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Preface

Thanks to the contribution of leading experts in cosmetology, the first editions of the *Handbook* were successful and received excellent reviews. The editors appreciate the excellent author contributions.

The first edition, published in 2001, reviewed the multiple facets of the cosmetic field including the physiology of cosmetics targets and the safety, legal and regulatory context worldwide. It gave a broad overview of cosmetic ingredients, vehicles and finished products, and described the main methodologies used for microbiology, safety and efficacy testing. In the second edition (2006), we examined the future of cosmetology by the addition of chapters related to new ingredients, new delivery systems and new testing methodologies, but also by asking the previous authors to update their chapter with their speculation about the future in their field of expertise. To make the information more accessible, chapters were significantly reorganized.

Cosmetic science is a fast moving area. Furthermore, rapid and extensive changes in the worldwide regulatory context of cosmetics, increasing constraints and limitations in the choice of cosmetic ingredients and regular pressure from the media force the cosmetic formulator to think differently about his products. For all those reasons and due to more and more demanding and educated consumers asking for additional benefits from their cosmetic products, we have been asked to initiate the third edition of the *Handbook.*

Several chapters, from previous authors, are key in *Handbook of Cosmetic Science and Technology* and have been updated with the latest developments in the given field. However, it is the intention of the editors to give this version a new and important dimension that will complement the previous editions; a focus on the mechanism of interaction of the products or ingredients with their target.

Today, cosmetic products are of a high quality. If we want to further improve their quality, this will inevitably pass through an even better understanding of how those products or ingredients work to improve the appearance, protect their target or help maintain its natural functions. So, with the outstanding evolution of instruments to investigate in depth the skin or the hair, great progress is made daily in the understanding of the mechanisms of action of cosmetics. This understanding has been extensively covered in the third edition, which concentrates on skin, nail and hair cosmetics.

In the third edition, emphasis has been given to:

- Skin types, their relationship with age, sex, ethnic differences and the concept of sensitive skin.
- New bioengineering techniques for studying hydration of the skin – such as skin capacitance imaging and confocal raman spectroscopy – and for investigating skin friction and wettability.
- New developments in the description of skin aging and anti-aging treatments.
- In vitro skin tests using 3D reconstructed skin models.
- Specifically targeted cosmetics (decorative products, cooling and revulsive ingredients) and new forms such as oral cosmetics.
- An overview of the regulatory context for cosmetic preparations in the USA and in Europe, and of important ethical considerations in human testing.
- Finally, and controversially, the values and limitations of bioengineering measurements for the substantiation of efficacy claims.

The editors are grateful not only to the authors who contributed to previous editions and updated their chapters for the third edition, but also to the new authors who openly shared their "know how" in key areas.

Finally, we would like to invite readers' comments, criticisms and suggestions for improvements in order to ensure the continuous improvement of the *Handbook of Cosmetic Science and Technology*.

André O. Barel
Marc Paye
Howard I. Maibach

64 Revulsive Products: Way of Action and Evaluation of Their Efficacy

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INTRODUCTION

In Webster's dictionary, we found the following descriptions: "revulsive"—(*i*) to pull away and (*ii*) an act or technique of turning or diverting a disease or blood from a diseased region in one part of the body to another (as by counterirritation); "rubefacient"—substance for external application that causes redness of the skin.

Revulsive products (i.e., rubefacients and urticants) are known for several clinical and nonclinical applications. Clinically, they are used in the treatment of neuropathological [diabetic neuropathy, postherpetic neuralgia (PHN)] and/or muskeloskeletal disorders (e.g., osteoarthritis, rheumatoid arthritis, muscle soreness, and back pain). Nonclinically, they are used in some sports as passive warming-up products and in the cosmetic industry as an ingredient in skin products (1).

The capital active ingredient in these topical formulations is a nicotinate derivative [methylnicotinate (MN), hexylnicotinate (HN), and benzylnicotinate (BN)] or capsaicin. Nicotinates provoke an elevation of arachidonic acid and prostaglandin levels (prostaglandin D2). The produced prostaglandins act on the neuroreticular tissue of the arteriovenous anastomoses of the dermal vascular plexuses by means of an endothelium relaxant factor. The latter provokes a relaxation of the vascular smooth muscles resulting in an augmentation of the cutaneous circulation and a flooding of the superficial veins. This nonimmunological immediate contact reaction is visible as an erythema (2).

Capsaicin is an alkaloid, derived from chili peppers, with analgesic properties. Capsaicin binds to nocisensors in the skin, excitating neurons, which results in itching, pricking, or burning with a cutaneous vasodilation (3).

Stimulation of afferent C fibers with release of substance P is hypothesized, while the desensitization after prolonged treatment is believed to occur due to a depletion of substance P (3).

The topical application of capsaicin has equally been used to study reflex mechanisms of dermal vasodilatation (4,5) and as an experimental pain inducer to study the underlying nocisensoric mechanisms (6). Threshold levels of sensitization to increasing capsaicin concentrations have been used to study sensitive facial skin (7).

Besides these clinical and practical applications, rubeficiants (especially nicotinates) are often used in more fundamental research toward percutaneous penetration processes. The quantification of the physiologically induced vascular response has been found to be a good indicator for the skin bioavailability of these topically applied substances.

The response is often quantified by measuring the perfusion of the skin microcirculation (laser Doppler velocimetry), the skin color (redness), or the skin temperature. The laser Doppler instrument measures the increased perfusion of the arterial plexuses, while the skin color is not only an indication for the increased flux in the arterial part of the skin microcirculation but also for the flooding of the venous capacitance vessels.

This chapter describes the way of action and factors influencing the pharmacodynamic response to nicotinates under different experimental conditions, followed by possible clinical applications. For capsaicin, the emphasis will be mainly on clinical applications since this revulsive product is not often used for fundamental research. Finally, the use of revulsive products in physiotherapy (sport) will be discussed.

NICOTINATES

The onset of the nicotinate contact reaction depends on the derivative used. Application of MN (hydrophilic) results in an immediate response as measured with the laser Doppler instrument, while HN (lipophylic molecule) shows a lag time up to five minutes (8).

The intensity of the reaction is concentration dependent (9,10). Concentrations between 1 and 100 mM are reported. The duration of the response varies from 20 minutes up to 60 minutes for the laser Doppler response and up to 90 minutes for the color response. An increased temperature is noticed up to 90 minutes post application (10).

The pharmacodynamic response varies in function of the anatomical skin site (11). The strongest response was recorded at the forehead and the chest, while the response was weaker at the abdomen, forearm, and thigh. A significant relation was found between the nicotinate response and skin characteristics, such as TEWL, stratum corneum hydration, skin temperature, baseline perfusion of the microcirculation, and sebum gland density.

In the experiments of Marrakchi and Maibach, reactivity was tested on different regions of the face (forehead, nose, cheek, nasolabial and perioral areas, and chin), the neck, and the volar forearm (12). Experiments were carried out on young (29.8 ± 3.9 years) and older (73.6 ± 17.4 years) population. For both the age groups, the areas on the face and neck were more sensitive to HN compared with the forearm. A different sensitivity pattern for the face was detected between the two age groups, while peak values were significantly higher in the older group for the forehead, cheek, and nasolabial area. The authors explained the differences between the age groups by the photoaging effect on the sebum glands with more and enlarged glands in the older subjects. Roskos et al. did not find an effect of age when applying MN in young and older subjects (13).

Issachar et al. found a significant correlation between the percutaneous penetration of MN and sensitive skin. The intensity of the response to the nicotinates differed significantly between normal and sensitive skin, while the duration of the inflammation was comparable (14).

Racial differences in barrier function were demonstrated by quantification of the nicotinate response with a laser Doppler instrument (15,16).

Berardesca et al. compared nicotinate responsiveness in Caucasians and black volunteers before and after a delipidation of the challenged skin area (15).

A lower cutaneous response was noticed for the blacks compared with the whites under both experimental conditions. Kompaore and Tsuruta compared Asians, blacks, and Caucasians with a nicotinate challenge. The lag time between nicotinate application and onset of the vascular response was used as an indication of barrier permeability. Permeability was strongest in Asian skin, weaker in Caucasian skin, and weakest in black skin (16).

The response to nicotinates is significantly reduced after oral treatment with anti-inflammatory drugs (17,18) and with topically applied anti-inflammatory drugs (19–23). The reduced response in the presence of topically applied anti-inflammatory drugs was used as a model to study iontophoresis (24). In these experiments, the reduction in the MN response was used as an indicator for the presence of diclofenac in the stratum corneum.

In their experiments with penetration enhancers Tanojo et al. found a reduced lag time in the HN response after pretreatment of the skin with propylene glycol. The combination of propylene glycol with oleic acid was not more effective than propylene glycol alone (25).

The microvascular sensitivity (tested with increasing nicotinate concentrations) was increased in diabetic patients compared with controls, while the maximal microvascular responses were comparable (2). Similar findings were observed by Caselli et al. in healthy control subjects and diabetic neuropathy patients (1). These authors propose the addition of MN in the moistening products used to reduce the development of diabetic foot (1,2).

A reduced response was noticed in patients with Huntington's disease (26).

CAPSAICIN

Capsaicin (trans-8-methyl-*N*-vanillyl-nonenamide) is an alkaloid derived from the common hot pepper plant of the nightshade (*solanacae*) family. Capsaicin represents the main constituent of the total pungent acid amides present in the capsicum species and is responsible for the red-hot chili taste (27).

Besides being considered as food additive, capsaicin has also gained human exposure as oral supplement or topical analgesic (28).

Capsaicin is a selective agonist for the transient receptor potential (TRP) channel. The TRPV1 receptor is a ligand-gated, nonselective cation channel expressed on a subpopulation of primary small-diameter sensory Aδ fibers and C fibers, responsive to noxious heat and mechanical and chemical stimuli (29,30). The topical application of capsaicin on the human skin excitates the TRPV1-expressing nocisensors, resulting in an itching, pricking, burning sensation with a cutaneous vasodilation, hyperalgesia, and allodynia (30). Stimulation of afferent C fibers with release of neuropeptides, predominantly substance P is hypothesized, while the desensitization after prolonged treatment is believed to occur because of a depletion of substance P (31). Capsaicin inhibits axonal transport of neurotransmitters by depressing the release of the nerve growth factor (NGF) (32).

The resulting hypoalgesia is due to degeneration of epidermal nerve fibers (31–34). The desensitization of hyperactive nociceptive sensory axons is the basis for therapeutic topical application or intra-articular injections of capsaicin (35).

Peripheral neuropathy, provoked by axonal degeneration of sensory autonomic and motor neurons of the peripheral nervous system, is a common complication of diabetes and chronic alcohol abuse. The manifestations of peripheral neuropathy classically progress from the most distal extremities. Positive symptoms are lancinating pain, paresthesia, numbness, allodynia, and burning and itching sensations (36).

The Capsaicin Study Group (1991) conducted a multicenter, double-blind, vehicle-controlled study to establish the efficacy of topical 0.075% capsaicin cream in relieving the pain associated with diabetic neuropathy. Patients ($n = 252$) were randomly assigned to the capsaicin or placebo group. Capsaicin cream or vehicle was applied on the painful areas four times a day for eight weeks. Statistical analysis showed significant difference in favor of capsaicin compared with placebo for the following parameters: pain relief, decreasing pain relief, and pain improvement on the physician's global evaluation scale. The authors asserted that topical capsaicin cream is safe and effective in treating painful diabetic neuropathy (37).

These findings corroborate the results of the placebo-controlled studies by Scheffler et al. (38) and Tandan et al. (39). They demonstrated the superiority of capsaicin cream 0.075% versus placebo in pain control and improvement of daily activity during the treatment of diabetic neuropathy.

A meta-analysis of four randomized, double-blind, placebo-controlled trials using capsaicin in the treatment of diabetic neuropathy found capsaicin to be more effective than placebo (40). This is in contrast with the findings of Low et al. (41). In their study, using a four times daily application of capsaicin cream versus a nicotinate formulation as placebo, they failed to demonstrate significant improvement in chronic distal painful polyneuropathy after 12 weeks of treatment. Besides using different pain evaluation scales, physiological functions such as sudomotor axon reflex, nerve conductance, and sensory examinations were carried out before, during, and after the experiment (41).

PHN is the most common complication of Herpes Zoster. The incidence of Herpes Zoster and its associated complications mainly occur in older patients (42). The pain associated with PHN is often referred to as neurogenic pain and generated as a result of neural dysfunction and therefore unresponsive to conventional analgesics including opiates (43).

The hypothesized mechanism for capsaicin-induced analgesia in PHN is the interference with the biosynthesis of the neuropetide substance P, which has an important role in the central transmission of nociceptive signals (44).

Two published double-blind, placebo-controlled studies evaluated the clinical effectiveness of topical capsaicin cream in the treatment of PHN. The reported results of both the studies were in favor of capsaicin (0.075%) cream versus placebo. McCleane demonstrated that the mixed application of glyceryl trinitrate and capsaicin cream was significantly more effective than placebo in reducing pain. This combination had a positive effect on the tolerability of treatment with capsaicin cream in patients with osteoarthritis (44).

Painfull cutaneous disorders such as psoriasis, nostalgia paresthetica, and atopic dermatitis are characterized by intense itching, scaling, and erythema (45,46). Nonhistaminic itching, in contrast to histaminic itching, is difficult to treat, and therapeutic applications are often uneffective (47). The release of substance P increases the vascular permeability and the number of mast cells in the skin (48). The responsiveness of several forms of urticaria to

capsaicin treatment may be related to the effects of capsaicin on the microvasculature of the skin (47). The topical application of capsaicin seems to be effective in the treatment of a variety of painful clinical conditions affecting the skin (40,47,49). However, the absence of a "burning placebo" as a control vehicle makes it difficult to conduct double-blind studies, and further research is needed to assess the clinical effectiveness of capsaicin.

Detection threshold determined by applying increasing concentrations of capsaicin on facial skin was used as an objective parameter for sensitive skin (7). Using that procedure Jourdain et al. detected subjects with low and high threshold. This threshold level corresponded with the self-declared level of sensitive skin. The authors concluded that this skin neuro-sensitivity test appears to be a promising tool for cosmetic diagnosis of sensitive skin (7).

However, the use of capsaicin, in some cases, is accompanied with adverse effects. Initial exacerbation of symptoms, transient burning, and redness at application site is reported by patients in various capsaicin studies. Because of the need for frequent application in the treatment procedure, these side effects may be the major reason for the poor compliance (50,51).

PHYSIOTHERAPY AND SPORT

Although revulsive products are widely used in the physiotherapy practice, few studies report on the efficacy of these products (10).

In physiotherapy, revulsive products are mainly used for the relief of joint and muscle pain. In sports, these products are often used as passive warming-up for activities in cold environments. As active ingredients, the formulations contain analgesic substances, such as salicylates, camphor, menthol, oil of turpentine, and MN or HN as vasodilatory substances (10). Their effect is mainly because of vasodilatory components provoking a thermal effect in the superficial layers of the skin. Analgesic components (e.g., salicylates) may be added in the formulations, but the target tissue of these analgesic substances is not the skin but the underlying muscle, tendon, or joint tissue. Evaluation of the efficacy of regional therapy is beyond the scope of this chapter.

Our literature search did not find reports on the efficacy of revulsive products as used in physiotherapy. We evaluated the effects of three commercially available topical products commonly used in physiotherapy practice.

The thermal effect of these products was evaluated by means of noninvasive measurements of biophysical skin properties. Product 1 was a W/O (Water/Oil) emulsion containing MN at 1.5% and methylglycolisate at 5.0% as active ingredients. Product 2 was an O/W (Oil/Water) emulsion containing MN (1.0%) and α-bisabolol as active ingredients. α-Bisabolol is the active component of camomile and has an anti-irritant effect. Product 3 was a spray containing methylsalicilate (2.0%), menthol (3.0%), and oil of turpentine (5.0%).

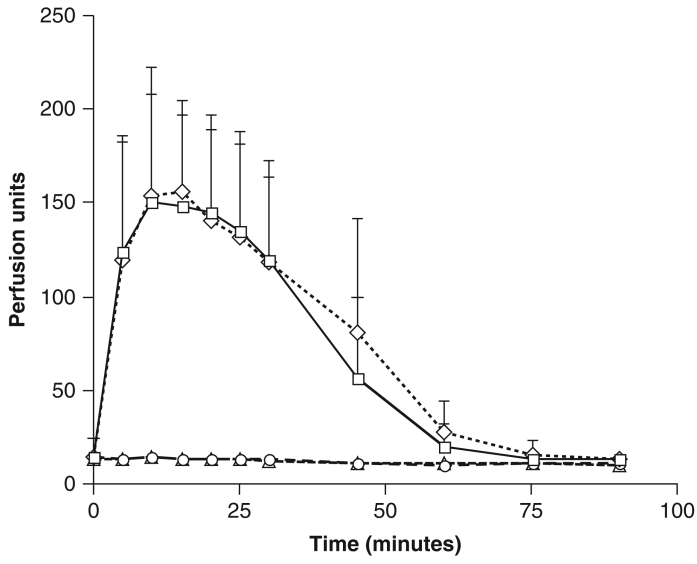

Figure 1 Perfusion of the skin microcirculation in function of time as measured after topical application of product 1 (—□—) product 2 (.....◇.....); product 3 (- - -o- - -). An untreated control is included (- - -△- - -). Mean ± s.d. ($n = 15$).

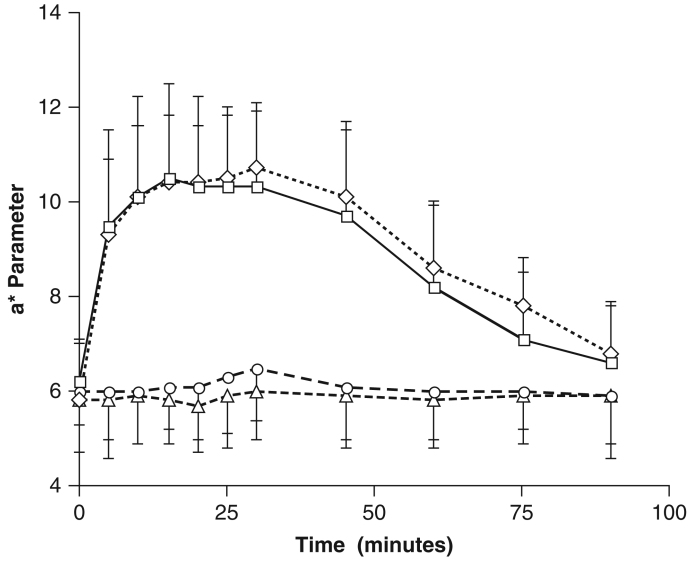

Figure 2 Skin color a* parameter in function of time as measured after topical application of product 1 (—□—) product 2 (.....◇.....); product 3 (- - -o- - -). An untreated control is included (- - -△- - -). Mean ± s.d. (n = 15).

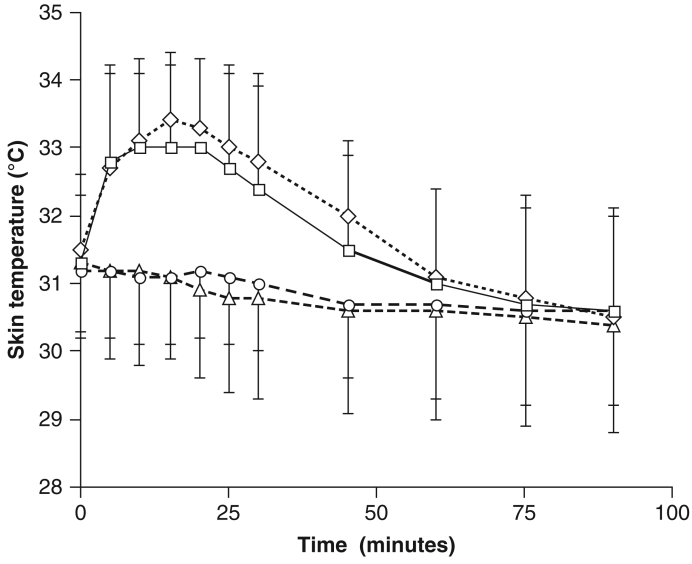

Figure 3 Skin temperature in function of time as measured after topical application of product 1 (—□—) product 2 (.....◇.....); product 3 (- - -o- - -). An untreated control is included (- - -△- - -). Mean ± s.d. (n = 15).

It was found that products containing nicotinates provoked a significant increase in the perfusion of skin microcirculation, a significant increase of the superficial skin temperature, and a significant reddening of the skin color (erythema) (see Fig. 1–3). The maximum increase obtained in skin temperature (±2°C) is believed to have little effect on the underlying tissues. However, the strong sensation in the skin can "pull away" the pain sensation from other tissues.

Comparison of the three measurement techniques gives information concerning the underlying mechanism of erythema production: the arterial vasodilatation causes an increased blood flow (reaching its maximum 10 minutes post application), resulting in an increased amount of blood in the superficial capacitance vessels. This results in reddening of the skin (maximum redness 15 minutes post application), and heat is lost by convection (reaching a maximum 15 minutes post application).

We assume that the effect of single application of revulsive products is mainly due to the thermal effect, which is easily quantifiable. The strong sensations in the dermal and epidermal skin layers will relieve the feeling of pain in other tissues or structures. The thermal effect is equally limited, since a maximal increase in skin temperature of ± 2°C was obtained

by nicotinate application. The heat transfer toward muscles and other structures is limited because of the hypodermal layers, containing mainly adipose tissue, which work as very good isolators (52,53). Moreover, deeper tissues have a temperature closer to the core temperature of 37°C. In our experiments, skin temperature reached about 33°C, which is lower than the temperature of deeper structures! This finding points equally to the inefficiency of these revulsive products, as passive warming-up is often used for sport activities in colder environments. On the contrary, the use of such products will provoke a greater transfer of heat toward the cold environment with a possible negative effect on the thermoregulation.

CONCLUSION

Revulsive products produce a reddening of the skin. This erythema is due to an increased perfusion of the microcirculation after a vasodilation of the arterial plexus at the different skin levels.

Nicotinates act via an endothelium relaxant factor, while capsaicin uses a neurogenic cascade with involvement of substance P.

The more clinical applications of nicotinates aim to increase the perfusion of the superficial microvasculature to obtain increased skin temperature and a kind of pain relief by "pulling away" the pain sensation located in the deeper tissues (gate control). In capsaicin treatments, desensitization is aimed by depletion of substance P at the nociceptive sensors. This can only be obtained by long-term multiple treatment regimes (up to 4 times a day for 12 weeks).

For nicotinates, no side effects are reported, while the adherence to capsaicin treatment is rather weak due to the inconvenience of the side effects at the site of application (burning, itching, etc.).

Despite nicotinates being widely used in physiotherapy (sport), there is only limited evidence for the efficiency of these treatments. Reports on capsaicin treatment indicate a moderate positive effect under different clinical situations. However, most of the designs lack an adequate placebo treatment. In the experiments of Low et al. using a nicotinate solution as "burning placebo," no difference was found between the capsaicin versus the burning placebo in the relief of pain (41). Hence, the use of nicotinates, in different clinical treatments, needs to be further elaborated. The absence of side effects may improve compliance.

Nicotinates are widely used in more fundamental research toward percutaneous penetration, since the quantification of the vascular response can be used as an indicator for the skin bioavailability. Other skin properties, such as the problem of sensitive skin can also be studied using a nicotinate challenge. In more recent reports, a capsaicin challenge has been developed to study the sensitive skin.

The instrumentation available nowadays allows a more precise evaluation and quantification of physiological responses. Using these techniques under experimental and clinical conditions may increase the knowledge and evidence in the use of revulsive products.

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