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Review Article

Skin Delivery and Innovative Carrier's Effectiveness

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Abstract

The skin serves as the body first protecting barrier against the external attacks of chemicals and microorganisms. On the other hand, it is an obstacle to penetration and transdermal delivery of any substance applied on its surface. Thus, a need to report some news on the skin composition for a better understanding of the transdermal delivery mechanisms of topical products applied on its surface. Therefore, due to the actual increased use of topical drugs, cosmetics, and diet supplement treatments, further feasibility research studies have been carried out to extend the knowledge of the percutaneous absorption 'rules and means. These studies are retained necessary to control the release through the skin layers of various selected active ingredients, loaded and carried out by different vehicles. The paper will focus on the effectiveness of innovative tissue carriers that, are able to deliver active ingredients throughout the skin layers, are made by a very low consumption of water, and are free of chemicals also. In conclusion, these novel eco-sustainable carriers, resulting skin- and environmentally friendly, might be used as innovative vehicles in substitution of the normal emulsions that, made by the use of preservatives, emulsifiers, fragrances, and other chemicals may often cause allergic and/or sensitization phenomena, consuming a great quantity of water also.

Keywords: skin, stratum corneum; transdermal delivery system; percutaneous adsorption; on-woven tissue; nicotinamide; fish collagen peptides; bamboo tissue

Introduction

This paper will explore the characteristics and functions of the skin to evaluate the potential for drugs, specialized cosmetics, and dietary supplements (cosmeceuticals and nutraceuticals) to penetrate its layers. The goal is to identify active ingredients that can be targeted for release at specific times, doses, and locations within the skin. This complex structure, in fact, with a surface area of about 2 meters square and less than 2 mm thick, is the largest organ of the body specialized that, interacting with the environment, represents the main protective barrier against the toxic agents and microorganisms' invasions as well as against a loss of essential body fluids. Naturally, the skin exhibits strong resistance to the penetration of any external compounds, whether they come from drugs, cosmetics, or food products. Therefore vehicles, utilized to load and carry the active ingredients, have to possess the function not only to momentarily modify the skin barrier organization (i.e. specifically the horny layer) for permitting the ingredients' penetration but also to "influence other features of the horny layer. such as smoothness, appearance, and subjective feelings" (1).

Skin structure and function

The skin is composed of three layers:(a)epidermis, the more superficial ones, which contains proliferating cells made by viable keratinocytes continually renewed to produce corneocytes dead cells ;(b)dermis, the middle layer, which supports and protects the deeper skin layers by the fundamental function of fibroblasts, and the hypodermis(subcutaneous layer) that by its fat cells, the adipocytes, stores energy and protects and maintains the body in a constant temperature (Figure 1).In turn, the epidermis is composed of four further sub-layers: Stratum corneum (horny layer), Stratum granulosum, Stratum spinosum, and Stratum basale where the staminal cells are living (Figure 1).

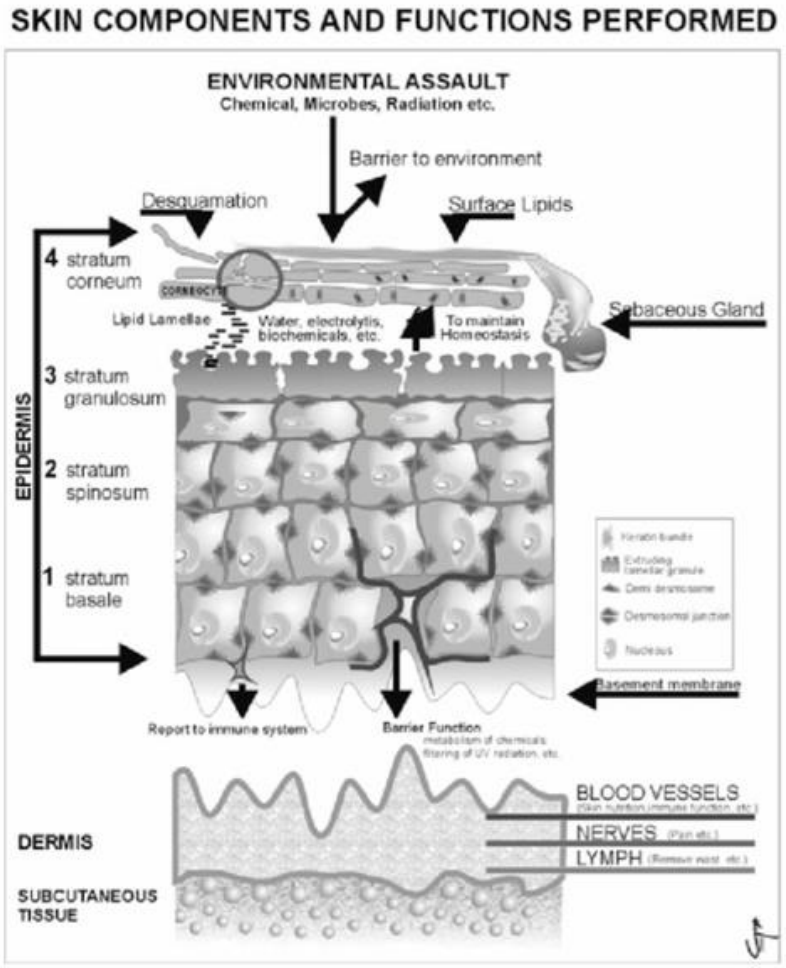


Figure 1: Skin components and functions

However, the uppermost layer, the Stratum corneum (SC), by its complex structure represents the real skin barrier layer. But how the SC structure is formed together with its corneocyte cells? The stratum corneum (SC) is a specialized structure continuously renewed through the cornification of living epidermal keratinocytes, which form corneocytes. This 24-day mitosis process aims to maintain skin homeostasis (Fig. 2). The process is characterized by a series of morphological and biochemical changes with cells, the keratinocytes. These cells transform into corneocytes surrounded by a dense protein layer, lose the capacity to divide, increase in size, have a polygonal flattened shape, and are piled up in 10 to 20 layers depending on the anatomical site (fig 3). On the other hand, the corneocytes, linked together by protein-made Corne desmosomes, diminish their content in water being principally constituted by hydrophobic cubic-like, close-packing keratin filaments filled inside of their structure. These keratins, composed of a tightly packed structure of filaments and matrix, make the skin resistant to many liquids and solvents, thereby impeding the penetration of substances applied to its surface. The intercellular space between these dead specialized cells is composed of lipidic lamellae orientated approximately parallel to the surface of the skin and formed by a mix of multiple bilayers of ceramide (~50%) fatty acid esters and cholesterol sulfate, they act as a strong barrier, serving as an interface between the hydrophilic corneocytes and the lipophilic environment (1-5).And this barrier can be modified, alternating the composition of the intercellular space and the cells' cohesiveness to obtain an effective penetration throughout the skin layers. Where are all these structures and functions beginning?

Figure 2: The skin continuous renewing process

During the corneocyte migration in the direction of the skin surface, the synthesis of lamellar bodies, located at stratum spinosum as keratohyalin granules, enriched in polar lipids (i.e.glycoshingolipids, free sterols and phospholipids) and catabolic enzymes, are secreted into the stratum granulosum for being released to the intercellular space of stratum corneum as barrier lipids. After their extrusion, in fact," glucosylceramides and sphingomyelin are converted into ceramides by the ceramide synthases, while phospholipases are responsible for the generation of free fatty acids from phospholipids" (5). In conclusion, lipid lamellae, arranged as bilayer membranes and consisting of repeating structures of alternating hydrophilic and lipophilic domains arranged respectively as a crystallin orthorhombic organization, less ordered hexagonal ones, and a disordered liquid structure, represent a fundamental part of the skin barrier (figure 4) (5). Moreover, during the corneocytes formation, another vital role is played by the pro-filaggrin contained in the keratohyalin granules. This protein is transformed in filaggrin by the enzyme kallikrein-5 and in turn, metabolized by kallikrein-7, caspase-14, calpain-1, and bleomycin hydrolase, giving rise to the formation of natural moisturizing factor (NMF), a family of hygroscopic amino acids and amino acids derivatives. Therefore, these compounds for their high water-holding capacity, are fundamental for maintaining the stratum corneum at its hydrated state and the skin healthy and in physiological conditions (6-8). However, both mechanics and hydration of stratum corneum seem to be intimately dependent on the structural organization of the keratin filaments and the molecular biology of filaggrin.

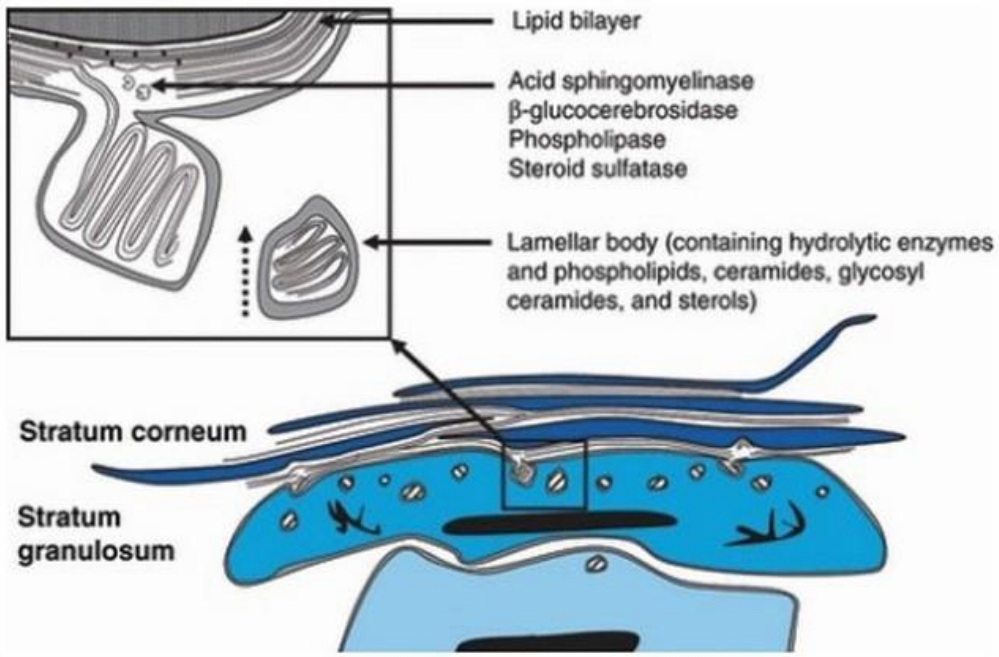


Figure 3: The transferring modality of lamellar body from stratum granulosum to stratu

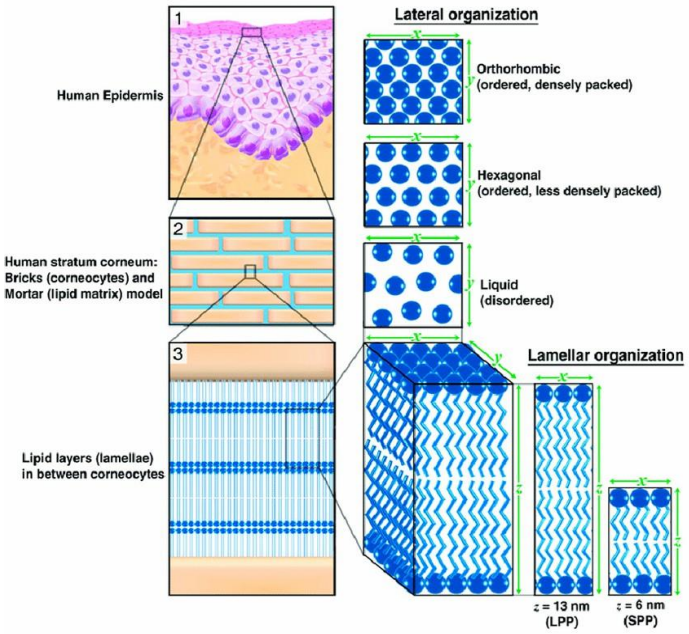


Figure 4: Lipid organization of the Stratum Corneum'lamellae Courtesy of Berkers et al [11] and Janssens et al [12].

Skin delivery system

The efficacy of any product containing a functional group is determined by the activity of the selected ingredients as well as the carrier effectiveness, that should possess the capacity to deliver in the body any compound at the selected site of action. Therefore," the role of a delivery system is to ensure that the right concentration of the right ingredient is reaching the right site in the body for a sufficiently long, the correct period", according to the so-called 4R's reported, from JW Wiechers in 2008(9).For this purpose the carrier could have the ability to modify the partitioning of the active ingredients into its structure, facilitating their penetration as well as modify its components 'ratio, mimicking the SC' lipid lamellae and/or altering its structure organization from the crystallin orthorhombic/hexagonal phase to the liquid ones. The liquid state of the intercellular lipids facilitates, in fact, the skin penetration of any kind of active ingredient (10-12). Therefore, the structure of stratum corneum, composed of a mix of keratins and lipids, results fundamental to blocking the penetration of environmental chemicals and microorganisms, as well as the substances applied on the skin surface by drugs, cosmetics, and diet supplements. In conclusion, for rendering the penetration of the ingredients throughout the skin and mucous membrane layers, it is important to consider not only the characteristics but also first of all the composition of the carrier selected to make cosmeceuticals and nutraceuticals. For this purpose, we are proposing the use of innovative tissue carriers for drugs, cosmeceuticals, and nutraceuticals made no more by emulsions but by specialized non-woven tissues. As reported the skin permeability depends on the effectiveness of the active ingredients selected and the capacity the carrier has to facilitate their load, penetration, and release at the level of the different skin and mucous layers (9)

Proposed carrier and further in vitro and in vivo study

According to many papers published by our group in the last ten years, the proposed carriers, used to make innovative cosme-nutraceuticals, have been realized by a non-woven tissue made by natural polymers, incorporating various active ingredients into their fibers (13-15). The last realized carrier was made by pullulan tissue made by the electrospinning technology, embedded by the complex chitin-lignin encapsulating nicotinamide, allantoin, and fish-collagen polypeptides (16). For this last proposed carrier, recently made for obtaining an innovative pro-aging cosmeceutical product, different in vitro and in vivo studies have been realized and published (16). This paper aims to add new data showing the penetrability of this tissue carrier compared to the classic emulsion also, because it has shown to be useful for realizing pro-aging products, resulting not only 100% skin- and environmentally friendly but also to be made at low consume of water (17).

Material And Methods

Skin penetrability

As previously reported and described by different papers (18,19), skin penetrability describes the rate of transport of active ingredients throughout the epidermis for cosmetic products (transepidermal route) and throughout the dermis for drugs and diet supplements also (transdermal route). However, the penetration depends on the ingredient and the carrier selected. The ingredients, as, for example, some surfactants, can disrupt the skin barrier function altering both the composition and organization of the lipid lamellae, thus favoring the transepidermal or transdermal penetration. It is important to note that cosmetic products are not intended to enter the bloodstream. According to current international regulations, they are permitted to have only transepidermal penetration. To try to show the skin penetrability of the proposed innovative tissue carrier, the Tipe Stripping Technique (TST) was selected because easy to be used (20-22). By TST it is possible to take off sequentially different layers of Stratum Corneum by adhesive tape strips, obtaining a good correlation between the ingredient concentration and the stratum corneum recovery.

Experimental in vivo procedure

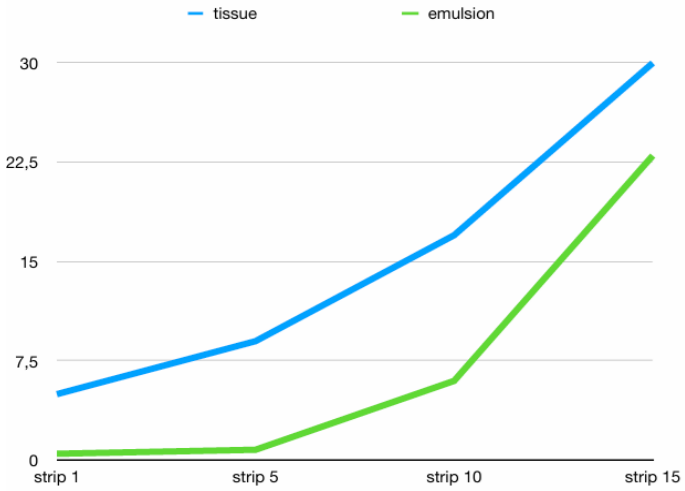
According to our study of many years ago(23) the participant's skin, pre-treated by both our active tissue and the control tissue in pre-signed areas of the arms, was stripped by 15 consecutive times by D-Squame Discs(QDerm Dallas, USA) to control the stratum corneum penetration of the active ingredient embedded into the in-study carrier tissue.The Tape- stripping specimens were collected from twenty healthy Caucasian volunteers enrolled with no history of dermatological diseases (10 women and 10 men of median age 35+/-5). All the participants received specific written information on the study and signed a written informed consent. The study protocol, based on recommendations from the 2024 revision of the Declaration of Helsinki, was approved by the Ethical Commission of

the Academy of History of Healthcare Art. At 8 a.m. all the participants, were acclimatized for 15 minutes into a conditioned office at 22 C and 50% humidity, the TEWL was measured by the 3C System (Dermotech, Rome, Italy) at the right and left dry pre-marked 3 cm square area of the outer forearms, pre-cleaned by distilled water (23). The instrument, used by our group from many studies, is based on a probe that, allowed perpendicularly to the skin surface(forearm) is allowed to equilibrate for 20 seconds The computerized 3C System collects up to 10/15 measurements over 25 second sampling period and records the mean value automatically standardizing the environment conditions. Verified the normality of TEWL of the skin to be treated recovered at 7g/h/m square, a 3 cm square of our active-tissue- product (16) was applied soon after on the dry right outer forearm area, of the participants, while on the left one, considered as control, was applied a formulated W/O emulsion, containing the same quantity of nicotinamide but free of allantoin and fish-polypeptides. Soon after, Two/three drops of distilled water were added to both the treated skin areas, which were gently massaged by fingertips until all tissues and emulsions were completely absorbed. The participants were instructed to not apply any skincare product on the arms at least 72 hours before beginning the study and during it, to wash the pre-signed areas with water only, during their staying at home. The day after, in the same acclimated room, the pre-signed forearms areas of all the participants were stripped repeatedly. by 15 different 22 mm diameter D-Squame disks (CuDerm Co., Dallas, TX) applied by controlled pressure of a few seconds, according, to our previous experience (22) and Serup et al methods (24-26).

Tape stripping results

All the 600 strips (300 actives and 300 controls) were collected separately into two glass containers and maintained separately under nitrogen before the analysis. The recovery of nicotinamide, released at the different SC layers, was compared with the control-emulsion treatments. For this purpose, it's important to remember that the tissue was made by pullulan, chitin, and other natural polymers contained in their fiber's nicotinamide together with other active ingredients such as fish-collagen peptides and allantoin, while the emulsion was formulated by nicotinamide only and different natural oils. All the samples of the 1st, 5th,10th ad15th stripped skin layers of the twenty participants, collected and maintained in distilled water under gentle agitation for 1 hour, at room temperature, were filtered, and added by a few micrograms of the alizarin reagent. After 90 minutes, the mean concentration of nicotinamide recovered by all the 15 tape-strips of stratum corneum of all the participants was obtained at pH5.54 measuring the intensity of light absorbance by the Spectrophotometer at the wavelength of 526 nm, according to Salem et al. (27). The mean nicotinamide resulting by 3 spectrophotometers (SP-UV 200 Shanghay Spectrum Instrument) measurements recovered from the 1st,5th,10th and 15th skin strip-tapes of each participant, are reported in Tab I, expressed in % of the nanogram/cm square. Naturally, the correlation between the color-light intensity and the nanograms of nicotinamide was obtained by comparing the sample colors to a defined stock-colored-solution scale, predetermined by the use of the differed quantity of nicotinamide.

Tab I Nicotinamide recovery from the strip-tapes Mean +/-SD amount of nicotinamide recovered in human stratum corneum by in vivo tape- strip measurements on 15 participants % Recovery of nm/cm^2



Stratum corneum layers: mean of three measurements for each strip All p values are highly significant as to all tape-trips ($p<0.005$)

Statistical analysis

The Student's Test was used in the evaluation of the data obtained by all strips. All the analyses were done using the SAS statistical package, version 5.18(SAS Institute Inc., Cary, N.C.). Probabilities less than 0.05 were considered not significant However, it was our great surprise to verify a better recovery of nicotinamide embedded into the tissue compared to the emulsion ones. Probably the reason is due to the contemporary use of the fish-collagen peptides and chitin embedded into the tissue as further active ingredients and not added into the emulsion (16). Collagen-peptides, in fact, are considered able to facilitate the penetration of different active ingredients through the skin layers (.28). On the other hand the positively charged chitin a component of the innovative tissue-carrier, could not only increase the nicotinamide penetration altering the corneocytes membrane structure negatively charged but also ameliorate the effectiveness of the novel cosmeceutical, stimulating the activity of the fibroblasts also (29). Naturally, these fascinating activities should be definitively proven by further specific research studies.

Conclusion

In our first study on a novel cosmeceutical, utilizing as a carrier a specialized innovative tissue (16), we have shown by in vitro methods the quick release of the active ingredients as well as their final effectiveness to realize a pro-age product. This cosmeceutical tissue resulted in effective to protect the skin from environmental assaults displaying an antioxidant and protective activity towards UV light, metalloproteinase release of aged fibroblasts as well as assessing inhibitor activity against collagen degradation. Moreover, it has shown antibacterial and antiinflammatory effectiveness, being skin- and environmental-Friendly. The aim of this paper has been to control the transepidermal penetration of nicotinamide, as one of the active ingredients embedded into this novel

cosmeceutical, to try to explain the effectiveness of the tissue carrier as an innovative vehicle. This tissue, in fact, free of preservatives, emulsifiers, fragrances, colors, and other chemicals could be used as the carrier for cosmeceutical products to be used for sensitive people to avoid the allergic and sensitization phenomena, always more frequent at the worldwide level. Naturally, we are going on with further studies to find new ways to bettering the production of cosmeceuticals and nutraceuticals more effective and safer.

Author contributions: the idea of manuscript PM.GF; writing original draft preparation PM, HD C; writing a review and editing PM, GM, SD, BA; supervision SD, PM, and H-D C. All the authors have read and agree to the publishing version of the manuscript

Institutional review board statement: The study was conducted by the 2024-revisioned Declaration of Helsinki and approved by the Ethical Committee of the Academy of History of Healthcare Art

Informed consent statement: written informed consent was obtained from all the voluntary participants involved in the study

Data availability statement: not applicable

Conflict of interest: the authors declare no conflict of interest

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