscosity. Therefore, rheological measurements were carried out on sodium alginate 0.5% (w/v) solutions in the presence of increasing amounts of PABA in order to determine the possible interaction between PABA and alginate.

The relative apparent viscosity obtained for a shear rate of 1385 s^{-1} (where 100% is considered the value of pure alginate) was plotted in function of PABA concentration (Fig. n. 1).

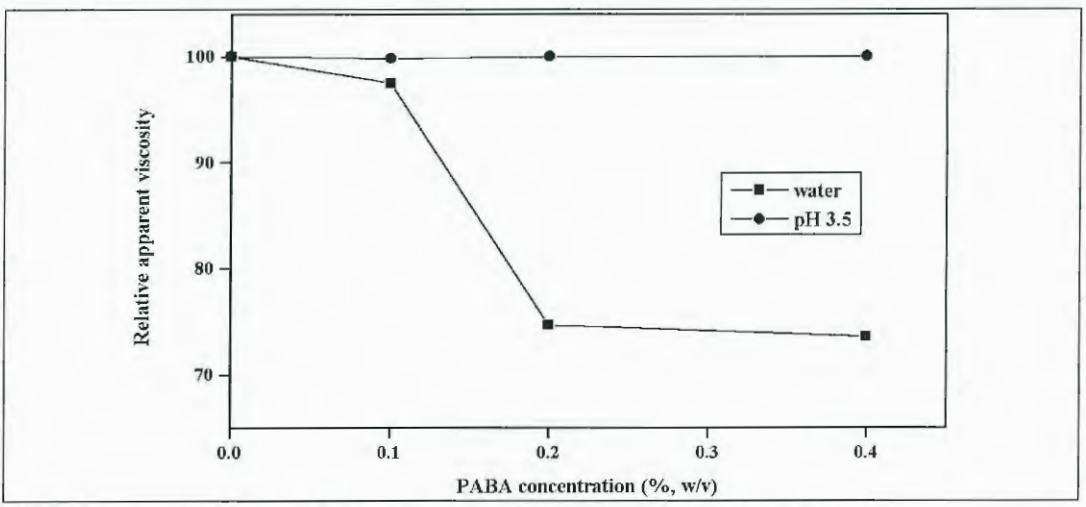

Fig. 1 Relative viscosity values of 0.5 % w/v alginate solutions at different PABA concentrations.

The presence of PABA led to a reduced viscosity of the alginate solution only in water, whereas no significant changes in viscosity were observed at pH 3.5. This finding suggests that the complexation involves an electrostatic interaction between dissociated PABA amino group and alginate carboxylic groups.

Difference Spectrophotometry. The binding between PABA and alginate was also evaluated by Difference Spectrophotometry, recording the absorbance spectra differences between solutions of PABA alone and PABA-alginate mixtures. Each difference absorbance spectra was characterized by positive and negative peaks, as shown in Figure n. 2.

These appear at wavelengths differing from that of the maximum absorbance of the compound under study. A curve was then generated by plotting the change in absorbance (ΔA), measured as the difference in absorbance of the positive peak from the baseline, versus concentration of PABA added (Fig. n. 3)

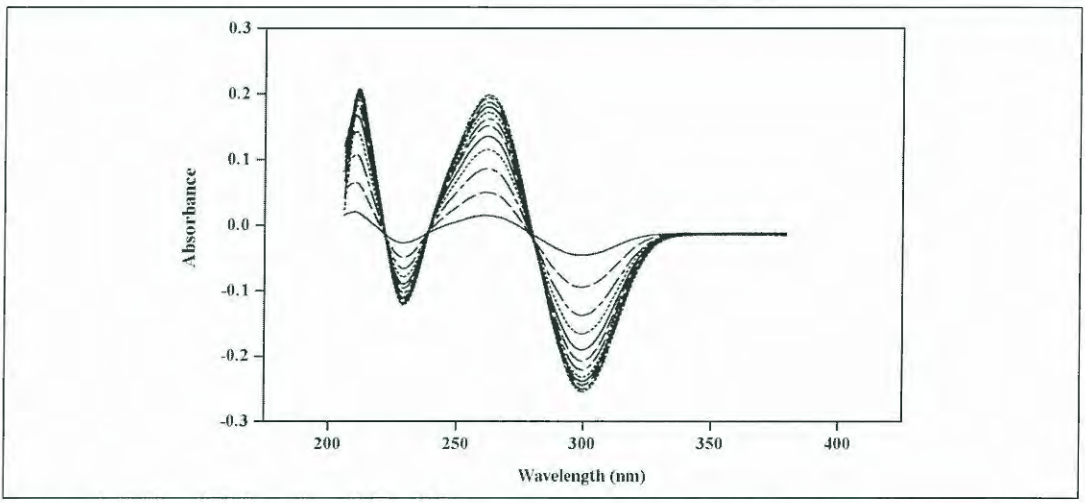

Fig. 2 UV spectra difference between PABA and PABA-alginate solutions obtained by Difference Spectrophotometry.

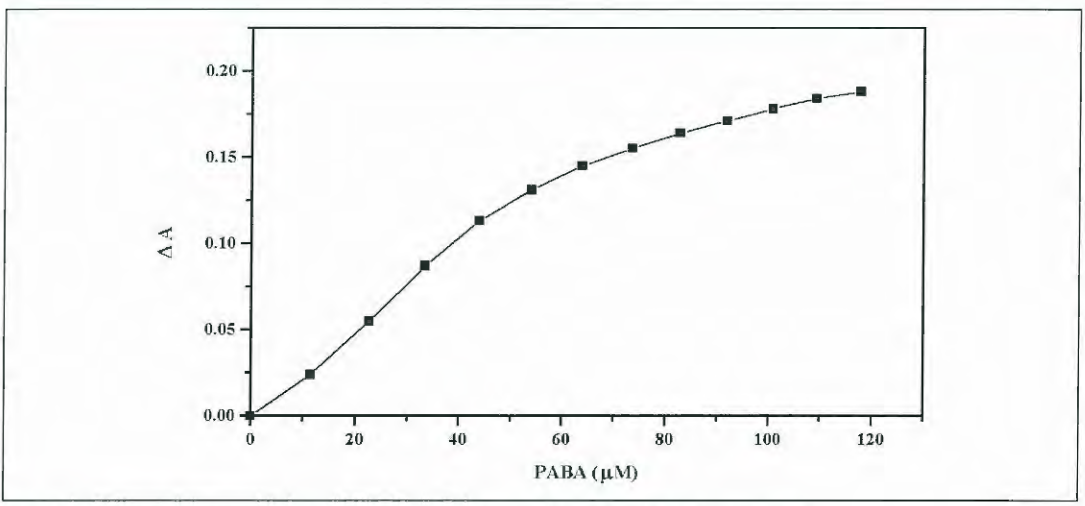

Fig. 3 Absorbance differences of PABA-alginate solutions as a function of PABA concentration.

ΔA increased along with PABA concentration value indicating the occurring of an interaction between PABA and alginate.

Photodegradation study. The UV spectra of both PABA and PABA complex obtained before irradiation are presented in Figure n. 4.

PABA complex showed a slight shift of the maximum absorbance wavelength, from 273 nm to 267 nm, in comparison with PABA and a substantial increase in absorbance values (the molar extinction coefficient was $21.37 \cdot 10^3$ at 267 nm for the PABA complex and $14.77 \cdot 10^3$ at 273 nm for PABA). The observed phenomenon could not be attributed or affected by PABA ionization change in function of the different solution pH value. In fact, no variations in PABA molar extinction coefficient were observed between PABA in acetate buffer at pH 5.9 (pH value of 29 mM PABA water solution) and PABA in acetate buffer at pH 6.5 (pH value of 29 mM PABA in alginate water solution).

The spectral changes of PABA and PABA-alginate complex exposed between 0 and 2 h are shown in Figure n. 5.

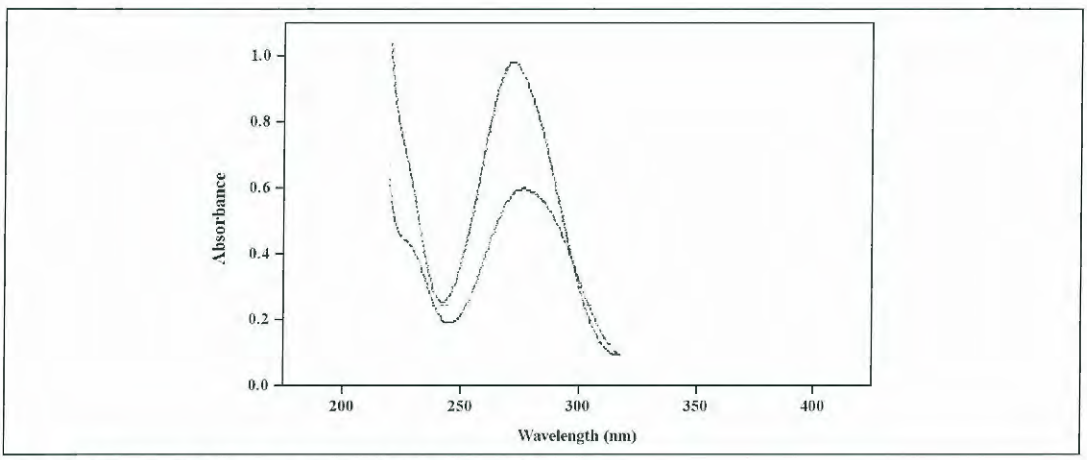

Fig. 4 UV spectra of PABA (lower line) and PABA-alginate (upper line).

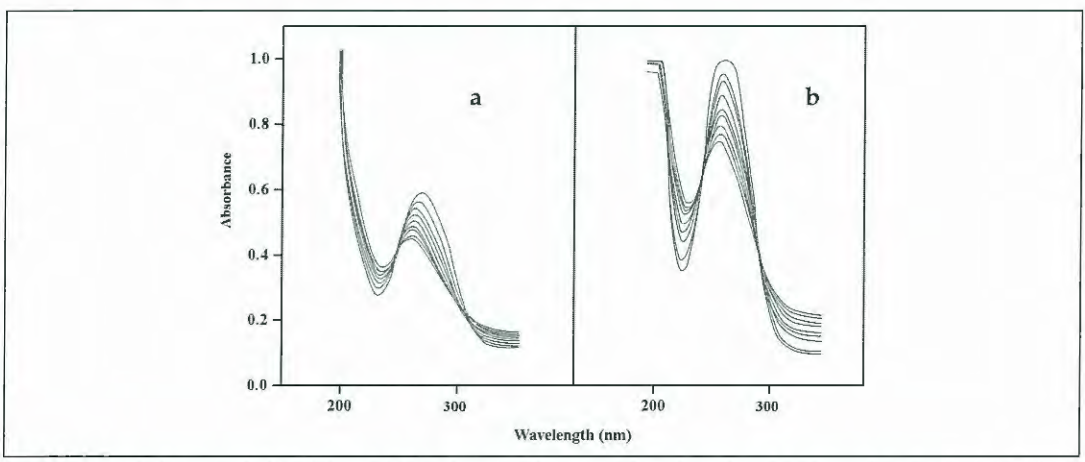

Fig. 5 Spectral changes of PABA (a) and PABA-alginate (b) exposed from 0 (top) to 2 h (bottom) to the solar simulator (tracings correspond respectively to 0, 15, 30, 45, 60,75, 90, 105 and 120 min irradiation time).

The isosbestic points of the spectra are well defined indicating a single process: sunscreen → photoproduct. After exposure, the absorbance values as well the maximum absorbance wavelength decreased along with the exposition time in both samples indicating the disappearance of the cromophor and the formation of photoproducts. The rate of disappearance, evidence of the photochemical degradation rate, was estimated by plotting both the maximum absorbance wavelength and the absorbance values versus time of exposure. PABA maximum absorbance wavelength decreased more rapidly than that of PABA-alginate complex. However, almost the same value of wavelength was reached by both products after 2 h sun exposure (Fig. n. 6).

No significant difference was found between the slopes of absorbance versus exposure time plot (Fig. n. 7).

These findings could indicate a similar disappearance of sunscreen by irradiation and then a similar photochemical degradation rate. Presumably, the amino group protection by electrostatic bindings do not prevent PABA photolysis reactions.

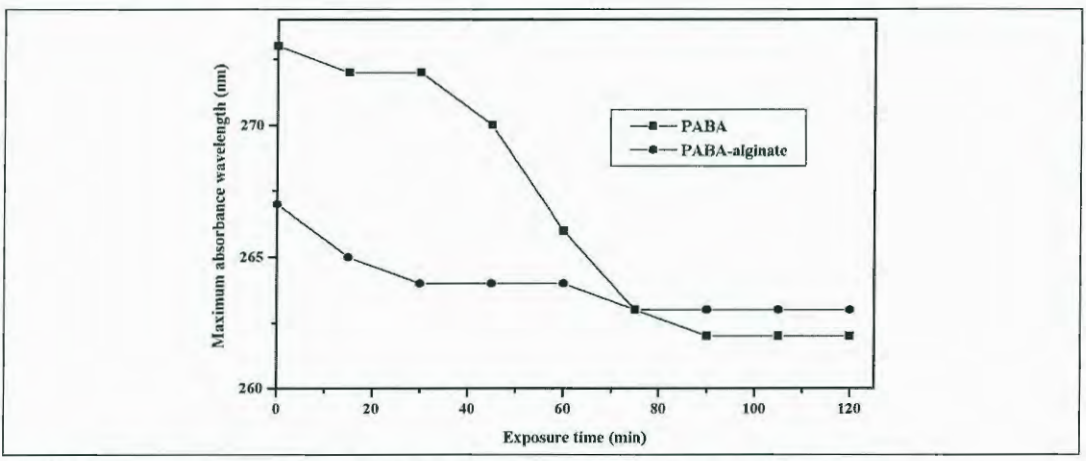

Fig. 6 Maximum absorbance wavelength shift of PABA and PABA-alginate solutions upon irradiation.

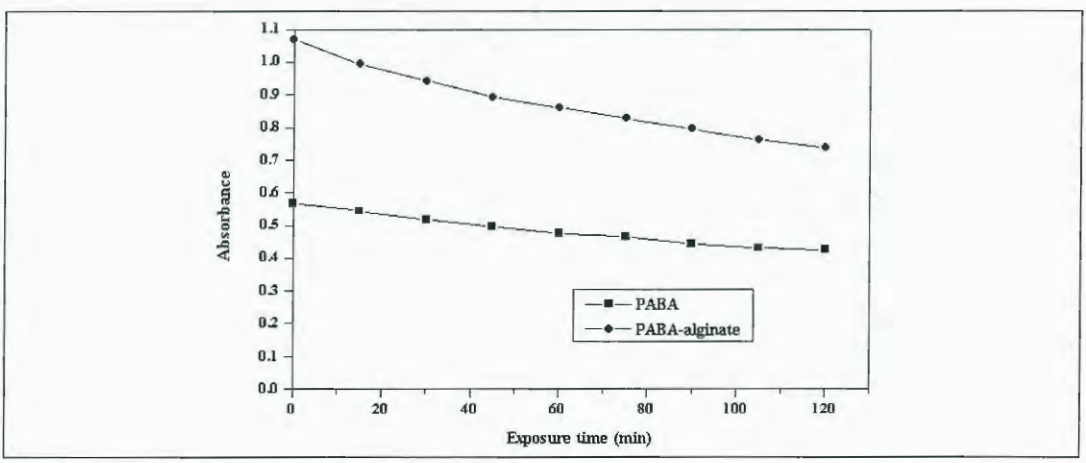

Fig. 7 Absorbance changes of PABA and PABA-alginate solutions upon irradiation.

CONCLUSIONS

PABA and PABA in a complex with alginate demonstrated a comparable photodegradation upon UV irradiation. Notwithstanding this, the complex showed a higher absorbance property and, consequently, higher photoprotection capacity than PABA. Therefore, lower screening amounts, inducing a less harmful photoproduct formation, would be requested to provide the same sun protection factor.

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Author Address:

Valentina Iannuccelli
Dept. of Pharmaceutical Sciences
University of Modena and Reggio Emilia
Via G. Campi, 183
41100 Modena, Italy
Tel.: +39-59-2055151
Fax: +39-59-2055131
e-mail: iannuccelli.valentina@unimore.it

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A NOVEL HERBAL FORMULATION ENHANCING PROTEIN SYNTHESIS SPECIFIC FOR HAIR GROWTH - A NORTHERN BLOT ANALYSIS

JR. Krishanamoorthy[1], S. Ranganathan[2], S. Gokulshankar[2], M.S. Ranjith[2]
[1]Dr JRK Sidda Research and Pharmaceuticals (P) Ltd., Kuntrathur, Chennai - INDIA
[2]Department of Microbiology, The New College, Chennai - INDIA

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Summary

The hair growth enhancing property of a herbal oil (Keshraksha oil) and herbal hair vitalizing cream (Keshraksha cream) was studied. The total hair count assay in the guinea pig model revealed that both the oil and the cream has a definite role in increasing the hair growth. To confirm the possible mechanism of action of the formulations on the hair growth, northern blotting was performed using the Shh gene. An increased m RNA synthesis was recorded in the dermal papillae cells of the hair of the animal treated either with oil or cream but not in the control. The present study suggests that the oil and cream treatment enhances protein synthesis in the matrix cells, thereby increasing the anagen phase of the hair.

Riassunto

E' stata controllata l'attività stimolante sulla ricrescita dei peli di un olio estrattivo di origine vegetale (olio di keshrasha) e di una crema rivitalizzante prodotta con lo stesso derivato.
Il conteggio totale dei peli di un porcellino d'India, utilizzato come modello, hanno posto in evidenza come entrambi i prodotti svolgano un ruolo interessante sulla ricrescita dei peli. Per confermare il possibile meccanismo di azione dei due prodotti è stata utilizzata una specifica metodica basata sull'uso del gene Shh.
È' stata così riconosciuta una incrementata sintesi del m RNA a livello delle cellule della papilla dermica dei peli degli animali trattati sia con l'olio che con la crema, mentre tale incremento non si è verificato nel controllo.
Lo studio suggerisce che sia l'olio che la crema sembrano essere in grado di incrementare la sintesi proteica a livello delle cellule della matrice, incrementando la fase anagen del pelo.

INTRODUCTION

Hair follicles are the anatomic "factories" that have as their principal function the production of hair. Hair follicle neogenesis occurs in the embryo by invagination of the epidermal placode into the surrounding dermis [1-4]. Postnatal follicles undergo a cycle of renewal in 3 phases: anagen (growth), catagen (regression), and telogen (resting) [5,6]. The first complete postnatal hair follicle cycle (first anagen, first catagen and first telogen) is completed in the first 3 1/2 weeks after birth and is followed by the second hair cycle (second anagen, second catagen and second telogen).

Hair forms the major cosmetic apparatus of man. Hair care has been in practice since antiquity. Even in the 14-16 century English literature, the importance of the hair in the cosmetic aspect of man has been well documented (Queen Elizabeth- W Shakespeare).

Similarly, the ancient Tamil literature too contains several mentions of hair care [7].

Hair loss and premature graying of hair especially in the early and mid age group are the major cosmetic concern that plague mankind all over the world. Use of wigs and hair re-plantation although available, as an alternative is not in wide use due to the exorbitant cost and clear distinctivity. As on date, no formulation effectively addressing a solution to this problem is available.

In the present paper we have studied the effect of Keshraksha oil and Keshraksha Hair vitalizing cream*, formulated based on the aqueous and or oil extracts of certain plants viz., Phyllanthus embelica, Bergera koenigit, Lawsonia alba, Indigofera tinctoria, Wrightia tinctoria, Hibiscus rosasinensis, Muraya paniculata, Terminalia chembula and black catachu on hair growth in Guinea pig model. All the above plants are well documented in the texts of Indian system of Medicine (Siddha and Ayurveda) for enhancing the hair growth [8,9].

The role of the Keshraksha oil and cream on hair growth in Guinea pigs was studied by total hair count technique. Further the mechanism of action of the above formulations on hair growth was studied by determining the expression of mRNA specific for hair growth using Sonic Hedge Hog Gene (Shh cDNA) as probe. Further, the expression of mRNA specific for tyrosinase, an enzyme essential for melanogenesis was also studied by Northern blotting.

MATERIALS AND METHODS

Preparation of Keshraksha oil and Keshraksha hair vitalizing cream

Oil extracts of Phyllanthus embelica, Bergera koenigit, Lawsonia alba, Indigofera tinctoria, Wrightia tinctoria and Hibiscus rosasinensis were prepared using Coconut oil and adjusted to a concentration of 250 μg of each of the plant extracts in 1 ml of oil using standard procedure (10-11). So prepared oil was referred as Keshraksha hair oil.

Similarly the aqueous extracts of Lawasonia.alba, Muraya paniculata, Wrightia tinctoria, Terminalia chembula and black catachu were prepared and incorporated into hair cream base at a concentration of 100μg of each of the extract in 1g of the cream. So prepared cream was referred as Keshraksha hair vitalizing cream.

Studying the effect of oil and cream on hair growth in Guinea pigs by total count technique

A total of 4 Guinea pigs were divided into 2 groups of 2 animals each. One group was used to study the effect of Keshraksha oil on hair growth while the other was used for studying

** registered cosmetic products of Dr. JRK' Siddha Research and Pharmaceuticals (P) Ltd., Chennai – INDIA*

the effect of cream. Left and right sides of the flank region in all the animals were tonsured in both the groups and 2-cm diameter zone was marked using a permanent marker pen. In one group, the oil was topically applied over the tonsured flank region in the right side, while the left side of the tonsured flank region in the same animal was left free without any applicant (control). Similarly, in other two animals, the cream was applied in the right side of the tonsured flank region, while the left side of the flank region was maintained as control without any applicant. The treatment procedure was continued for a period of 9 days with single application per day. The total number of growing hairs in the demarcated (2 cm diameter) zones treated either with oil or cream was counted separately using a magnifying hand lens at regular time intervals (3,6,9 days) and was compared with the control [12].

RNA QUANTIFICATION

The cells of the dermal papilla from the treated (cream and oil separately) and control hair were collected and the RNA was isolated. The quantification of the total RNA isolated was done spectrophotometrically at 260nm using standard procedure [13].

Northern blotting

Northern blotting was performed with the RNA isolated from the matrix cells (cream treated, oil treated and control separately) on the 9th day using standard procedure [14]. The isolated RNA (10mg/lane) was separated on a 1% agarose gel, transferred to a nylon membrane and hybridized with [^{33}P]-labeled Shh cDNA probe. Equal loading of RNA was confirmed by analysis of GAPDH mRNA. Similarly the tyrosinase gene expression was also studied [15,16]. The hybridized mRNA was subjected to autoradiography.

RESULTS

Effect of oil and cream on hair growth by total hair count technique

A significant increase in the total number of hair grown in either cream or oil treated areas in the flank region of Guinea pigs was recorded from 3 day of treatment through 9 days, but not in the control (Table-I).

Similarly, the length of the hair was also recorded to be long in cream or oil treated areas than the control (Table-II).

Northern blotting

The mRNA expression specific to Shh cDNA was recorded in the matrix cells isolated from either oil or cream treated hairs but not in the control. The molecular weight of the transcript was recorded to be 3.1 kb corresponding to the probe length (Fig 1 and Fig 2).

Similarly, gene expression specific to tyrosinase enzyme was recorded in the matrix cells of the treated hair, but not in the control (data not shown).

Table I

Effect of cream and oil treatment on hair growth by total hair count technique

Treatment group	No. of animals	Total No. of hair grown at Different time intervals (days)					
		3		6		9	
		Mean	SD	Mean	SD	Mean	SD
Cream	2	170	0,72	280	0,28	212	0,57
Oil	2	190	0,83	264	0,51	279	0,18
Control	4	87	1.34	91	1.23	107	1.83

Table II

Effect of cream and oil treatment on hair growth – determination of length of the hair (mm)

Treatment group	No. of animals	Mean length of the hair grown at different time intervals (days)		
		3	6	9
Cream	2	+	++	+++
Oil	2	++	+++	+++
Control	4	-	+	++

- \- Negligible hair length
- \+ Hair length up to 2mm
- ++ Hair length 2 to 4 mm
- +++ Hair length 4 to 6 mm

DISCUSSION

Hair follicle is one among the human tissues containing stem cells [17]. The stem cells are interspersed within the basal layer of the outer root sheet and also in an area called bulge. From these reservoirs, the stem cells migrate to the hair matrix and then divide and differentiate to hair [18]. The division of the hair matrix is controlled by numerous cytokiues produced by the cells of the dermal papilla [12]. The hair fall resulting in baldness is mainly due to the androgens, which influence the synthesis and release of cytokines by the dermal papilla cells [19-21]. The production of androgen as a single entity largely affects the hair growth than any other physiological process in a mammalian system. The cytoplasm and nucleus of the dermal papilla cells have abundant collection of androgen receptors.

An increased anagen phase requires an effective involvement of both matrix and dermal papilla cells. The basic fibroblast growth factor (bfGF) and platelet-derived growth factor (PDGF) are known to potentiate the growth of dermal papilla cells. Similarly, the insulin like growth factor I (IGF-I) is known to accelerate the hair growth in a concentration dependent manner [22-24].

The action of IGF-I is modulated by proteins (insulin like growth factor binding protein – IGFBPs) produced by dermal papilla cells.

Northern blot analysis of mRNA specific to Shh cDNA in treated and control animals

Fig.1 **Fig.2**

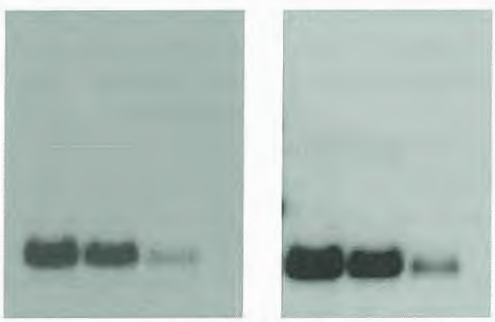

Fig. 1 *mRNA expression patterns specific to Shh cDNA in the hair follicle cells (matrix) collected from oil treated and control area.*
Lane 1 and 2 are the mRNA expression pattern of oil treated hair.
Lane 3 Untreated (control).

Fig. 2 *mRNA expression patterns specific to Shh cDNA in the hair follicle cells (matrix) collected from cream treated and control area.*
Lane 1a and 2a are the RNA expression pattern of cream treated hair.
Lane 3a Untreated (control).

However, the exact mechanism of modulation is not yet understood [25]. It has been shown that IGFBP3 (which is the most abundant type present in the dermal papilla cells) forms a complex with free IGF-I (available for the stimulation of hair elongation and maintenance of the anagen phase) and thereby influences the hair growth.

Animal studies have shown that substance P induces transition of hair from telogen to anagen phase [26]. The same effect has been observed with the active principle of chilli and pepper, which release substance P from the nerve endings in the skin. The snbstances P also known to bind to receptor on C-type afferent nerve fibers and produce pain [26].

The currently available drugs for hair growth can be broadly classified into 3 categories viz., cytotoxic drugs, anti-androgens and drugs acting on potassium channels. Anti-androgen drugs, either reduce the androgen hormones or block the transfer of testosterone to 5-DHT or block the androgen receptors in the dermal papilla cells, have met with severe consequences due to various side effects.

The action of cyclosporine, minoxidil and diazoxide on hair growth is by opening the potassium channel in the cell membrane leading to hypertrihotic action [27].

The total hair connt assay has revealed that the topical application of the Keshraksha oil and Keshraksha hair vitalizing cream has a significant effect on hair growth in Guinea pig model. Interestingly, the length of the hair in the oil and cream treated areas was also found to be longer than the hair in the untreated (control) area during the study period. Although the observation we made in the animal model could not be directly extrapolated to humans, where the hair growth in humans is in a mosaic pattern instead of the wave pattern as seen in animals [16]. However, we have recorded an increased RNA synthesis in the matrix cells of either cream or oil treated hair but not in the control. In the light of the increased hair growth recorded in the oil and cream treated region coupled with increased RNA synthesis appears significant.

We have studied the possible mechanism of action of oil and cream formulations on hair growth by northern blot analysis. For this purpose, we used the Sonic Hedge Hog gene (Shh cDNA) as probe to determine the specific mRNA expression. Shh is one of the well-known and well-studied genes responsible for hair growth in both pre-natal and post- natal skin [16,28,29].

In our study, we have recorded an increased mRNA expression specific to Shh cDNA in the matrix cells treated either with cream or oil but not in the control. The molecular weight of the transcript was recorded to be 3.1 kb, which was comparable to the length of probe. The above finding suggests that the oil and cream treatment may enhance the protein synthesis essential for hair growth. However it is not clear, whether, the ingredients in the oil and cream can also increase the production of various cytokines by dermal papilla and other mechanisms involved in the hair growth. Interestingly, mRNA expression specific to tyrosinase gene was also recorded in the matrix cells treated eitber with cream or oil but not in the control. It is already known that, tyrosinase enzyme catalyze the amino acid tyrosine, which is transformed through dopa to dopaquinon, an essential biochemical product in the melanin synthesis.

We have already established that the oil extract of Wrightia tinctoria and Muraya paniculata can enhance the phagocytosis and phagocytic killing of an antigen by the peritoneal macrophages (data communicated for publication). The uptake of synthesized melanin by the matrix cells are through the process of phagocytosis. Therefore we presume that, the application of cream and or oil besides enhancing the anagen phase of the hair, can also enhance the melanogenesis

and uptake of melanin by the hair.

At present we are evaluating the hair growth enhancing property of cream and oil formulations in humans. Nevertheless, the findings of the present study suggest that an herbal solution to baldness is in near future.

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Author Address:

Dr. S. Ranganathan
No.21 (Old No.6),
Sivaji Street, T. Nagar,
Chennai-600 017 - INDIA
Phone: 044 4338982.
Email: drsranganathan@yahoo.com

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AZELOYL-GLYCINE: A NEW ACTIVE IN SKIN DISEQUILIBRIUM

L. Rigano[1], M. Cucchiara[2]
[1] ISPE S.r.l. - Milano - Italy
[2] Sinerga - Pero (Milano) - Italy

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Summary

The dermatological uses of Azelaic acid are related to its anti-sebhorreic, anti-mycotic and anti-acne properties. However, its limits in topical formulations are well known, even when it is used at lower concentrations than the pharmacological ones.
Firstly, a high percentage amount is required to be effective. Secondly, being insoluble at high concentrations, it provides poor cosmetic properties to the formulations, which result to be thick and difficult to spread over the skin. Finally, its solubilisation by adequate chemical methods (e.g. neutralisation) brings to loss of Azelaic acid content during shelf life, as it decarboxylates. In order to overcome these problems a new molecule, Potassium Azeloyl di-Glycinate, has been produced. It exhibits very high water solubility, high specific activity at low concentration, low toxicity and adequate chemical stability and compatibility. Serial cosmetic efficacy essays have been carried out with informed volunteers. The preliminary results are very interesting. It proved very effective as skin whitening agent and sebum normalizer. In addition, other skin parameters like moisturization and some elastic properties show remarkable improvements.
As far as applications are concerned, a pre-systematic study on all the cosmetic functionalities has identified the most proper cosmetic forms for preparing topic formulations. Finally, complete formulations have been developed, in order to use the sebum normalizing and skin lightening properties of this new raw material.

Riassunto

Gli impieghi dermatologici dell'acido azelaico sono correlati alle sue proprietà anti-seborreiche, anti-micotiche e anti-acne. Tuttavia, i suoi limiti applicativi nelle formulazioni topiche sono ben noti, anche a dosaggi più bassi di quelli farmacologici.
Innanzitutto, sono necessarie alte concentrazioni per ottenere adeguata efficacia.
Poi, la sua insolubilità a tali concentrazioni dà scarse proprietà applicative alle emulsioni, che sono pesanti e difficili da distribuire sull'epidermide. Infine, la solubilizzazione con metodi chimici ade-

guati (es. neutralizzazione) ha come conseguenza la caduta del titolo in acido azelaico, che lentamente si decarbossila. Per eliminare questi problemi, è stata sintetizzata una nuova molecola, il Potassio Azeloil di-Glicinato.
I suoi vantaggi principali sono: alta solubilitàin acqua, alta attività specifica a basse concentrazioni, bassa tossicità, stabilità chimica e compatibilità adeguate. Una serie di valutazioni di efficacia cutanea è stata condotta con volontari informati. I risultati preliminari sono molto interessanti. E' stata dimostrata l'efficacia significativa come schiarente cutaneo e normalizzante delle secrezioni sebacee. Inoltre i parametri di idratazione cutanea e alcuni parametri relativi all'elasticità cutanea sono notevolmente migliorati dopo uso continuato della sostanza. Per quanto riguarda le applicazioni, uno studio pre-sistematico ha permesso di identificare le forme cosmetiche di impiego più adatte. Sono state poi sviluppate alcune formulazioni finite, adatte a mettere in evidenza le proprietà schiarenti e sebo-normalizzanti di questa nuova molecola.

INTRODUCTION

Azelaic acid (heptanedicarboxylic or nonanedioic acid) is a linear, saturated dicarboxylic acid formed by nine carbon atoms. It is a dietary and physiological constituent, produced endogenously from dicarboxylic acids having longer chains and from the metabolism of superior fatty acids (e.g. oleic). Industrially it has been prepared by disruptive oxydation of ricinoleic acid. It possesses bacteriostatic properties in-vitro against many aerobic micro-organisms, like *Staphylococcus aureus, Staphylococcus epidermis, Proteus mirabilis, Escherichia coli, Pseudomonas aeruginosa, Candida albicans* and *Propionibacterium acnes,* and it shows, at high concentrations, even bactericidal properties for some of the above species *(S. epidermis and P. acnes)* probably because of its inhibition of cellular protein synthesis.

EFFECTS ON THE SKIN

It is used extensively to treat acne, as it reduces the density of the cutaneous microflora and the amount of free fatty acids in the skin surface lipids. While the mechanisms of its effects on the sebaceous glands are not clear, subjective reports of noticeable reduction in skin greasiness after 1 to 2 months treatment with Azelaic acid creams at 15 or 20% concentrations have been described.

Azelaic acid is an-vitro inhibitor of tyrosinase, the most important enzyme involved in melanogenesis, via the inhibition of its hydroxylation. Apparently it inhibits the generation of the oxygen reactive radicals, superoxide anion and hydroxy radical, in biological systems; this property has been related to its anti-inflammatory characteristics.

Moreover, it reduces the differentiation of human keratinocytes by acting on the synthesis of filaggrin, thus behaving as an antikeratinising agent. This property has been associated with its beneficial effects in the treatment of acne. In other words, the antimicrobial effects against P. acnes and the anti-keratinising effects on the follicular epidermis, associated to its anti-inflammatory actions are the reasons for the efficacy of Azelaic acid against many acne phenomena.

APPLICATION PROBLEMS

Even if Azelaic acid is a rather safe material (in fact it lacks over systemic toxicity; it has no use limitations according to the European Cosmetic Law; it is not allergenic; its 20% suspensions are applied to the skin without adverse effects except mild transient erythema and cutaneous irritation), an extended use in skin treatment products is limited because of its almost total insolubility in water and in many common skin compatible solvents, even at dosage which could be lower than therapeutic concentrations. It is currently employed as atomised suspension in emulsions. As a rule, its solubility increases with its neutralisation degree performed by common alkaline solutions. However this gives rise to a new problem. In fact alkaline solutions are unstable and a quick loss of the acid title is found.

A NEW SOLUTION

By reacting the chloride of Azelaic acid with two molecules of Glycine, a new compound is formed, having two peptidic bonds with two carboxymethyl groups instead of the two original carboxylic groups. It is a sort of di-amido di-carboxylic acid, 1,7 di-carboxymethyl-amido eptane or azeloamido-diacetic acid or Azeloyl di-glycine , which results in a very interesting soluble salt by neutralisation with potassium hydroxide. In fact 30% solutions are permanently

stable at pH between 3 and 11, are self-preserving and keep their water content even at low relative ambient humidity. Dilute solutions (3% aq) were employed for a set of in-vivo trials in order to test its interaction with the skin and the influence on skin properties.
The solution is compatible with most aqueous ingredients and it does not induce important changes in the structure and stability when added to O/W emulsions at concentrations up to 10%.

IN-VIVO EVALUATIONS

The first group of *in-vivo* evaluations was carried out on a small number of volunteers in order to establish which study area was to be further investigated. For this purpose five volunteers for each evaluation type were selected.

Evaluation of the sebum normalisation effects

The 3% aqueous solution was used on the skin of five volunteers, previously selected on the basis of the sebometric levels (higher than 130 $\mu g/cm^2$) on their forehead, nose and chin. Measurements were taken with a Sebumeter (Courage & Khazaka). The volunteers applied the solution twice a day over the face, with a cotton wad, for 3 weeks. As a result significant reductions of the sebometric values were found in all three face areas (Tab I):

Tab I

Sebometric results after 21 day application of Potassium Azeloyl di-Glycinate, 3% aq solution, on the face of 5 volunteers with greasy skin

Position	average decrease	relative decrease	p
Forehead	50 $\mu g/cm^2$	29.4%	< 0.05
Nose	44 $\mu g/cm^2$	27.0%	< 0.05
Chin	52 $\mu g/cm^2$	31.5%	< 0.05

The results showed that, in spite of the very low number of selected volunteers, efficacy values are statistically significant and indicated a strong effect on the casual level of skin lipids.

Evaluation of skin moisturisation, elasticity and wrinkle parameters

The same solution was used for the skin of five additional volunteers, having low skin moisture content as measured by the Corneometer (Courage & Khazaka). The values were below 100 units. The solution was applied twice a day over the face, with a cotton wad, for 3 weeks. The results showed a significant increase in the moisture content of the stratum corneum as proved by the corneometric values (Tab II):

Tab II

Corneometric values after 21 days treatment with Potassium Azeloyl Diglycinate, 3% aqueous solution, on the face of 5 volunteers with dry skin. Comparison between initial and final values

Position	average increase	relative decrease	p
Forehead	9.7 corneometric units	12.7%	= 0.01
Cheek	6.4 corneometric units	8.2%	= 0.005

Also in this case, it can be seen that efficacy results are highly statistically significant and proved a remarkable moisturising power, in spite of the very low number of selected volunteers. On the same volunteers the elasticity parameters were measured. They are reported in Tab III.

Tab III

Elasticity values after 21 day treatment, twice daily, with Potassium Azeloyl di-Glycinate, 3% aq solution, on the face of 5 volunteers with dry skin. Comparison between initial and final values. R9 is the value related to skin elasticity, R2 to the elasticity of the first curve, Ro is the maximum extensibility and R1 is the recovery after extension.

Position	value	average increase	relative decrease	p
Forehead	R9	0.022	2.5%	= 0.02
	R2	0.057	5.7	> 0.05
	Ro	0.016	9.7	> 0.05
	R1	0.001	38.5	> 0.05

The values on the cheek were also measured but they did not show significant differences. On the same subjects, measurements of skin wrinkledness were taken by making a skin replica with a special resin (Silflo) at the beginning and at the end of the treatment with Azeloyl di-Glycinate. Results are reported in Table IV.

Tab IV

Changes in wrinkle parameters values after 21 day treatment, with Potassium Azeloyl di-Glycinate, 3% aq solution, on the face skin of 5 volunteers with dry skin. Comparison between initial and final values.

Position	Value	relative decrease	p
Forehead	average of greys	6.7%	> 0.05
	sigma	11.7%	> 0.05
Cheek	average of greys	9.4%	> 0.05
	sigma	5.1%	> 0.05

It is not possible to say if the non significant results obtained are due to a lack of efficiency in modifying the skin wrinkledness or to the insufficient number of tested volunteers.

5.1. Evaluation of skin colour

3% aqueous solution was used on the skin of five additional volunteers, having dark cutaneous spots on their skin, and the same application method was used. Skin colour was measured by a Minolta Colorimeter, both on the dark spots and on the surrounding skin, taking into account the "L" (luminosity, related to the whiteness degree) "a" (red component) "b" (green component) parameters in order to define the skin colour. In order to compensate the physiological changes, non treated sites were controlled at the beginning and the end of the 21 days' period of the test, as internal reference. Results are reported in Tab V.

Tab V

Changes in L, a, b values of the skin, treated and non treated areas, for 21 days, twice a day, with Potassium Azeloyl di-Glycinate, 3% aq solution. Dark spots and the surrounding skin were examined. Increases and decreases refer to the initial values of the sites to be treated. t = treated n= non treated. Minolta Colorimeter.

Skin site	'L' relative	p	'a' relative	p	'b' relative	p
Dark spot	t 3.2%	< 0.05	10.1%	> 0.05	3.6%	>0.05
Dark spot	n 1.6%	>0.05	- 4.6%	> 0.05	3.5%	>0.05
Normal skin	t 5.4%	< 0.05	12.2%	< 0.05	5.5%	>0.05
Normal skin	n 0.9%	> 0.05	0.2%	> 0.05	-1.6%	>0.05

In spite of the low number of volunteers, the skin whitening effect of Potassium Azeloyl di-Glycinate is evident. This is more active on normal skin than on melanotic sites, similarly to what was previously reported for Azelaic acid. The significant skin whitening effect is accompanied by the simultaneous significant reduction of the red components in the skin colour.

INNOCUITY EVALUATIONS

The concentrated (30%) solution of Potassium Azeloyl di-Glycinate was submitted to dermatological evaluations of skin innocuity on twenty volunteers and proved non irritant and non sensitising. In-vitro ocular irritation test with the Het-Cam test yielded very satisfactory results.

APPLICATIONS

From the application point of view, the evaluation of the technical performances consisted of two different parts:

1. Different systematic trials have been made in order to define and optimise the use of Azeloglicina® in the main cosmetic forms.
2. We have also realised some finished products by exploiting the knowledge acquired in the systematic trials.

SYSTEMATIC TRIALS

Azeloglicina® has been used at 5%. The cosmetic forms tested were: Solution (LSA01) Surfactant (LSA02) Non-ionic gel (LSA03) Anionic gel (LSA04) Non-ionic gel (LSA05) Anionic emulsion O/W (LSA07) O/W Anionic emulsion (LSA08) W/O Emulsion (LSA09) O/W Non-ionic emulsion (LSA10). Parallel formulation trials not containing the functional ingredient have also been made, in order to evaluate possible organoleptic modifications induced by the product. In non-ionic emulsions, we observed a tendential viscosity decrease due to the saline

PRODUCT	COMPATIBILITY	INCOMPATIBILITY
AZELOGLICINA	• Anionic surfactants • Non-ionic surfactants • Rheological modifiers - Ex: Guar Gum - Ex: Hydroxyethylcellulose • Anionic emulsifiers: - Es: Potassium Palmitoyl Hydrolyzed Wheat Protein + Glyceryl Stearate,+ Cetearyl Alcohol • Non-ionic emulsifiers - Ex: Cetearyl Alcohol + Cetearyl Glucoside • Rheological modifiers sensitive to electrolytes • Substances of cationic nature	• Rheological modifiers sensitive to electrolytes • Substances of cationic nature

nature of Azeloglicina®. We suggest to increase the amount of rheology modifiers or consistency factors in order to maintain the desired viscosity.
The remarked compatibility aspect are here described:

FINISHED FORMULAE

Some cosmetic formulations have been prepared according to the information obtained in the systematic trials. Due to its functionality, Azeloglicina® has been employed at 5% in sebum-normalising products, and, at 6%, in skin lightening products.
The following products have been prepared:

- Sebum normalizing tonic
- Elasticizing, lightening gel for decolleté and hands
- Cream for impure skin (O/W emulsion)
- Anti-age lightening cream (O/W emulsion)

Some formulations examples of finished products, complete with final organoleptic characteristics of the product and manufacturing method are here described:

MANUFACTURING METHOD:

A. Weight 1 and add components 2,3,4 in this order, by mixing after each addition until system is homogeneous.
B. Premix 5+6 and add to A, until system is homogeneous.
C. Finally weight 7 and add to AB. Mix until system is clear.

* This frangrance is a natural parfum endowed with antibacterial properties.

TONIC SEBUM NORMALIZING LOTION		
N°	INCI	%
1.	AQUA	q.b. 100
2.	PROPYLENE GLYCOL, DIAZOLIDINYL UREA, METHYLPARABEN, PROPYLPARABEN	0,90
3.	PROPYLENE GLYCOL, CITRUS MEDICA LIMONUM	2,50
4.	ALCOHOL	5,00
5.	DECETH-7, PEG-40 HYDROGENATED CASTOR OIL, PPG-26-BUTETH-26	0,50
6.	PARFUM 0,10	
7.	POTASSIUM AZELAOYL DIGLYCINATE	10,00

CHEMICAL-PHYSICAL CHARACTERISTICS		
Aspect	:	clear solution
Color	:	pale yellow
pH	:	7,03

ELASTICIZING, LIGHTENING GEL FOR HANDS AND DECOLLETE'		
N°	INCI	%
1.	AQUA	q.b. 100
2.	DISODIUM EDTA	0,10
3.	DIMETHICONE COPOLYOL	1,00
4.	GLYCERIN	2,00
5.	HYDROXYPROPYL GUAR	1,50
6.	PARFUM *	1,00
7.	LYSINE CARBOXYMETHYL CYSTEINATE	2,50
8.	POTASSIUM AZELAOYL DIGLYCINATE	6,00
9.	AQUA, ALGAE	5,00
10.	PPG-BUTETH 26 PEG-40 HYDROGENATED CASTOR OIL	0,40
11.	PARFUM	0,20

CHEMICAL-PHYSICAL CHARACTERISTICS		
Aspect	:	opaque gel
Color	:	pale yellow
Odor	:	characteristic
pH	:	6.60
Viscosity (at 25°C)	:	2600 mPa.s

MANUFACTURING METHOD:

A. Weight in in the homomix and heat to 65°C. Add 2,3,4,5 and homomix till homogeneous system.
B. Cool down to 40°C and add 6,7,8,9
C. Finally premix 10+11, add to AB and mix until system is homogeneous.

MANUFACTURING METHOD:

A. Weight 1,2,3,5 and heat to 65°C. Add to the melted blend 4,6 and mix till system is homogeneous
B. Weight 7,9,11, heat to 65°C and add 8 by homomixing for 10' (verify proper dispersion)
C. Create emulsion by adding phase A into phase B and and homomix for 10'
D. Cool down to 50°C, add 10 and homomix for 10'
E. Cool down to 30°C, add 11,12,13 (dissolved into some water), and homomix for 5'.

From the results obtained, Azeloglicina®, due to

CREAM FOR IMPURE SKIN		
N°	INCI NAME	%
1.	POTASSIUM PALMITOYL HYDROLYZED WHEAT PROTEIN, GLYCERYL STEARATE, CETEARYL ALCOHOL	7,50
2.	ETHYLHEXYL ETHYLHEXANOATE	5,00
3.	CAPRYLIC/CAPRYC TRYGLYCERYDE	2,00
4.	SIMMONDSIA CHINENSIS	1,00
5.	DIMETHICONE	0,50
6.	STEARYL GLYCYRRETINATE	0,10
7.	AQUA	q.b.100
8.	XANTAN GUM	0,25
9.	GLYCERIN	1,50
10.	PARFUM	1,00
11.	DISODIUM EDTA	0,10
12.	POTASSIUM AZELAOYL DIGLYCINATE	5,00
13.	LYSINE CARBOXYMETHYL CYSTEINATE, LYSINE THIAZOLIDINE CARBOXYLATE	3,00

CHEMICAL-PHYSICAL CHARACTERISTICS		
Aspect	:	viscous emulsion
Color	:	white
Odor	:	characteristic
pH	:	6.03
Viscosity (at 25°C)	:	5000 mPa.s

its saline nature, is not compatible with gelling agents sensitive to electrolytes, such as carbomers. It resulted perfectly compatible with anionic emulsifiers such as, for example the blend Potassium Palmitoyl Hydrolyzed Wheat Protein, Glyceryl Stearate, Cetearyl Alcohol, as well as with the non ionic emulsifiers blend Cetearyl Alcohol with Cetearyl Glucoside.

The general effect of Azeloglicina® on organoleptic characteristics of formulations is a light tendency to decrease viscosity, especially in gels and non ionic emulsions.

It reveals good technical characteristics, being perfectly soluble in water. Being non sensitive to heat, it may be added at any step of formulation production.

Azeloglicina® is a handy ingredient, with multifunctional properties; it is highly skin friendly, absolutely non toxic, safe and very easily handable.

FURTHER STUDIES

Further studies are being carried out in order to establish a dose-effect relationship for the different activities of Potassium Azeloyl di-Glycinate (commercial name Azeloglicina®). The first group of results, concerning the skin whitening effects, seem to be confirmed even at lower concentrations.
Clinical trials of a cosmetic cream containing Potassium Azeloyl di-Glycinate at 1% are being carried out. The product appears capable of reducing the skin redness.

CONCLUSIONS

Derivatization of the sparingly soluble molecule of azelaic acid led to the formulation of a new derivative, Potassium Azeloyl di-Glycinate. This is totally water-soluble, stable in aqueous solution, compatible with many cosmetic ingredients and shows many beneficial effects on skin mechanical and physical properties. The skin whitening effect and the oily skin treatment seem the most interesting properties of the new derivative, thanks to its peculiar chemical nature and the capability of interfering with skin colour and sebum level even at low concentrations. Formulations are easy prepared, keeping in mind the salt content of the raw material ant its interference with some hydrophilic polymers.

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Author Address:

Luigi Rigano
ISPE
Via Bruschetti, 1
20125 MILANO - Italy
Fax: 02.66.98.85.60
Email: rigano.labor@iol.it

A THERAPY OF MODERATE-TO-SEVERE PSORIASIS. SECOND REVISED EDITION

By G.D. Weinstein and A.B. Gottlier

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The goal of this 15 chapters book is to provide guidelines on state-of-art clinical management of moderate-to-severe psoriasis.

Psoriasis is a chronic skin disease that occurs in 1% to 3% of the population world wide. It is characterized by thickened, red areas of skin covered with silvery scales and is genetically transmissed. The extent of skin involvement can range from discrete, localized areas to generalized body. Joints, nails and mucous membranes may also be affected by the disease. Moreover, the majority of patients show evidence of scalp involvement. When scalp psoriasis predominates with or without associated facial involvement, seborrheic dermatitis may produce the clinical variant known as sebopsoriasis. Traditionally, two distinct forms of psoriasis have been noted: type I disease with early onset (before age of 40) and type II late onset (over 40 years age).

The disease is lifelong and characterized by chronic recurrent exacerbations and remissions that are emotionally and physically debilitating. Extent and severity of psoriasis vary widely and may be influenced by stress physical trauma, systemic drugs and environment and for most patients is more emotionally than physically disabling. It erodes the self-image and forces the victim into a life of concealment and self-consciousness. Patient avoid activities, including sunbathing, the very activity that can clear the disease, for fear of being discovered. Therefore, even when a patient has only a few asymptomatic chronic plaques, the disease is more serious than it appears. When severe, the effects of psoriasis can have a deleterious impact on work performance, social performance and acceptability, sexual function, and mental health.

The therapeutic approaches to psoriasis today include topical or local medications, phototerapeutic modalities, and systemic drugs. The continuing stress and psoriasis controversy makes also research into treatment programs that combines this dermatological therapies with psychological intervention (worth investigating).

Moreover the issue of cosmesis may be more distressing than anything else, leading to psychological difficulties because of an altered self-image. As matter of fact, the use of emollients increase the patient's comfort by relieving dryness, scaling, and pruritus.

Therefore the strategy of therapy starts with an educational process that informs the patient as to the nature of psoriasis and therapeutic capabilities available today for the type and extent of disease in

the particular patient.
The final discussion has to research the real goal, which is to improve the patient's quality of life without producing undue harm medically, fiscally or emotionally. The physician has to present to the patient a realistic, but optimistic big picture of therapy, keeping in mind the chronicity of this disease.
The Overview of Psoriasis and Topic Agents in the Treatment of Moderate-to-Severe Psoriasis are discussed in chapter 1 and 2.
UVB-phototherapy is focused on chapter 3. Ultraviolet light (UVB) is one of the oldest therapeutic modalities for the treatment of psoriasis, ultraviolet light in intensity high enough to be effective can be obtained from natural sunlight or commercially available light cabinets. There is a significant positive correlation between the patients' responses to sunbathing and their responses to short-wave UVB phototherapy.
Sunlight non responders have a 70% chance of failure with UVB phototherapy; sunlight responders have an 80% chance that clearance treatment will succeed.
Thus UVB regimens range from simple treatments in a UVB phototherapy box, with or without concurrent use of commercially available topical or systemic agents, to a much more elaborate and aggressive modality in which the intensity of UVB radiation used varies not only among patients, but also according to different anatomical regions within the same patient.
Of course this therapy is contraindicated in patients who react badly to light, but it represents one of the safest therapeutic option available for treating widespread psoriasis. For moderate psoriasis, UVB phototherapy is usually reserved for patients whose disease does not adequately respond to topical medications such as steroids, calcipotriol tarazotene, tar, or anthralin.
Chapter 4 is focused on the treatment, known as PUVA, the artificial source of ultraviolet A. This treatment is so designed because of the use of a class of drugs called psoralens (abbreviated P) along with exposure to long-wave ultraviolet light (abbreviated UVA).
Patients ingest a prescribed dose of methoxsalen (8-methoxypsoralen) approximately 2 hours before being exposed to a carefully measured amount of UVA in a uniquely designed enclosure. The drug apparently couples with and inhibits DNA synthesis after activation with ultraviolet radiation (320-400nm) thereby decreasing cellular proliferation. A major advantage of PUVA is that it controls severe psoriasis with relatively few maintenance treatments and it can be done on an outpatient basis. Light does not penetrate hair: scalp psoriasis must be treated with conventional therapy. However successful of PUVA therapy requires a well-informed physician, a trained staff, and a careful evaluated, educated and motivated patient.
A significant disadvantage of this therapy (like other form of UV therapy) is its cost in terms of time and money.
Therapy of Moderate-to-Severe Psoriasis with Methotrexate is the topic of chapter 5. These patients have an involved body surface area greater than 15-20%. Methotrexate (MTX) blocks the synthesis of DNA by inhibiting dihydrofolic acid reductase, preventing the donation of methyl groups during synthesis of purine and pyrimidine nucleotides. Therefore, this drug may exert a therapeutic effect in psoriasis by directly interfering with epidermal cell proliferation.
In fact, psoriatic skin contains twice as many proliferating cells and eight times as many cells in the synthesis phase of cell division as normal skin.

In addition, the proliferating cells have a cell cycle of 36 h, which is eight times faster than normal. The pre-therapy evaluation starts with an appropriate history and physical examination that concentrates mainly on the patient's renal and liver function. MTX is excreted, in fact, mainly by the kindeys and patients, receiving this drug, have to be monitored for its effect on hematopoietic and liver function.

The dosage schedule is to be initiated with a 2.5-5.0 mg at 12-h interval for 3 doses each week and gradually increased by 2.5 mg/h every 2-4 weeks with appropriate monitoring of laboratory tests. The total weekly maintenance dosage is usually between 7.5 and 25.0 mg. However, dosage as high as 37.5 mg per week may be required.

Concomitant administration of folic acid (1-5 mg/day) can reduce side effects such as nausea and megaloblastic anemia without affecting the effects of MTX.

Having a good cost/benefit and benefit/risk the MTX therapy remains an important drug for the therapy of moderate to severe psoriasis.

The treatment of psoriasis with acitretin is reported on chapter 6 where clinical investigations on new retinoid analogs are also mentioned.

Acitretin is the principal active metabolite of the prodrug etetrinate, and it is 50 times less lipophilic. For his reason acitretin has a much shorter half-life (approximately 50 h), than etetrinate (approximately 120 days), which, for its high lipophilicy, is accumulated in adipose tissue.

This relatively new retinoid modulates the cellular differentiation of the epidermis, which results in decreased scaling, erythema, and thickness of the psoriasis plaques.

Acitretin should be considered as monotherapy in generalized pustular psoriasis.

In this case the initial dosage is 25-50 mg/day, but higher dosage may be required in some patients. A rapid resolution of generalized pustular psoriasis is achieved usually within 10 days of initiating acitretin, which is probably the drug of first choice for the treatment of this condition. After the clearance of postulation, the psoriasis can continue to be controlled by reducing the dosage. For combination therapy, the optimum dosage is 0.3 mg/kg/day, either 2 week prior to starting UVB or UVA phototherapy or at the same time.

Concomitant treatment with acitretin, and topical calcipotriene may help to reduce psoriatic plaques better than with either alone. In addition, acitretin, at 25 mg/day together with hydroxyurea 500 mg twice daily has been effective for some patients with chronic plaque psoriasis and pustular psoriasis.

New retinoids such as tazarotene seems to have a good safety profile for other combination therapy. Moreover the new immunomodulatory biological agents may play pivotal roles in the future treatment of psoriasis.

The use of Cyclosporine in the Treatment of severe Psorisis is described in chapter 7.

Cyclosporine prevents the activation of T cells, which is important in the immune system induced propagation of psoriasis. It inhibits the enzyme calcineurin, preventing the transcription of interleukin-2 (IL-2) gene.

Moreover cyclosporine prevents the egress on the skin of various inflammatory cells from the vascular system by reducing adhesion molecules on the vessel surface. Furthermore, reduction of adhesion molecules in the skin means that inflammatory cells traversing the area, are less likely to stay in the skin and be activated.

Because cyclosporine is an immunodepressive drug which can also produce nephrotoxicity, its use

should be limited to the treatment of patients with moderately severe to severe psoriasis.
The recommended starting dosage is 2.5 mg/kg/day. When the response appears clearly insufficient, the dosage may be increased by 0.5-1 mg/kg to the maximum dose.
If the patient shows no improvement after receiving 4/5 mg/kg/day for 3-4 months, cyclosporine should be stopped by tapering off over the next month.
Cyclosporine is recommended as an intermittent therapy for psoriasis. But patients taking this drug tend to have more severe psoriasis when it is discontinued and therefore are likely to demonstrate recurrences when it is discontinued or shortly thereafter.
Thus a new systemic therapy such as acitretin, must be instituted during the cyclosporine taper. Side effects of cyclosporine are usually dose-dependent.
Combination, Rotational and Sequential Therapy is the topic of chapter 8.
By rotating treatments, the cumulative toxicity of each individual form of therapy could be minimized. Topical treatment has its limits. Many patients do not respond to the most vigorous topical programs or the disease may be so extensive that topical treatments is not practical. Thus a number of systemic drugs are available but all of them have potentially serious side effects. The use of topical therapy with phototherapy offers unique advantages and disadvantages.
Photochemotherapy is the technique most commonly used for extensive , chronic, plaque psoriasis. But also this has some contraindications.
For example, UVA inactivates calcipotriene and both UVA and UVB inactivate calcitriol. Therefore by rotating these treatments, the cumulative toxicity of each individual form of therapy could be minimized, thus reducing the carcinogenesis of PUVA, the hepatic fibrosis and need for liver biopsies with MTR, and the muscoloskeletal toxicity of retinoids or nephrotoxicity of cyclosporine. For this reason the concepts of rotational, combination and sequential therapy are born.
Sequential therapy involve three phases: a clearing phase, a transitional phase, and a maintenance phase.
As an example, cyclosporine at maximal dosage may be used for the clearing phase followed by the addition of acitretin in the transitional phase. Finally phototherapy with UVB or UVA may be used for the maintenance phase.
In conclusion, the availability of so many psoriasis treatments offers to the patients many options to reduce the toxicities of the used therapies.
The treatment of psoriasis in children involves a conventional therapeutic regimen of emollients, steroids, calcipotriene, tars, keratolytics, antibiotics and/or antihistamines. On the other hand, severe unresponsive psoriasis require ultraviolet light therapy or treatment with systemic agents, such as MTX, acitretin or cyclosporine.
Pediatric psoriasis is the well described topic of chapter 9, meanwhile chapter 10 reports description and management of Psoriasis Arthritis, (PsA) recognized now as a more severe form of arthritis than some years ago.
The course and prognosis of this disease suggest that early diagnosis and more aggressive treatment are crucial. Therefore, it is important for dermatologists to recognize the features of the arthritis, and it is important for rheumatologists to look for evidence of psoriasis in patient with arthritis.
The management of patients with PsA is best performed with team effort so that both aspects of the disease are dealt with.

However management plan begins with educating the patient that the condition is chronic, inflammatory in nature, and that consistent therapy is required. Patients should also be instructed to maintain a healthy lifestyle, as many patients with PsA have risk factors for coronary artery disease.
All the other chapters from 11 to 15 are entirely dedicated to the biotechnology-created immunobiologicals drugs, such as Etanercept, Alefacept, Infliximob and Efalizumab.
In fact psoriasis is an inflammatory T1, mediated T-cell disorder, but however, what causes activation of these T cell is still unknown.
However activated T cells are pivotal in maintaining psoriatic plaques and T lymphocytes are secondarily activated by keratinocytes. Therefore the inflammatory response in psoriatic plaques is initiated in part by activated T cells and dendritic cells in the epidermis and dermis.
From these considerations experimental treatment of patient with moderate to severe psoriasis with biologics has been successfully targeted on T cell activation, memory T cells, T-cell migration into the skin, Cytokines such as TNFa, induction of immune deviation from type 1 to type 2 cytokenes in plaques.
Using these five therapeutic strategies is possible to reverse clinical and histological pathology in psoriatic plaques.
These new compounds not only improve patient care but also produce good science.
At this purpose, Etanercept recombinant human protein has demonstrated efficacy as monotheraphy for moderate to severe psoriasis; acting as a competitive inhibitor of turnover necrosis factor (TNF). This drug is well tolerated by both adult and pediatric patient populations, and its long use have demonstrated an excellent safety profile.
Alefacept, also, significantly improves severity of psoriasis, producing durable clinical remission, without rebound following treatment cessation. Moreover the incremental effectiveness of a second course of its use provides strong support for the use of this drug as an intermittent therapy for psoriasis as a chronic disease.
Infliximob, targets the activity of TNFa and by interrupting the inflammatory cascade, has the potential to rapidly relieve the signs and symptoms of psoriasis and psoriatic arthritis.
Given the unique structure of this drug, it appears to have a high degree of efficacy and specificity.
Finally Efalizumab represents a significant new advance in the management of chronic plaque psoriasis .Several large phase III trials have demonstrated both safety and efficacy in both short-and long-term settings.
To date, there has been no evidence of drug interactions or organ toxicity.
In conclusion, with so many therapeutic approaches to the treatment of moderate to severe plaque-type psoriasis, it will be important to better define how they should be used, to determine which patients are candidate for these therapies, and to determine how they are to be administered.
Additionally, it will be necessary to have published trials with more large numbers of psoriasis patients treated with these targeted immunobiologicals for prolonged periods of time and to also have data on the confirmation of target immunobiological with each other and with current , in order to better control its efficacy and to assess safety risks to patient more accurately.
With these hopes, this interesting book full of new approach to therapies of moderate-to-severe psoriasis ends.
For the wide range of news on biological-genetic and clinical psoriasis and for the therapies sugge-

sted, this book will be a useful tool for dermatologists, medical doctors and rheumatologists wanting to enlarge their horizons on this common and difficult to treat pathology.

P. Morganti
Editor-in-Chief

POLYMER AND CELL DYNAMICS

by W. Alt, M. Chaplain, M. Grifrel and J. Lenz

2003. 290 pages; 16 color pages. Hardcover
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This book is the result of the international workshop on Numerical Simulations of Polymer and cell Dynamics which took place in June 2000 in Bad Honnef (Bonn).
Divided in three parts and for a total of 17 chapters, it reports the scientific results obtained from this interesting meeting.
All the scientists involved try to find quantitative solutions to basic questions on Molecular and Cell Biology by the use of physical and mathematical theories. Therefore the topics presented represent an attempt to understand the borderlines between the passive dynamics of pure matter, as molecules or polymers, and the active processes of structuring, organization, and regulation within living units, such as biological cells, tissues, or organs.
Part I, with its three chapters on Molecular Dynamics and Protein Configuration, shows how to represent the assembly and formation of elementary lipid or protein aggregates and how to study and classify geometric configuration changes in functional domains of enzymes or motor proteins.
As a matter of fact, the function of a biomolecule is closely related to its structure in three-dimensional space together with the possible changes of its conformation and variability over time. Knowledge of this structure is, therefore, essential to fully understand the function of a protein. At this pnrpose molecular dynamics (simulation methods) are used to study supra-molecular self-assembly.
These methodologies allow a better understanding of the processes on the molecnlar and macromolecular level and are a helpful tool to explore the dynamics, the structure, the conformations, and thus the function of proteins and other biomolecules.
Therefore with the aid of high-performance computers and the use of mathematical models it is feasible to extend the understanding of the factors governing molecular self-assembly.
Simplified chemical models seem to be capable, in fact, of elucidating the equilibrium and dynamical behavior and thus the function of proteins and other biomolecules. Therefore, on any level of dynamics phenomena in biophysics or biology, namely, for proteins, polymers, cells, tissues, organisms, populations, and ecosystems, mathematical modeling and numerical simulation have to find and use the appropriate strata of spatial and corresponding temporal scales.
It is obvious that, in order to explore the modeling of such phenomena in this wide range of biochemical, biotechnical, and biomedical applications-from molecular dynamics to tissue formation, very differing scales have to be considered: spatial scales reaching from nanometers to centimeters, temporal scales from microseconds to hours.
Thus the approach used in Part I is based on mesoscopic approximations of field potentials gained

from more microscopic quantum dynamics and finally leads to relatively macroscopic geometric and dynamic descriptions of whole proteins or even of protein assemblies (micelles or capsoids).
Polyhedral protein capsides forming the external shells of spherical viruses are described in chapter 1 by means of molecular dynamics simulation of micelles in surfactant solutions; two proteins, saponin B and saponin C are mentioned in chapter 2 as structural models to study the biological functions of these molecular machines; a database that classifies proteins into a limited number of categories, first on the basis of size and then on the basis of packaging, is the topic of chapter 3. This database is useful in both analyzing and classifying individual proteins and in generating a statistical picture of motions in the motions database as a whole.
All the reported models ought to be capable of elucidating the equilibrium and dynamical behavior that occur in a variety of biological lipid or protein aggregates, rooting in the molecular structure and interaction of its constituents.
Similar phenomena occur in binary mixture of simple liquids, such as oil and water that can form either a macroscopically homogeneous phase or a heterogeneous state in which the fluids are separated by an interface; the particular thermodynamic state depends on external variables such as relative concentration and temperature.
The situation becomes much more complicated in ternary systems, one of the better-known examples being amphiphilic surfactants in an oil-water mixture, a multitude of distinct phases appear in such systems, including micelles, bilayer vesicles, staks of bilayer membranes, and liquid crystals of various symmetries.
As a matter of fact, one of the goals of surfactant research is to quantitatively relate physico-chemical behavior to molecular structure.
Further studies aimed at exploring the mechanisms for transferring oil from a droplet to a micelle, and to a limited extent, the manner in which micelle shape depends on the size of the surfactant head group.
The underling structure and interactions of these micelle models can be varied to establish how the various features impact the nature of the biological phenomena of lipids and proteins and how to study and classify geometric configuration changes in functional domains of enzymes or motor proteins.
Moving to the more complex realm of polymer organization, **Part II** on Polymer Dynamics and Cell Motility in six chapters, deals with typical deformations of polymer chains, filaments, or networks and their interaction with surrounding media, ligands, cross-linkers, or molecular motors.
Active motility and locomotion of animal tissue cells are based on the interaction of actin and myosin, which form a contractile network within the cell. The advantage of modeling these biochemical phenomena or by computer simulations is, therefore, evident.
In this second part of the book, lumped groups of protein-monomers and their elastic interaction properties are used as mesoscopic ingredients to simulate the more macroscopic motion of single polymer chains. The different situations addressed in this extends from single polymer motion, to polymer cross-linking and network formation, and, finally, to single cell deformation and motility, both essentially depending on passive or active mechanical properties of actin filaments.
Cytoskeletal polymer chains like actin filaments, in fact, should be modeled as semi-flexible polymer chains since they are not compressible or stretchable but undergo elastic bending only.
Therefore, in these other three chapters, stochastic multiparticle models supplementary to each other are presented. Moreover they call for a more detailed and complete modeling framework and a cor-

responding simulation tool that can quantitatively reproduce the chemical kinetics and mechanical dynamics of actin filament systems as reactive and interacting semi-flexible polymers, as they are experimentally observed in living cells or artificial vesicles.
The subsequent three chapters rely on continuum models of cell motion, either described by viscoelastic fluid dynamics in a deformable domain with suitable numerical discretizations or, by a directly discretized dynamic system for elastic body deformation and motion.
In fact, these last chapters of Part II is exclusively based on the consideration of cell-objects, proposed as model of real cells and defined as 3D elastic physical objects with specific geometry and internal (sub-cellular) structure. This so-called POO approach (Physical Object Oriented) provides not only an efficient and versatile modeling tool for the validation of biological hypothesis, but also give quantitative information that can be compared to real experimental data at different level (sub-cellular, cellular, tissues) and scales (in time and space).
Part III, in eight chapters, deals with multicellular systems, developing individual-based multiparticle models using mesoscopic interaction potentials or fields derived from more microscopic sub-models for chemical or mechanical cell-cell interactions, in order to simulate aggregation and tissue-formation dynamics.
This focus on multiscale modeling has led to the development of novel modeling techniques that are capable of combining and, examining events at individual levels with events at a continuum level.
All the models, used in this last part of the book, are firmly grounded in biophysical reality and can be placed within an appropriately chosen and rigorous mathematical setting.
Platelet aggregation and coagulation are the two components of blood clotting, both of the normal homeostasis, that maintains vascular integrity, and of the pathological thrombosis that is the cause of most heart attacks and strokes.
The first chapter of Part III reports two approaches to modeling aspects of clotting. The first emphasizes fluid and cell interactions, while the second simplifies the mechanics and emphasizes the biochemistry. Both types of models can give important insight about the clothing process.
The second chapter (part I) reports the first results towards microscale simulations of flow, transport, reactive, and growth processes in 3D biofilm geometries obtained from Co focal Laser Scanning microscopy images of a small and defined monoculture biofilm setup.
The review paper of the third chapter (part III) provides and excellent and comprehensive survey of several key individual-based modeling approaches and simulation tools that have arisen recently in modeling the dynamics of multicellular biological systems. Presenting various lattice models, with discrete interaction, motion, and transition rules on spatial grids differently scaled, many illustrative examples are offered pointing to applications such as tumor growth, embryonic cell sorting, and morphogenesis of intestinal crypts and other endo-or epithelial growth and differentiation dynamics.
A series of chapters dealing specifically with individual-based models for multicellular systems follows.
The first considers the phenomenon of aggregation of individual cells into larger groups (cohort formation) generated through the active migration and interaction of the individuals. Cohort migration of cells is, in fact, a phenomenon particularly prevalent in vivo during embryogenesis, when groups of cells have to migrate to their final destination within organs or tissues.
Successively, the general concept of a bime (Biological Interacting and Moving Entity), is introduced. It is supposed that communication between bimes is performed via a specific medium by establishing a dynamic interaction field, whose perception stimulates the dynamic response and motile

activity of each single bime. This model may help to formulate and simulate collective cell movement with direct cell-cell contact, as occurs in models for wound healing and other cell dynamics. Contractile tissue cells such as fibroblasts placed in a collagen gel are able to deform the gel under certain conditions.

This is another treated topic. From measurements of gel deformation or boundary tension, it is possible to estimate cell traction parameters, which describe the amount of traction force exerted by each of cells.

The last two articles of Part III combine again continuum models with discrete models for collective cell motion. A novel modeling technique that provides a simple but effective way of linking macro – and microscale events are reported. The three problems considered are (i) angiogenesis in response to a solid tumor, (ii) tissue invasion by cancer cells, and (iii) aggregation in the slime mold Dictyostelium discoideum.

Tumor–induced angiogenesis is the formation of blood vessels from a preexisting vasculature in response to chemical stimuli, produced a secreted by the solid tumor.

The mathematical model describes the formation of the blood-vessel network in response to chemical stimuli supplied by a solid tumor. The model also takes into account essential cell-matrix interactions via the inclusion of the matrix macromolecule fibronectin.

This innovative book on Polymer and cell Dynamics let us know new methods of stndy necessary to better understand cell-cell and cell-medium interactions, to add the necessary modeling elements for cell growth kinetics, cell adhesion, or cell-cell communication by chemical signaling and control loops or by mechanical force transduction via extracellular matrices.

In particular, the book reports new results on mathematical modeling and computer simulation, offers a critical evaluation of existing methods counected with experimental results, showing practical examples to help understand the used methods. For all these reasous Polymer and cell Dynamics will be of great help for all the scientists and researchers in the field of biotechnology, biomedicine, applied mathematics, biomathematics, biophysics and bioinformatics and to all the students interested to better understand the reality of the modern Cosmetic Dermatology.

Pierfrancesco Morganti
Editor-in-Chief

SAFE LIPOSUCTION AND FAT TRANSFER

By Rhoda S. Narins

2003. 581 pages. Hardcover
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New York, NY, 10016
Fax. +212-685-4540
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The transplantation of fat from a new area of the body is an effective procedure. Safe liposuction and fat transfer is the focus of this interesting book.

The best clinical scientific knowledge of fat transfer and prevention of complication are, in fact, the most important aspects to prevent and reduce the probability of complications. Safe liposuction requires that surgeons avoid unnecessary risks and all factors must be taken into consideration and addressed to maintain and improve outcomes.

As the technology of medicine and surgery continue to evolve so do the clinical scientific aspect of fat transfer. For this reason liposuction become an exciting and challenging area of Cosmetic Surgery.

The book is divided in 11 sections and 34 chapters.

After the introductory remarks on liposuction reported on chapter 1, chapter 2 focuses on Initiating the Practice Liposuction. With the advent of the tumescent technique liposuction is now an elegant, satisfying procedure which effectively aspirates localized subcutaneous fat deposits. Thus tumescent liposuction is an extremely safe procedure but it has to be performed by a board-certified dermatologic surgeon.

Performing liposuction is exciting and gratifying and the beginning liposuction surgeon must have good traiuing. This may be obtained through exposure to liposuction at professional meetings, review of textbooks or special issues of journals devoted to liposuction, regular reading of the literature, and attendance at a live course prior to beginning liposuction in one's own practice.

A safe liposuction has to be performed by a board-certified dermatologic surgeon and, therefore, it requires as outpatient setting an appropriate Surgical Suite, and tumescent anesthesia together with a real patient's education. These are the topics of chapters 3, 4 and 5.

Thus the operating room walls (large enough for the surgeon and assistant to operate) should be smooth surfaced for easy cleaning. The floor and walls need also to surfaces resistant to corrosion and cracking. Excellent lighting from either high-intensity halogen lights or ceiling fluorescent light can provide adequate visualization for the surgeon. The aesthetics of the operating room has to have soft, cool colors like blue and green to allay anxiety and sedate patient.

Goals of the tumescent technique include targeting anesthesia locally, expanding the adipose, minimizing drug toxicity, and maximizing anesthetic efficacy. The basic solution used for tumescent anesthesia combines normal saline, lidocaine, epinephrine, sodium bicarbonate, and triamcinolone acetonide.

Concentrations of lidocaine greater than 0,5% provide a dose-dependent inhibition of bacterial growth, including gram-negative and gram-positive organisms. In concentration as low as 0,05% lidocaine has been shown to be bacteriostatic for Staphylococcus aureus. Moreover, sodium bicarbonate, in vitro, has been shown to augment the bactericidal activity of lidocaine.
Therefore, the concentration of lidocaine in the tumescent solution used delivered by blunt-tipped small-diameters cannulas, can range from 0.05 to 0,125% and its proper dosage and administration is essential to obtain a safety and efficacy liposuction.
However any patient being seen for safe liposuction and fat transfer should have routine history taken, carefully questioning and evaluating his/her family history. If the initial consultation is successful, a second visit is scheduled to prepare the patient for the day of surgery.
To remember that the ideal patient has to be in excellent health, not over weight having fatty deposits out of proportion to overall body shape. Moreover it is important that the patient's weight has been stable for several months prior to surgery.
The professionalism and friendliness of the surgeon and staff will earn the patient's trust. It is a time to demonstrate competency, attention to detail a caring attitude, and honesty.
Computer imaging is the topic of chapter 6. The photographic images necessary to create 3D interactive movie of a liposuction case can be created by taking a series of photographs of a patient at a set number of different angles. One the photos have been taken with a digital camera they will need to be transferred to a computer system to be fully utilized. Thus the proper documentation and organization of these images can be handled with a graphical database program. All the information on the advancement of digital photography and equipment commonly used for obtaining computer imaging are reported in this interesting chapter. The correct Photography for Liposuction Surgery is discussed on chapter 7. In fact, the medical photos have to be both of high technical quality and reproducible.
They are helpful in planning the procedure and for patient education and are indispensable for documenting and evaluating the results of surgery. With good basic equipment even a person with limited photo-graphic knowledge can take high quality, reproducible medical photographs in an office setting. Naturally as with all medical procedures one must obtain consent to take photographs and a patient release to use them.
Abdominoplasty and other abdomen procedures are discussed in chapter 8.
The shape of the abdomen plays an important role in a person's view of himself or herself as well as in how a person fits into their clotbes. Also in this case, the consultation procedure plays the must important role. Although the best results are always seen in the young slim patient with minimal fat deposits, gratifying results can be obtained in the realistic older, larger patient.
However the patient is given written information describing the tumescent technique of liposuction and is shown pictures of other patients who have had the planned procedure. Once it has been determined that the patient is realistic and a good candidate for the surgery and the patient has decided to go ahead with the procedure, correlate blood tests are done. To remember that most patients are very realistic about the results they can expect from tumescent liposuction and happy to be able to achieve them with such a safe procedure and minimal downtime. Therefore liposuction is a very gratifying procedure for both the patient and the surgeon.
Violin: Hips, Outer thighs, and Buttocks is the topic treated in chapter 9.
The Violin–shaped deformity describes the common pattern of fat overlying the iliac crest and the subtrochanteric area with an intervening gluteal depression.

Liposuction can restore aesthetic balance to this disharmonious physique by treating and eliminating regional deposits of fat, as well described by interesting reported photos. However evaluation of the violin-shaped body requires addressing the cosmetic units of the hips, buttocks, and thighs. Isolated treatment of one area without addressing the others often produces suboptimal results. Additionally in some patients it may be difficult to separate treatment of the lateral thigh from treatment of the anterior, posterior and medial areas.

Chapters 10th to the 14th are dedicated to the Anatomical approach of the tumescent liposuction surgery. In each chapter the techniques to be used is described and accomplished by very clear photographic pre and post operative results.

Therefore from the lectures it may be easily understood as the calf and ankle areas are more difficult to treat because there are no distinct bulges to flatten, the working surface is curved, and there is only one relatively small layer of fat.

On the other side liposuction of the arms and back presents an interesting challenge to even the most experienced of liposuction surgeons. The circumferential requirements of arm liposuction allow, in fact, a truly artistic sculpturing of the area and the fibrous nature of the back makes liposuction of this area not so easy to obtain the best aesthetic results.

However liposuction of the arms and back is an excellent way to recontour the upper body.

Effects of time, sun damage, and gravity can include increased deposition of fatty tissue in the submental area sagging jowls and neck skin redundancy. This often gives appearance of excessive healthy person. Therefore the neck can be a challenging anatomic region to rejuvenate, and complications are a legitimate concern, for the presence of the marginal mandibular branch of the facial nerve. But, with careful patient selection, neck recontouring can be performed in a safe and efficient manner.

About face it is interesting the alternative treatment to the traditional face-lift proposed in the chapter 14. It combines liposculpture of the face and neck with laser surgery performing very interesting results obtainable over the week-end.

This procedure utilizes tumescent liposculpture to remove excess fat from the face, jowls, and neck. With the tumescent technique, the operative area is infiltrated with a large volume of very dilute lidocaine solution which also contains epinephrine. The large volume of solution causes the operative area to swell, or tumesce, greatly improving the safety of procedure. This technique also includes resurfacing to the dermis from the underside to promote tightening of the skin application of the platysma muscle and removal of prominent platysma bands to reduce neck banding, and transection of the septal of the anterior and lateral neck so that complete redraping of the skin will occur. When indicated, a chin implant is also inserted. Using laser technology, these surgical procedures can be performed under tumescent local anesthesia at the same time as the liposculpture.

As an adjunct to liposuction, Ultrasonic Liposoction employs the use of ultrasonic energy to disrupt the adipocytes and liquefy the fat, making it easier for the surgeon to remove. This is the topic of chapter 15.

Powered Liposuction, reported on chapter 16, seems to offer other significant benefits for both patient and surgeon, resulting in safer and more precise surgical outcomes. However there are a number of situations and body sites in which the results of liposuction may be inconsistent and/or the approach to treatment may present unusual challenges or controversy as described on chapters 17 and 18.

Postoperative Care and Liposuction Safety and Complications are reported respectively in chapters

19, 20 and 21. According with the conclusions reported in these chapters, Tumescent Liposuction is a safe and effective procedure with high patient satisfaction when performed in suitable surgical candidates by qualified physicians.
In fact, tumescent liposuction performed totally under tumescent local anesthesia by dermatologic surgeons has a superior safety record compared to more aggressive form of liposuction. This technique has contributed greatly to patient safety allowing liposuction to be performed with minimal complications and excellent results.
Accreditation of office surgical facilities, whether voluntary or mandated by the states, will further assume patient safety. As a matter of fact, maintaining the patient's trust is essential when an adverse medical event occurs. Physicians should take positive measures and be honest with the patient and the family yet reconcile facts with the health care team before arriving at premature conclusions. Nevertheless, the effectiveness of that physician as an expert witness will depend on whether he or she is perceived to be honest and unbiased.
Managing Adverse Events and Handling the Dissatisfied or Difficult Patient are focused and discussed on chapters 22 and 23.
It is not common, for patients, in fact, who are dissatisfied with prior procedures to seek consultation from another physician. Because they have already had negative reinforcement for surgical procedures they threshold for dissatisfaction is very low. Therefore they should be approached with greater caution and care. Using the techniques outlined in these chapters, cosmetic surgeons should be able to minimize the sometimes-unavoidable consequences of patient dissatisfaction.
Different techniques from microliposuction, to injecting fillers into the subcutaneous tissues through harvesting, refining and transferring the autologous fat, are reported from chapter 24 to 32.
For every technique the first step is, of course, determining the patient's problems. But the grafting is intrinsically related to the technique used. Also, maximizing the surface area of contact encourages integration and anchoring of the newly placed fat tissue. Moreover fat characteristic may be helpful in determining which area of fat is more likely to be retained. But survival of adipocytes depends also on the instrumentation used for harvesting and injecting the fat. Naturally the presence of blood in the fat injected has to be removed by washing the cells in a physiological solution prior to injection and sterility of fat must be maintained. Finally the combined use of autologous fat and autologous collagen allows better refining of esthetic corrections than either method alone. Each type of tissue has the problem of resorption, but reinjection allows long-term satisfactory results.
In the last two chapters of the book, the complementary usage of topical cosmetics, massage exercise and calorie restriction for a complete weight control are reported.
As a matter of fact, caloric restriction or increased energy expenditure can change overall body weight, but stubborn areas of sub cutaneous fat often remain. For this reason liposuction is needed to improve the shape of these areas of excess fat.
In fact, statistics show that many adults who initially succeed in losing weight regain most or all of the weight within 5 years. Therefore many liposuction patients can benefits from nutritional education. Proper eating habits and nutrition foods can assist the patient in maintaining lean body mass while achieving a normal weight/height ratio.
This interesting book can be considered a useful tool for all the plastic surgeons and dermatologists who intend to use a safe liposuction methodology.
All the chapters report news indispensable for cosmetic chemists, nutritionists and for all the people working in Cosmetic Dermatology and Aesthetic Surgery.

The need to select the right technique to apply in order to improve women and men well being, is the main focus of the book and could suggests the setting up of cosmetics and dietary regimens to complement lisposuction and fat transfer techniques.

Pierfrancesco Morganti
Editor-in-Chief

Index to Volume 21, 2003

Contents:

Book Reviews

Original Laboratory Studies

General Articles

Author Index

Subject Index

The VII ISCD International Congress
FIRST ANNOUNCEMENT

International Society of
Cosmetic Dermatology
Application & Research

THE INTERNATIONAL SOCIETY OF COSMETIC DERMATOLOGY
in collaboration with
ACCADEMIA DI STORIA DELL'ARTE SANITARIA

PRESENTS

The New Frontiers of Dermo-Cosmetology: Efficacy, Stability and Safety
4-6 November, 2004
Roma, Italy

The International Society of Cosmetic Dermatology (I.S.C.D.) a non profit scientific association founded in 1980, is focusing on creating a synergy between Cosmetic Chemists, Dermatologists, Biologists, Plastic Surgeons and all the Scientists involved in the study of Cosmetic Dermatology by means of diffusing and exchanging scientific information and promoting a real scientific knowledge transfer from Academia to Industry and vice versa.
The main objective of this VII International Congress

The New Frontiers of Dermo-Cosmetology: Efficacy, Stability and Safety

is to promote and enhance the efficiency of worldwide research in the field of **Cosmetic Dermatology,** giving about the latest information on the development of science and technology in the new fascinating area of wellbeing.

CALL FOR PAPERS

We have the pleasure to invite you to participate at this happening as attendee or as a speaker giving your personal contribute to its success!

→ Follows

This meeting will include 8 different Sessions:

1. The Skin Barrier in Normal and Pathological Conditions
2. Cosmetic Delivery to the Skin
3. Biological Function and Efficacy of Cosmetic Ingredients
4. Efficacy and Safety of Cosmetics: the Evaluation Methodologies
5. Thermalism and Cosmetology
6. Plastic Surgery and Medical Devices for wellbeing
7. Nutraceuticals : the Cosmetic Connection
8. The worldwide role of Medical Doctors and Beauticians in SPA

GENERAL INFORMATION

Venue: The Congress will take place at SALA LANCISI, in the Monumental and Historical S. SPIRITO HOSPITAL in Roma, Italy.

Second announcement and **Call for papers** is scheduled for February 2004.
It will include a detailed program, registration and a call for free communications and posters.

To receive it, send us your request by E-mail at:
secretariat-congress@iscd.it

The official language of the meeting is English. Italian-English translation is planned for the scientific sessions in dependence of sponsor support.

The social program will include a reception at Senato Library Hall and a banquet.
For accompanying persons there will be excursions in outside and underground Roma and its environs. Post-Congress tours will include Napoli, Capri, and Pompei-Ercolano.

Technical Exhibition Suppliers of raw materials Products and service will find the opportunity to meet with an estimated 800 medical and chemical specialists from worldwide different countries.
It will take place within the Conference Centre.

Hotel accommodation and transport: all categories of accommodation will be offered at the more convenient price.

The official flight carrier is Alitalia that with its sky team and code-sharing partners covers the whole globe.

Weather: November is not cold in Roma. The medium temperature is o18/20 °C

FOR FURTHER INFORMATION

congress.iscd.it

In copertina /Front cover

Microsfere di N-metilpirrolidone chitosano - su gentile concessione del prof. C. Muzzarelli, Università, Ancona
Microspheres of N-methylpyrrolidone chitosan - on kind permission of prof. C. Muzzarelli, Univ. Ancona, Italy

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