UNIVERSITAT DE BARCELONA

Facultat de Farmàcia
i Ciències de l'Alimentació

Final Degree Thesis

Pharmacy Degree

BIOPHARMACEUTICAL AND PHARMACODYNAMIC STUDY OF TOPICAL NIACINAMIDE

LUCÍA MOREIRO VARGAS

Biopharmacy and Pharmacokinetics

Physiology and Physiopathology; Pharmacology and Therapeutics

Department of Pharmacy and Pharmaceutical Technology,
and Physical Chemistry
Faculty of Pharmacy and Food Sciences
Universitat de Barcelona

Barcelona, April 2026





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Abstract

Biopharmaceutical and pharmacodynamic study of topical niacinamide

Niacinamide is a key active ingredient in dermatology and cosmetics due to its ability to improve skin barrier function, reduce hyperpigmentation and regulate sebum, among other activities. This study aimed to characterize the biopharmaceutical and pharmacodynamic profile of topical niacinamide to determine its optimal cutaneous concentration and establish a rational framework for formulation. A comprehensive literature review of *in vitro*, *ex vivo*, and *in vivo* studies was conducted. Effective cellular concentrations from *in vitro* data were quantitatively translated into target tissue concentrations (μg of niacinamide/g of skin). The synthesized evidence reveals that physiological targets for niacinamide are relatively low (e.g., < 50 μg/g for antioxidant effect and melanogenesis inhibition). Furthermore, clinical efficacy establishes an optimal therapeutic window for topical formulations between 2% and 5%. Because niacinamide's passive diffusion is fundamentally vehicle-dependent, achieving these targets requires optimized delivery systems and validation through *in vitro* permeation testing using Franz diffusion cells, rather than mere concentration increases. Consequently, the current cosmetic market trend of 10%–20% "megadoses" is not strongly supported by current biopharmaceutical evidence. Such concentrations do not appear to provide additional clinical benefits, may represent inefficient use of raw materials, and increase the risk of cutaneous irritation due to pH-dependent hydrolysis to vasodilatory nicotinic acid. Future dermatological research must prioritize evidence-guided rational design, sustainable practices, and greater industry transparency regarding active ingredient percentages.

Key words

Niacinamide, nicotinamide, nicotinic acid, topical delivery, skin permeation, stability, dermatology, activity, efficacy.

Resumen

Estudio biofarmacéutico y farmacodinámico de la niacinamida tópica

La niacinamida es un ingrediente activo clave en dermatología y cosmética debido a su capacidad para mejorar la función barrera de la piel, reducir la hiperpigmentación y regular el sebo, entre otras actividades. Este estudio tuvo como objetivo caracterizar el perfil biofarmacéutico y farmacodinámico de la niacinamida tópica para determinar su concentración cutánea óptima y establecer un marco racional para su formulación. Se llevó a cabo una revisión bibliográfica exhaustiva de estudios *in vitro*, *ex vivo* e *in vivo*. Las concentraciones efectivas en células procedentes de datos *in vitro* se tradujeron cuantitativamente a concentraciones tisulares diana (μg de niacinamida/g de piel). La evidencia sintetizada revela que las dianas fisiológicas de la niacinamida son relativamente bajas (ej., $< 50\ \mu$g/g para el efecto antioxidante y la inhibición de la melanogénesis). Además, la eficacia clínica establece una ventana terapéutica óptima para las formulaciones tópicas entre el 2% y el 5%. Dado que la difusión pasiva de la niacinamida es fundamentalmente dependiente del vehículo, alcanzar estas dianas requiere sistemas de liberación optimizados y validación mediante ensayos de permeación *in vitro* utilizando celdas de difusión de Franz, en lugar de meros aumentos de concentración. En consecuencia, la tendencia actual del mercado cosmético de formular ”megadosis” del 10%–20% no está firmemente respaldada por la evidencia biofarmacéutica actual. Dichas concentraciones no parecen proporcionar beneficios clínicos adicionales, pueden representar un uso ineficiente de materias primas y pueden aumentar el riesgo de irritación cutánea debido a la hidrólisis dependiente del pH en ácido nicotínico vasodilatador. La investigación dermatológica futura debe priorizar el diseño racional guiado por la evidencia, las prácticas sostenibles y una mayor transparencia de la industria respecto a los porcentajes de ingredientes activos.

Palabras clave

Niacinamida, nicotinamida, ácido nicotínico, administración tópica, permeación cutánea, estabilidad, dermatología, actividad y eficacia.

Integration of fields

The principal field of study of this Final Degree Thesis is Biopharmaceutics and Pharmacokinetics, focusing on the challenge of topical drug delivery. Specifically, this research details the journey of skin penetration of a hydrophilic molecule like niacinamide, with a low partition coefficient. Understanding these kinetics is important for predicting whether the active ingredient can cross the skin layers and reach its target site.

To understand the action of topical niacinamide, a deep knowledge of Physiology and Pathophysiology is required. Comprehending the architecture of the skin, with a special focus on the lipid matrix of the stratum corneum, is essential to comprehend the barrier properties that limit permeation and the impact this has on niacinamide's activity. Furthermore, exploring the pathophysiology of conditions such as acne and hyperpigmentation allows for a better understanding of the molecular mechanisms by which niacinamide restores cutaneous homeostasis.

Lastly, Pharmacology and Therapeutics will provide the relevant context to evaluate the pharmacodynamic profile by analyzing any dose-response relationship and whether the increased concentrations currently present in some commercial preparations would translate into an improved therapeutic effect or simply an enhanced risk of adverse reactions.

By combining these disciplines, this study provides an integrated understanding of the biopharmaceutical and pharmacodynamic profile of topical niacinamide that can help bridge the gap between formulation science and clinical application, with the ultimate goal of promoting the development of skincare products grounded in solid scientific evidence.

Sustainable development goals (SDG)

This Final Degree Thesis is developed within the department of Pharmacy and Pharmaceutical Technology, and Physicochemistry impacting a broad community ranging from patients with specific dermatological disorders (such as acne, rosacea, and hyperpigmentation) to the general population consuming skincare products. Currently, the last community faces a significant lack of rigor in the cosmetic market, where the use of high percentages of actives without sufficient scientific backing could be compromising safety or promising fake results. This project addresses this need by providing a critical evaluation of the biopharmaceutical profile of niacinamide to distinguish marketing claims from scientific evidence.

In this context, the project contributes directly to SDG 3: Good health and well-being, aligning specifically with Target 3.4, which aims to promote mental health and well-being. Skin conditions are often associated with psychological distress and low self-esteem. By analyzing the biopharmaceutical and pharmacodynamic profile of topical niacinamide, this study aims to offer concrete guidelines to optimize treatments. This ensures that patients receive effective care without unnecessary adverse effects like flushing, thereby improving their quality of life. While Indicator 3.4.2 focuses on the suicide mortality rate, mitigating the psychological burden of severe chronic skin conditions indirectly supports this broader public health objective.

Furthermore, the research addresses SDG 9: Industry, innovation and infrastructure, specifically Target 9.5, which calls to enhance scientific research and upgrade the technological capabilities of industrial sectors. The project involves key agents: the academia (University of Barcelona) acting as the source of critical knowledge, and the cosmetic industry, which requires these insights to innovate responsibly. By applying biopharmaceutical principles to formulation science, this work supports the transition towards evidence-based dermocosmetics and could also leave some space for science-based innovation. The final projection of this study, if continued, would be the establishment of stricter regulatory or formulation standards that prioritize skin bioavailability over high concentrations, fostering a more sustainable and scientifically robust industry. Regarding the indicators, they present an exclusively macroeconomic and demographic approach, designed to evaluate state policies and work places, making them poorly applicable to this context.

Contents

1 Introduction and context 1

1.1 General principles: skin structure and skin permeation 1

1.1.1 Skin structure 1

1.1.2 Skin permeation 3

1.2 Niacinamide: characteristics, properties and safety 6

1.3 Niacinamide activities in skin and mechanisms of action 7

1.3.1 Anti-aging effect 7

1.3.2 Sebostatic activity 7

1.3.3 Improvement of skin barrier function 8

1.3.4 Inhibition of hyperpigmentation 9

1.3.5 Anti-inflammatory effect 9

1.3.6 Antioxidant activity 10

1.3.7 Photoprotection and DNA repair 10

1.3.8 Antimicrobial activity 11

1.4 Current products in the market 11

2 Objectives and hypotheses 13

3 Materials and methods. Study design 13

3.1 Literature search strategy 13

3.2 Inclusion and exclusion criteria 14

3.3 Organization and analysis of information 14

4 Results and discussion 15

4.1 *In vivo* studies and clinical efficacy of niacinamide 15

4.1.1 Anti-aging effect 15

4.1.2 Sebostatic activity 17

4.1.3 Improvement of skin barrier function 17

4.1.4 Inhibition of hyperpigmentation 18

4.1.5 Anti-inflammatory effects: Acne and rosacea management 20

4.1.6 Antioxidant activity 21
4.1.7 Photoprotection and DNA repair 21
4.1.8 Antimicrobial activity 22
4.2 Summary of clinical evidence 22
4.3 *In vitro* studies as a tool for the development of effective topical formulations 24
4.3.1 Defining quantitative tissue targets 24
4.3.2 Formulation strategies and *in vitro* permeation testing 26

5 Conclusions **26**

References **28**

1 Introduction and context

1.1 General principles: skin structure and skin permeation

1.1.1 Skin structure

Skin plays a critical role in the regulation of external substances and the protection of internal organs. In the field of drug administration, the delivery of active ingredients through the skin has emerged as a promising strategy, offering potential benefits in terms of local efficacy and minimization of systemic side effects, as well as an alternative to the oral route, even if looking for a systemic effect, for those active compounds that meet certain biopharmaceutical and pharmacokinetic requirements.

The skin covers the external surface of the body and is the largest organ of the body in weight. In adults, the skin covers an area of about 2 square meters and weighs 4.5–5 kg, about 7% of total body weight. Over most of the body it is 1–2 mm thick (1). It has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics, which enables us to withstand a considerable range of environmental challenges (2).

It is essential to have a detailed understanding of skin architecture to comprehend the interaction of drugs with the skin and to achieve the desired topical, regional, or systemic effect. Figure 1 illustrates the structure of human skin.

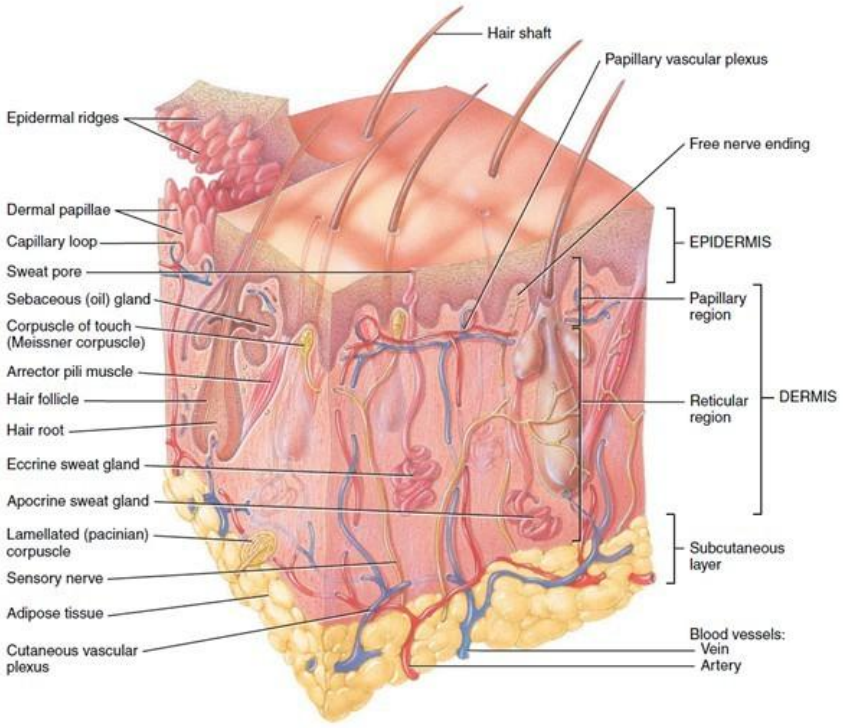


Figure 1: Components of the integumentary system. Sectional view of skin and subcutaneous layer (1).

It consists of three main layers, from the innermost to the outermost: the hypodermis, the dermis and the epidermis. The hypodermis, also known as the subcutaneous layer, separates the muscle from the skin and is not considered part of it in terms of skin permeation. It is composed of areolar connective tissue and adipose tissue. It stores most of the body's triglycerides, serves as an insulating layer that reduces heat loss, and protects the muscles from physical trauma (1).

The dermis, which makes up most of the skin, is mainly composed of dense irregular connective tissue containing collagen and elastic fibers, and it is highly vascularized. Within it are found pilosebaceous units, sweat glands, adipocytes, mast cells, and infiltrating leukocytes (3). The presence of this interwoven fiber network gives the skin great resistance to tension and to pulling or stretching forces.

The epidermis is the outer layer and therefore forms the rate-controlling barrier for diffusion for almost all compounds. It is stratified and can be divided into the non-viable epidermis and the viable epidermis. The layers and the cells that form it are schematized in Figure 2.

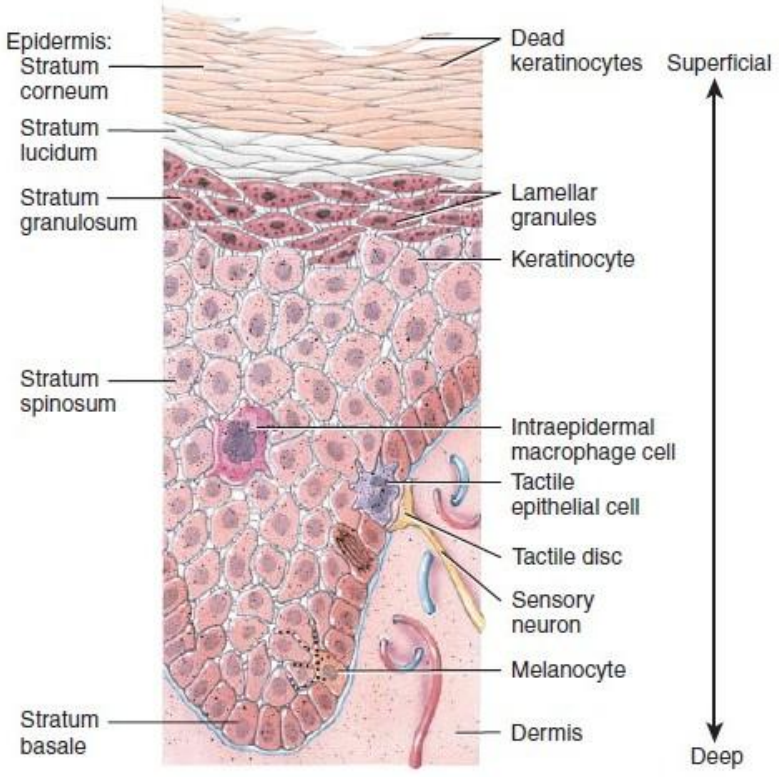


Figure 2: Schematic representation of the epidermis (1).

The non-viable epidermis comprises the stratum corneum, which forms the rate-controlling diffusion barrier for almost all topical compounds (2). Structurally, it is universally described by the "brick and mortar" model (3). The "bricks" consist of 15–20 layers of dead, anucleated, and flattened cells called corneocytes. These keratin-rich cells, with diameters ranging from 20 to 40 μm, are continuously shed and renewed (1). The "mortar" is a highly organized crystalline lamellar lipid matrix that fills the intercellular spaces (4).

This intercellular lipid matrix is predominantly composed of ceramides (approximately 50%), cholesterol (25%), and free fatty acids (10–15%) (4). The precise stoichiometric ratio and lamellar organization of these intercellular lipids are critical for maintaining skin elasticity, structural integrity, and preventing transepidermal water loss (TEWL) (5, 6). Furthermore, the outermost surface of the stratum corneum is coated with a hydrolipidic film. This protective emulsion consists of sweat and sebum, a complex mixture of triglycerides, wax esters, and squalene secreted by the sebaceous glands (7) resulting in the skin's acid mantle (pH 4.5–5.5). Understanding the distinction between the structural intercellular lipids and the superficial sebaceous film is fundamental, as topically applied active ingredients like niacinamide can independently modulate both systems to repair the epidermal barrier (8) and regulate oiliness (9), respectively.

Directly below the stratum corneum lies the viable epidermis, which is avascular and consists of three primary layers (from outermost to innermost): the granular layer, the spinous layer, and the basal layer. An additional lucid layer is present exclusively in the thick skin of the fingertips, palms, and soles (3). The predominant cells in the viable epidermis are keratinocytes, which present a hexagonal shape that flattens and alters its morphology as the cells differentiate and migrate upwards (1). This layer also comprises melanocytes, Langerhans cells, and Merkel cells, along with various catabolic enzymes such as esterases, phosphatases, proteases, nucleotidases, and lipases, which are highly relevant for cutaneous metabolism (10, 11).

1.1.2 Skin permeation

Drug absorption through the skin occurs via a process of passive diffusion. This process can take place through three different pathways, as shown in Figure 3: (i) by intercellular penetration through the lipid matrix, (ii) by intracellular penetration through the corneocytes, and (iii) through sweat pores and hair follicles (a very minor route not depicted in Figure 3), with the predominant route being the intercellular one. Many factors can influence the permeation capacity, such as the molecular weight, lipophilicity, the interactions established with the stratum corneum, and the obstructive effects of the corneocytes. Drugs suitable for permeation through the skin must possess very specific physicochemical characteristics: molecular weights below 500 daltons and high octanol/water partition coefficients ($\log P > 1.5$) (12, 13), with $\log P = 2$ being the optimal value (14). Corneocytes are covalently coated with long-chain lipids that are highly nonpolar and hydrophobic, which allows nonpolar drugs to permeate around them (15).

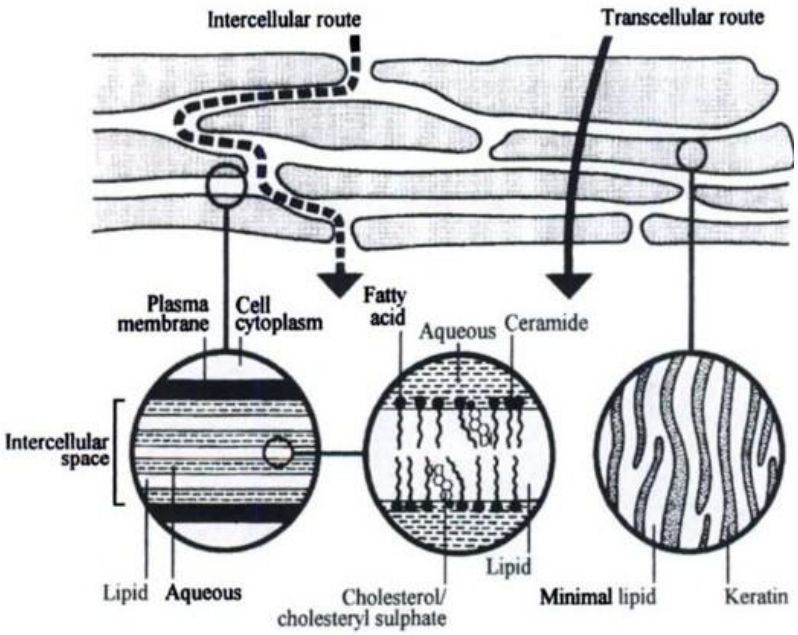


Figure 3: Schematic representation of the stratum corneum and two main possible drug permeation pathways (15).

As explained above, drug absorption through the skin occurs via a process of passive diffusion. According to Fick's first law, the steady-state flux (J) across a membrane is expressed as (16):

$$J = \frac{D \cdot K \cdot \Delta C}{h}$$

Where D is the diffusion coefficient of the drug within the stratum corneum, K is the partition coefficient of the drug between the stratum corneum and the vehicle, ΔC is the drug concentration gradient, and h is the thickness of the diffusion path (stratum corneum). Consequently, for the same site of application, formulation strategies focus on increasing K or D to increase the skin permeation of an active ingredient.

To better visualize this process, it is essential to understand the concentration and flux profile of the active ingredient as it permeates. Figure 4 illustrates a simplified steady-state concentration gradient across a homogeneous membrane for an infinite-dose application to human skin. However, the topical application of a cosmetic vehicle presents a more complex scenario, as depicted in Figure 5.

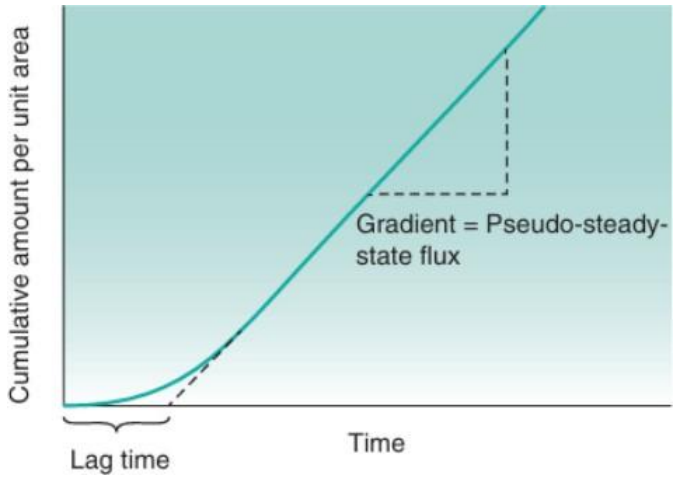


Figure 4: Typical permeation profile for an infinite-dose application to human skin, obtained from a plot of the cumulative amount per unit area of diffusant passing into the receptor compartment with time. Steady-state flux is seen when the gradient becomes linear. Extrapolation of this line to the time axis gives the lag time (16).

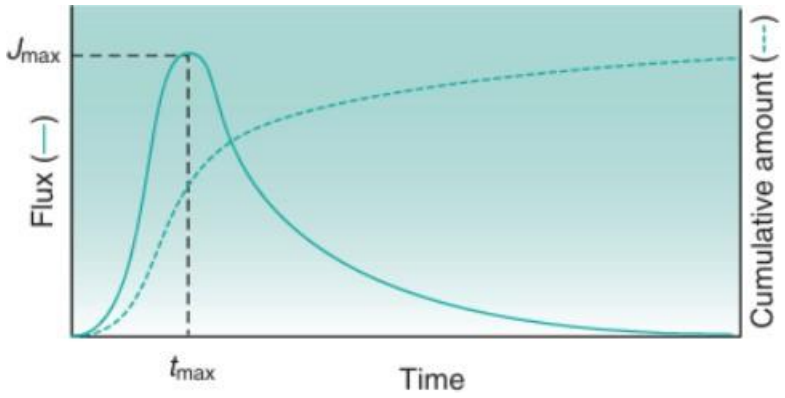


Figure 5: Typical permeation profile for a finite-dose application to human skin, showing increasing flux (amount transported per unit area with time) to a maximum value, beyond which it falls as the drug concentration in the donor solution declines, resulting in a drop in the concentration gradient across the membrane. The cumulative amount of drug passing the membrane thus reaches a plateau (16). Abbreviations: *Jmax*, maximum flux; *tmax*, time to maximum flux.

When a finite dose is applied, such as the application of a small amount of gel or cream, then the amount of the drug in contact with the skin surface will diminish with time. In this case the flux initially increases to a maximum value (*Jmax*), beyond which depletion of the drug in the donor solution means that the concentration difference across the membrane, which drives diffusion, starts to fall. Finite-dose profiles can be characterized by the time to maximum flux (*tmax*), by the maximum flux (*Jmax*) and from the area under the curve (16).

1.2 Niacinamide: characteristics, properties and safety

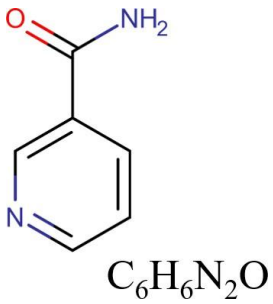


Figure 6: Chemical structure of niacinamide (17).

Niacinamide also known as nicotinamide, is a heterocyclic aromatic amide that is also an amide derivative of vitamin B3 (niacin or nicotinic acid). Its structure (3-pyridinecarboxamide) is shown in Figure 6. It has been incorporated into multiple cosmetic products due to its multiple topical effects such as anti-aging, antihyperpigmenting, reduction of sebum level among others. It is believed that its dermal effects happen due to its role as a component of coenzymes including nicotinamide adenine dinucleotide (NAD+), reduced nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADP+) and reduced nicotinamide adenine dinucleotide phosphate (NADPH). These coenzymes are essential for cellular energy metabolism, basically adenosine triphosphate (ATP) production, and serve as substrates for enzymes involved in DNA repair and genomic stability. By replenishing the intracellular pool of these cofactors, niacinamide modulates multiple physiological processes in the skin (17, 18).

Regarding its physicochemical properties, these are shown in Table 1. Although some of them such as its molecular weight or its melting point, make it a great drug candidate for topical administration, niacinamide possesses a low logP of -0.37 due to its high aqueous solubility which could present a challenge for skin permeation.

Table 1: Experimental properties of niacinamide (17).

Property	Value	Source
Molecular weight	122.12 g/mol	DrugBank
Melting point	130 °C	PhysProp
Boiling point	157 °C at 5.00×10^{-4} mmHg	PhysProp
Water solubility	5×10^5 mg/L (at 25°C)	MERCK INDEX (1996)
logP	−0.37	HANSCH, C ET AL. (1995)
logS	0.61	ADME Research, USCD
pKa	3.35 (at 20°C)	PERRIN, DD (1965)

Niacinamide has been proved as a safe compound (19, 20). Although it is generally well-tolerated, its chemical stability is a critical factor in formulation. Recent toxicological data by Barré et al. (21) confirms that niacinamide undergoes a hydrolysis reaction, converting into niacin (nicotinic acid). This conversion is clinically significant because niacin is a vasodilator responsible for adverse cutaneous reactions, specifically flushing (warmth and erythema). They identified that this hydrolysis is modulated by physicochemical parame-

ters, specifically acidic pH and high temperatures (> 45°C) during manufacturing. Their study established a direct correlation: acidic formulations showed higher levels of niacin and poorer skin tolerance compared to those with skin-compatible pH. Niacinamide's stability is maximal at a pH between 5.0 and 7.0 (22).

1.3 Niacinamide activities in skin and mechanisms of action

Niacinamide exerts multiple dermatological effects through several biochemical and cellular mechanisms. The main activities of topical niacinamide are: anti-aging effect, sebostatic activity, skin barrier protection, inhibition of hyperpigmentation, anti-inflammatory and antioxidant effects, photoprotection and DNA repair and antimicrobial activity.

1.3.1 Anti-aging effect

Skin aging is a complex biological process driven by both intrinsic chronological factors and extrinsic environmental aggressors, primarily chronic ultraviolet (UV) radiation. This UV-induced photoaging significantly accelerates the up-regulation of matrix metalloproteinases, which are the primary enzymes responsible for the degradation of structural collagen and elastin fibers in the dermis (23). Niacinamide's role in photoprotection is discussed in section 1.3.7.

Niacinamide is considered a promising active compound for the management of skin aging and to target the consequences of skin cell senescence (24). A decline in NAD+ availability and abnormal NAD+/NADH redox state are tightly linked to age-related metabolic diseases and neurodegenerative disorders (25). When talking about skin, NADPH usually acts as an electron donor in anabolic processes for protein synthesis in the skin such as collagen and elastin (26).

Different *in vitro* studies using human fibroblasts have demonstrated the anti-aging effects of niacinamide by restoring cellular energy levels (NAD+/NADH ratio) and safely stimulating physiological collagen synthesis (27, 28).

1.3.2 Sebostatic activity

Increased sebum excretion is a major concurrent event that parallels the development of acne lesions, although seborrhea alone is not a sufficient condition for the pathology (7). This lipid-rich microenvironment facilitates the colonization and proliferation of *Cutibacterium (C.) acnes* (formerly known as *Propionibacterium acnes*). Rather than merely hydrolyzing triglycerides, *C. acnes* actively triggers inflammatory cascades by acting on pattern recognition receptors, specifically Toll-like receptor 2 (TLR-2), located on follicular keratinocytes and macrophages (7). This activation stimulates the secretion of potent

pro-inflammatory cytokines, including interleukins IL-6 and IL-8, leading to the clinical manifestation of inflammatory acne lesions.

Although the sebostatic activity of niacinamide has been demonstrated, the precise molecular mechanism remains unclear (9, 29). Interestingly, its structural analog, niacin (nicotinic acid), has been shown to directly activate HCA2 receptors (hydroxycarboxylic acid receptor 2) on human sebocytes. This interaction triggers a transient intracellular Ca^{2+} elevation that ultimately down-regulates sebum synthesis (30).

However, the binding to the HCA2 receptor strictly requires a carboxylic acid fraction. Because niacinamide possesses an amide group instead, it lacks the ability to directly bind to this receptor. Consequently, it is currently hypothesized that the clinical sebostatic action of niacinamide may occur indirectly through its cutaneous bioconversion into niacin, which subsequently interacts with the HCA2 receptors to exert the observed sebum-regulating effects.

1.3.3 Improvement of skin barrier function

Topical niacinamide significantly reinforces the epidermal barrier architecture through a dual mechanism: the upregulation of intercellular lipid biosynthesis to strengthen the lipid matrix, and the stimulation of keratinocyte differentiation.

Regarding the lipid matrix, niacinamide upregulates the synthesis of crucial stratum corneum lipids, particularly ceramides, by stimulating serine palmitoyltransferase, the rate-limiting enzyme in sphingolipid synthesis. Consequently, this reinforced lipid matrix is directly associated with a markedly reduced TEWL and an increased cutaneous resistance to potentially harmful exogenous agents (8).

The second mechanism responsible for barrier improvement involves the cellular compartment. Niacinamide accelerates keratinocyte differentiation, notably influencing the expression of keratin K1, a basic structural protein synthesized in the stratum spinosum (8). The increased concentration of intracellular reduced nicotinamide coenzymes (NADH and NADPH) by niacinamide discussed previously may cause upregulation of the biosynthesis of involucrin and filaggrin in human epidermal keratinocytes. These proteins are essential in the differentiation and formation of fully integral keratinized corneocytes that enhance skin barrier function (18). Ultimately, the synergistic combination of enhanced lipid production and accelerated cellular turnover results in a thicker stratum corneum that is associated with greater hydration retention capacity (31).

In addition to its biochemical effects on lipid synthesis and cellular turnover, recent research has elucidated a direct structural interaction between niacinamide and the corneocyte's protein matrix. A 2025 study by Sjöberg et al. (6) utilizing X-ray diffraction demonstrated that, particularly under low-humidity conditions, niacinamide significantly swells the spacing between keratin monomers. By intercalating within the soft keratin structure,

niacinamide acts as a molecular plasticizer. This newly identified mechanism effectively increases the flexibility and mechanical resilience of the stratum corneum in dry environments, providing a direct hydrating and softening effect.

1.3.4 Inhibition of hyperpigmentation

Visible skin pigmentation relies on a highly regulated physiological process in which melanin, once synthesized within melanocytes inside specialized organelles called melanosomes, must be transported through cellular dendrites and physically transferred to adjacent keratinocytes for distribution throughout the epidermis (32). In melanocyte and keratinocyte co-culture, reconstituted skin tissue model, or live skin, nicotinamide consistently decreased melanin content or pigmentation (33, 34). Unlike traditional skin-lightening agents such as hydroquinone, which directly inhibit tyrosinase activity to stop melanin production (35), niacinamide has been shown to act through a different pathway in different studies, although Lei et al. (36) demonstrated that it can inhibit tyrosinase activity in melanocytes cocultured with keratinocytes in a dose-dependent manner, but has little effect on melanocytes alone.

Clinical and *in vitro* studies conducted by Hakozaki et al. (33) demonstrated that topical niacinamide significantly decreases hyperpigmentation by preventing the transfer of intact melanosomes from melanocytes to surrounding keratinocytes. Furthermore, Greatens et al. (34) corroborated these findings, highlighting that this inhibition is a reversible process; once the niacinamide treatment is discontinued, melanosome transfer resumes its normal physiological rate. This reversible mechanism is crucial, as it provides a robust depigmenting effect without causing melanocyte toxicity, thereby offering an excellent safety profile for long-term dermatological use.

1.3.5 Anti-inflammatory effect

Niacinamide also has anti-inflammatory potential. Lembo et al. (37) demonstrated *in vitro* that the combination of niacinamide and azeloglycine significantly down-regulated the release of key pro-inflammatory mediators such as IL-8, which is clinically relevant for acne management. Niacinamide also inhibits the major histocompatibility complex class II (antigen presenting cells) from immune response initiation that leads to inflammation (38).

It can reduce Prostaglandin E_2 (PGE_2), IL-6 and IL-8 levels induced by environmental stressors. Additionally, *in vivo* skin pretreatment with niacinamide can reduce UV-induced erythema and skin surface inflammatory biomarkers (39). These findings add to the body of evidence that niacinamide can mitigate the skin's inflammatory response elicited by environmental stressors.

1.3.6 Antioxidant activity

The skin is constantly exposed to environmental stressors such as UV radiation and urban pollution, which induce the generation of Reactive Oxygen Species (ROS). The accumulation of ROS leads to oxidative stress, driving lipid peroxidation, DNA damage, and the degradation of extracellular matrix proteins. Niacinamide has potent intrinsic antioxidant properties primarily through its metabolic role as a precursor to the coenzymes NAD^+ and $NADP^+$. The reduced form, NADPH, acts as an essential cofactor for the regeneration of potent endogenous antioxidants, most notably intracellular glutathione (GSH), thereby restoring the cellular redox balance and neutralizing ROS cascades (29).

Furthermore, recent research has highlighted niacinamide's cytoprotective efficacy against atmospheric pollution. An *in vitro* study by Zhen et al. (40) utilizing human HaCaT keratinocytes demonstrated that niacinamide effectively mitigates oxidative stress induced by fine particulate matter ($PM_{2.5}$). The introduction of niacinamide dose-dependently inhibited PM-induced ROS generation and blocked the subsequent oxidation of lipids, proteins, and DNA. Additionally, it prevented the abnormal accumulation of intracellular Ca^{2+} triggered by the pollutants, effectively protecting the keratinocytes from membrane depolarization and apoptosis. These findings support the role of niacinamide as an antioxidant capable of protecting cellular integrity from a wide spectrum of environmental aggressors.

1.3.7 Photoprotection and DNA repair

As previously discussed, UV radiation is a ubiquitous environmental stressor that profoundly impacts skin physiology. While its role in generating ROS and accelerating extracellular matrix degradation has been addressed in the antioxidant and anti-aging sections, respectively, UV radiation also exerts direct effects on cellular integrity. Specifically, UV exposure induces DNA damage in human keratinocytes, primarily in the form of cyclobutane pyrimidine dimers (CPDs), and simultaneously triggers profound local immunosuppression (41).

The primary mechanism by which niacinamide exerts its photoprotective effect is fundamentally energetic. DNA excision repair is a highly ATP-dependent process. Upon UV irradiation, the activation of the DNA repair enzyme Poly (ADP-ribose) polymerase-1 (PARP-1) rapidly consumes cellular NAD^+, leading to severe ATP depletion. This energy crisis critically impairs the cell's ability to complete the repair pathways (42).

In vitro and *ex vivo* studies utilizing human keratinocytes and skin explants have demonstrated that the administration of niacinamide effectively prevents this UV-induced energy crisis by replenishing the intracellular NAD^+ pool. By sustaining cellular ATP levels, niacinamide significantly enhances the rate of DNA repair, reducing the accumulation of photolesions and preventing UV-induced immunosuppression (43).

Philips et al. (44) evaluated the response of human dermal fibroblasts exposed to UVA radiation, finding that the application of niacinamide significantly stimulated the expression of fibrillar collagens (types I, III, and V) as well as regulatory heat shock proteins (HSPs). This suggests a dual mechanism: protecting existing structural proteins from oxidative cleavage while actively promoting the synthesis of new extracellular matrix components. All these studies demonstrate that topical niacinamide contributes to protection against UV-induced DNA damage.

1.3.8 Antimicrobial activity

A study from 2024 by Ziklo et al. (45) explored niacinamide's antimicrobial mode of action against four common cosmetic pathogens including Gram-negative and Gram-positive bacteria, yeast, and spore forming mold. They found that niacinamide was causing microbial cell cycle arrest; while cells were found to increase their volume and length under treatment to prepare for cell division, complete separation into two daughter cells was prevented. Fluorescence microscopy revealed expanded chromatin, along with decreased RNA expression of the DNA-binding protein gene. Finally, niacinamide was found to directly interact with DNA, hindering successful amplification.

Beyond its general ability to arrest the microbial cell cycle, niacinamide also tackles more complex bacterial defense structures, such as the biofilms of *C. acnes* responsible for the persistence and antibiotic resistance of acne vulgaris. In addition to the standard treatments for acne vulgaris, a common adjunctive treatment is the topical administration of nicotinamide. However, the effects of niacinamide on biofilms of *C. acnes* had never been explored. A study by Shih et al. (46) investigated it using *in vitro* and *in vivo* approaches. The results showed that niacinamide decreased the formation and increased the degradation of biofilms in *C. acnes* and potentiated the efficacy of suboptimal dosing of tetracycline against *C. acnes*.

1.4 Current products in the market

Although its logP value apparently doesn't make it the best candidate for dermal application, niacinamide's excellent safety profile and dermal benefits, have promoted its incorporation into numerous cosmetic products. The concentrations vary from product to product. Several marketed skincare products containing niacinamide are summarised in Table 2.

Table 2: Examples of several marketed skincare products in Spain containing niacinamide.

Product type	Product name	Niacinamide concentration
Cleansing water	CeraVe Micellar Cleansing Water Ultra Gentle Hydrating Formula	Not known
Facial cleanser	CeraVe Foaming Cleanser For Normal to Oily Skin	Not known
	Garnier Pure Active 3 in 1 Salicylic Clay	Not known
Serum	CeraVe Resurfacing Retinol Serum with Ceramides and Niacinamide for Blemish-Prone Skin	Not known
	Kiehl's Ultra Pure High-Potency Serum	5%
	The Ordinary Niacinamide 10% + Zinc 1%	10%
	La Roche-Posay Mela B3 Serum	10%
	The INKEY List™ SuperSolutions 20% Niacinamide Serum	20%
	Paula's Choice Clinical 20% Niacinamide Treatment	20%
Moisturiser	Olay® Niacinamide 24+ Vitamin E Night Moisturiser With 99% Pure Niacinamide & Shea Butter	Not known
	Deliplus Sebum-Regulating Facial Gel	Not known
Tonic	Garnier Vitamin C Brightening Liquid Care	Not known (below 10%)
Eye cream	Olay® Niacinamide 24+ Vitamin E Eye Cream	Not known
	Garnier Brightening 4% [Vitamin C, Niacinamide, Caffeine & Banana Powder] Eye Cream	Not known (below 4%)
Mask	PUCA&CARE® Niacinamide Sheet Mask	Not known
	Garnier SkinActive Ampoule 2% Niacinamide+Kale Detox Ampoule Sheet Mask	2%
Sunscreen	Garnier Delial Super UV Daily Anti-Imperfection Fluid with Niacinamide SPF 50+	Not known (below 3.5%)
	Neutrogena® Hydro Boost Hydrating Fluid SPF 50	2%
Patches	Peace Out® Dark Spots Microneedling Dots	Not known

2 Objectives and hypotheses

The primary objective of this study is to characterize the biopharmaceutical and pharmacodynamic profile of topical niacinamide to determine the optimal active content of niacinamide in the skin. To achieve this goal, the following specific objectives have been established:

- To evaluate published *in vivo* clinical trials to analyze the relationship between the therapeutic efficacy and the concentration of niacinamide in the applied formulation.
- To review published literature correlating niacinamide concentration with its biological activity through *in vitro* studies and quantitatively translate these cellular requirements into target tissue concentrations (μg of niacinamide/g of skin).
- To establish a rational theoretical framework for formulation optimization, ensuring that topical products meet the calculated skin retention targets efficiently and safely, ultimately promoting the development of commercial products based on rigorous scientific evidence.

Based on the physicochemical properties of niacinamide and general principles of dermopharmacy, this study proposes the following hypothesis: Although the cosmetic market shows a trend towards increasing concentrations of niacinamide (up to 20%) in the dermal products, therapeutic efficacy does not increase linearly with concentration. It is hypothesized that lower concentrations could be sufficient to achieve saturation of biological targets if the formulation vehicle is optimized to enhance skin permeation, while higher concentrations likely provide diminishing returns in efficacy and, in some cases, could lead to a higher risk of skin irritation.

3 Materials and methods. Study design

As this work is a literature review, the methodology includes the identification, selection, and integrative analysis of relevant scientific studies. Through a systematic integration of findings, this work assesses the methodological quality of the available evidence and discusses the discrepancies found between scientific data and current market practices.

3.1 Literature search strategy

The search was conducted in major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science, supplemented with open-access academic literature (Google Scholar) and specialized textbooks on anatomy, pharmacology, biopharmaceutics, and dermatology. Combinations of keywords were used, such as: “niacinamide”, “nicotinamide”,

”nicotinic acid”, “topical administration”, “skin permeation”, “formulations”, “dermatology”, ”in vitro”, ”ex vivo”, ”in vivo”, ”Franz”, ”clinical evidences”.

3.2 Inclusion and exclusion criteria

Articles published primarily in the last 20 years were included, although classic studies considered relevant to biopharmaceutical fundamentals were also reviewed.

To ensure the relevance of the data, specific eligibility criteria were applied to the search results. The review included original articles, reviews, *in vitro* and *ex vivo* studies, clinical trials, and systematic reviews evaluating topical niacinamide, specifically focusing on its cutaneous effects, permeation, and commercially available formulations.

Publications were excluded if they were unrelated to the topical administration of the active ingredient, lacked evident methodological rigor, or if sufficient quantitative data could not be extracted from either the full text or a detailed abstract.

3.3 Organization and analysis of information

The selected works were organized according to the study objectives, grouping the information into the following thematic areas:

- *In vitro* evidence detailing the mechanisms of action and the correlation between niacinamide concentration and its biological activity.
- *Ex vivo* skin permeation studies evaluating how different formulation vehicles and active concentrations impact the steady-state flux (J_{ss}) of niacinamide.
- *In vivo* clinical trials assessing the therapeutic efficacy, dose-response relationship, and safety profile of topical niacinamide.
- Analysis of currently marketed topical formulations to critically evaluate their concentrations and rational design.

The information was synthesized and critically discussed, assessing both the methodological quality of the reviewed studies and the coherence between experimental biopharmaceutical findings and their actual clinical application.

4 Results and discussion

4.1 *In vivo* studies and clinical efficacy of niacinamide

Having explained the biochemical mechanisms of action of topical niacinamide through various *in vitro* cell culture models, it is crucial to evaluate how these theoretical cellular dynamics translate into real-world dermatological practice. The following section critically analyzes the available *in vivo* clinical evidence. By bridging the gap between cellular pharmacodynamics and macroscopic clinical outcomes, this analysis aims to determine the actual therapeutic efficacy and establish the optimal skin concentration window for treating different skin conditions as a tool for the development of topical niacinamide formulations.

4.1.1 Anti-aging effect

In vivo studies conducted to prove niacinamide's anti-aging effect have demonstrated its benefits and safety profile. Kawada et al. (47) proved that a topical 4% niacinamide-containing cosmetic reduced wrinkles in the eye area of Japanese women at 8 weeks. Bissett et al. (48) also carried out a study to prove this effect with a moisturizer product containing 5% niacinamide. Niacinamide was well tolerated by the skin and provided significant improvements versus control regarding fine lines/wrinkles, hyperpigmentation spots, texture, and red blotchiness. In a randomized, double-blind, placebo-controlled, split-face comparative study by Chiu et al. (49), 4% nicotinamide alone reduced pores and skin unevenness after 8 weeks and improved wrinkles after 12 weeks. Furthermore, the formulation containing 0.03% kinetin + 4% nicotinamide significantly reduced erythema and hyperpigmented spots in addition to pores, roughness, and wrinkles after 8 weeks.

Recent clinical investigations have also highlighted the benefits of combining niacinamide with other active ingredients to maximize anti-aging results. For instance, a comparative study by Fu et al. (50) demonstrated that a formulation containing 5% niacinamide, peptides, and 0.3% retinyl propionate significantly improved fine lines and wrinkles after 8 weeks, achieving an efficacy comparable to a prescription 0.02% tretinoin treatment but with a superior tolerability profile. Similarly, Farris et al. (51) evaluated a synergistic blend of 4.4% niacinamide, 0.5% retinol, and antioxidants, reporting an accelerated onset of clinical benefits; patients exhibited improvements in fine lines and skin radiance as early as 2 weeks, and a significant reduction in deeper wrinkles and hyperpigmentation by week 4. Furthermore, Bogdanowicz et al. (52) demonstrated that combining 6% niacinamide with hyaluronic acid leads to a significant clinical improvement in the signs of skin aging. The daily application of this combination yielded visible enhancements in skin smoothness and luminosity within 4 weeks, culminating in an average reduction of 20%

in wrinkle depth after 8 weeks. To validate these *in vivo* findings, the authors correlated the clinical outcomes with an *ex vivo* human skin model, confirming that the macroscopic smoothing of wrinkles observed in patients was directly supported by the structural preservation and redensification of the skin tissue. Ultimately, these findings confirm that the structural benefits of niacinamide translate effectively into tangible clinical outcomes, and that multi-ingredient formulations can significantly accelerate this process.

To synthesize the findings of these clinical trials, Table 3 summarizes these results.

Table 3: *In vivo* studies evaluating the anti-aging efficacy of topical niacinamide: Niacinamide content, clinical outcomes, and timeframes required to observe the effects.

Reference	Niacinamide content	Main anti-aging outcomes	Time to results
Bissett et al. (48)	5% Niacinamide	Improvement in fine lines, hyperpigmentation spots, texture, and red blotchiness.	12 weeks
Chiu et al. (49)	4% Niacinamide (monotherapy)	Reduced pores and skin unevenness (8 weeks); improved wrinkles (12 weeks).	8–12 weeks
Kawada et al. (47)	4% Niacinamide	Reduction of wrinkles in the periorbital area.	8 weeks
Chiu et al. (49)	4% Niacinamide + 0.03% Kinetin	Significantly reduced erythema, hyperpigmented spots, pores, roughness, and wrinkles.	8 weeks
Fu et al. (50)	5% Niacinamide + Peptides + 0.3% Retinyl Prop.	Improvement in fine lines and wrinkles, comparable in efficacy to 0.02% prescription tretinoin.	8 weeks
Bogdanowicz et al. (52)	6% Niacinamide + Hyaluronic Acid	Improved smoothness and luminosity (4 weeks); 20% reduction in wrinkle depth (8 weeks).	4–8 weeks
Farris et al. (51)	4.4% Niacinamide + 0.5% Retinol + Antioxidants	Improvement in fine lines and radiance (2 weeks); reduced wrinkles and hyperpigmentation (4 weeks).	2–4 weeks

As seen in Table 3, achieving significant macroscopic anti-aging results with niacinamide monotherapy typically requires a consistent application period ranging from 8 to 12 weeks. However, the impact of synergistic formulations is visible. When niacinamide is combined

with other targeted active ingredients, such as kinetin, hyaluronic acid or retinol, the time period required to observe visible improvements in skin texture, luminosity, and wrinkle depth is reduced (2 to 4 weeks).

4.1.2 Sebostatic activity

The sebostatic effect proposed theoretically has been confirmed clinically across different ethnic groups and evaluated through precise biophysical measurements. Draelos et al. (9) utilized Sebumeter® and Sebutape® analyses to demonstrate that the topical application of 2% niacinamide significantly lowered the sebum excretion rate in Japanese individuals after just two to four weeks of use. In the same study, but in a split-face trial involving Caucasian subjects, the same 2% formulation successfully reduced casual sebum levels after six weeks, alongside a noticeable macroscopic improvement in facial shine and oiliness. By reducing the amount of sebum, primarily triglycerides, available for *C. acnes* colonization, formulations containing 2% to 5% niacinamide directly address one of the primary pathogenic factors of acne *in vivo* (29).

To further validate these findings, an *in vivo* study by Leite and Campos (53) evaluated the clinical efficacy of a 3% niacinamide gel cream. Using non-invasive devices to objectively quantify skin parameters, the researchers confirmed that the topical application of niacinamide effectively controlled objective oiliness parameters while simultaneously improving the overall texture and appearance of the skin.

The clinical translation of this sebostatic activity becomes particularly relevant when treating pathological conditions like acne vulgaris. While traditional treatments focus solely on bacteria or inflammation, niacinamide's ability to regulate sebum adds a crucial therapeutic dimension. This was robustly demonstrated by Khodaeiani et al. (54), who, when comparing a 4% niacinamide gel to a 1% clindamycin antibiotic gel, discovered that the niacinamide treatment was significantly more efficacious specifically in patients with oily skin types.

Niacinamide, unlike topical retinoids, which often induce severe dryness, erythema, and barrier disruption to control oiliness (55), offers a physiological down-regulation of lipid output, making it an ideal, well-tolerated option for long-term sebum management.

4.1.3 Improvement of skin barrier function

While *in vitro* studies establish niacinamide's role in upregulating ceramide synthesis, clinical trials confirm that these molecular changes effectively translate into a fortified epidermal barrier. The primary clinical indicators of this barrier properties are the reduction of TEWL and the increase in stratum corneum hydration.

To understand the biophysical changes occurring *in vivo*, Mohammed et al. (5) evaluated

the stratum corneum of healthy volunteers after 28 days of topical niacinamide application. Their findings revealed not only a significant decrease in TEWL but also an increase in stratum corneum thickness and the presence of larger, more mature corneocytes.

More recently, Permatasari and Tan (56) evaluated the efficacy of a formulation containing 4% topical niacinamide versus a placebo in healthy volunteers. Utilizing a corneometer, the authors demonstrated a significant increase in stratum corneum hydration in the niacinamide group as early as week 4, which was successfully maintained through week 8.

The therapeutic potential of this structural reinforcement is particularly evident in compromised skin barriers, such as in atopic dermatitis. In this regard, Soma et al. (57) conducted a left-right comparison study on patients with atopic dry skin, demonstrating that a 2% niacinamide cream significantly decreased TEWL and was more effective at increasing stratum corneum hydration than white petrolatum, a traditional occlusive agent. More recently, Zhu et al. (58) developed a study involving 122 patients with mild atopic dermatitis which corroborated these results: they observed that the daily use of a niacinamide-containing emollient significantly improved both TEWL and the stratum corneum water content after 14 days of the treatment.

Niacinamide has also been shown to be effective in treating xerosis cutanea: Christman et al. (59) evaluated the stratum corneum integrity benefits of body moisturizers, finding that formulations containing niacinamide provided rapid and prolonged functional improvements to the skin barrier compared to conventional moisturizers. Although the authors did not disclose the exact niacinamide concentration used in these commercial formulations, these macroscopic findings, alongside the aforementioned studies, confirm that niacinamide, even at concentrations as low as 2%, was a highly effective active ingredient for restoring the hydrolipidic film and maintaining cutaneous moisture balance.

4.1.4 Inhibition of hyperpigmentation

The theoretical mechanism of melanosome transfer inhibition translates into robust clinical efficacy, particularly in the management of facial hyperpigmentation and photoaging spots. Hakozaki et al. (33) evaluated the *in vivo* efficacy of topical niacinamide in Japanese women. The study demonstrated that the twice-daily application of a 5% niacinamide moisturizer significantly decreased facial hyperpigmentation and increased skin lightness compared to the vehicle alone after just 4 weeks of use.

Furthermore, niacinamide has proven to be a highly competitive alternative to hydroquinone, the historical gold standard for depigmentation, in treating complex conditions such as melasma. In this regard, Navarrete-Solís et al. (60) conducted a double-blind, randomized, split-face clinical trial on patients with melasma, applying 4% niacinamide on one side of the face and 4% hydroquinone on the other for 8 weeks. The colorimetric analysis revealed no statistical differences in lightening efficacy between the two treatments.

While hydroquinone showed a slightly higher rate of ”good-to-excellent” subjective improvement (55% vs. 44%), niacinamide presented a significantly superior safety profile, inducing adverse effects in only 18% of patients compared to 29% with hydroquinone. Additionally, niacinamide uniquely reduced the inflammatory mast cell infiltrate and improved solar elastosis, addressing both the pigmentary and inflammatory components of melasma.

It is important to critically address the current cosmetic market trend of formulating niacinamide at significantly higher concentrations, such as 10% or even 20%. While recent clinical trials have reported successful depigmenting outcomes using 10% niacinamide, these formulations are invariably embedded within potent polytherapeutic regimens. For instance, a recent trial by Xiong et al. (61) evaluated the efficacy of a 10% niacinamide formulation for the treatment of chloasma (a common skin hyperpigmentation condition). Although the treatment demonstrated a significant reduction in melasma severity scores, the niacinamide was actively combined with 30% salicylic acid (a keratolytic agent). The question is whether this combination of active ingredients would be effective with a lower concentration of niacinamide.

Beyond facial application, the inhibition of melanosome transfer proves effective even in challenging conditions. Castanedo-Cazares et al. (62) evaluated a 4% niacinamide emulsion for axillary hyperpigmentation (phototypes III–V). While 0.05% desonide (a corticosteroid) was slightly superior, niacinamide showed good-to-excellent responses in 24% of cases, offering a safe, non-steroidal alternative for long-term treatment.

To synthesize the clinical evidence regarding niacinamide’s depigmenting efficacy, Table 4 summarizes the key *in vivo* studies comparing its performance against control vehicles and other actives.

Table 4: *In vivo* studies evaluating the depigmenting efficacy of topical niacinamide.

Reference	Niacinamide concentration	Comparator	Main clinical outcomes
Hakozaki et al. (33)	5%	Control (vehicle)	Significant decrease in facial hyperpigmentation and increased skin lightness at 4 weeks.
Navarrete-Solís et al. (60)	4%	4% Hydroquinone	Comparable pigment reduction (8 weeks). Niacinamide showed fewer side effects (18% vs 29%) and improved solar elastosis.
Xiong et al. (61)	10% (+ 30% Salicylic Acid)	Control (vehicle)	Significant reduction in melasma severity; however, the specific effect of niacinamide cannot be isolated due to potent keratolytic polytherapy.
Castanedo-Cazares et al. (62)	4%	0.05% Desonide	Good-to-excellent reduction of axillary hyperpigmentation in 24% of cases. Safe non-steroidal alternative.

4.1.5 Anti-inflammatory effects: Acne and rosacea management

Niacinamide has emerged as a highly viable and safe alternative to topical antibiotics in the treatment of inflammatory acne. The foundational clinical trial by Shalita et al. (63) demonstrated that a 4% nicotinamide gel was as effective as a 1% clindamycin gel in reducing inflammatory lesions (papules and pustules) over an 8-week period. This clinical equivalence was later corroborated by Khodaeiani et al. (54), who reported that a 4% niacinamide gel not only showed comparable efficacy to 1% clindamycin in treating moderate inflammatory acne, but also achieved superior results specifically in patients with oily skin types. This efficacy was further confirmed by Shahmoradi et al. (64), who found that 5% niacinamide was as effective as 2% clindamycin.

It should be noted that, while prolonged topical antibiotic use frequently leads to resistant strains of *C. acnes*, niacinamide exerts its anti-inflammatory effects without exerting selective pressure on the skin microbiome. This makes it an ideal, sustainable therapeutic option for the long-term management of acne vulgaris, coupled with an excellent tolerability profile.

This anti-inflammatory effect is also clinically relevant for other inflammatory dermatoses. Wozniacka et al. (65) demonstrated that the vitamin B3 pathway is crucial for rosacea; even using 1-methylnicotinamide (a primary metabolite of niacinamide), they observed significant clinical improvements in facial erythema and inflammatory papules. This

validates the use of this family of molecules for down-regulating cutaneous inflammation while simultaneously repairing the compromised epidermal barrier characteristic of rosacea patients.

4.1.6 Antioxidant activity

The potent intracellular antioxidant mechanisms observed *in vitro*, specifically the regeneration of glutathione and the neutralization of ROS, translate into tangible macroscopic benefits *in vivo*. While it is complex to measure oxidative stress directly on the skin surface of living patients, clinical dermatology utilizes specific macroscopic markers, such as skin yellowing (sallowness) and environmentally-induced erythema, to evaluate antioxidant efficacy. Chronic oxidative stress accelerates the oxidation and glycation of dermal proteins, a process known as the Maillard reaction, which results in cross-linked fluorescent proteins that impart a yellowish, sallow appearance to aged skin. In the pivotal 12-week clinical trial conducted by Bissett et al. (48), the twice-daily application of a 5% niacinamide moisturizer significantly reduced skin sallowness in Caucasian women compared to the vehicle. This *in vivo* reduction in yellowing serves as a direct clinical macroscopic marker of niacinamide's ability to inhibit oxidative protein cross-linking.

Regarding the environmentally-induced erythema, clinical studies evaluating the skin's response to environmental aggressors demonstrated that topical pre-treatment with niacinamide effectively reduced UV-induced and pollution-induced erythema (39). By neutralizing the free radical cascades before they can trigger the release of pro-inflammatory cytokines, niacinamide clinically mitigates the visible signs of environmental oxidative stress.

4.1.7 Photoprotection and DNA repair

The critical *in vitro* observation that niacinamide replenishes the NAD^+ pool and fuels the PARP-1 enzyme for DNA excision repair translates *in vivo* into a powerful defense against photoimmunosuppression (42, 43). In clinical dermatology, the immune status of the skin is frequently evaluated using the Mantoux delayed-type hypersensitivity (DTH) reaction. When the skin is exposed to UV radiation, this local immune response is profoundly suppressed, creating a "permissive" environment for the survival and proliferation of cells with DNA mutations (41).

To evaluate this mechanism in a clinical setting, Sivapirabu et al. (66) conducted a double-blind, randomized study on healthy human volunteers. They demonstrated that the topical application of a 5% niacinamide formulation immediately following solar-simulated UV exposure significantly protected the skin against UV-induced immunosuppression. By restoring cellular energy levels, niacinamide allowed the local immune system to remain active and functional despite the radiation.

The long-term clinical relevance of this metabolic rescue is profound. By accelerating the clearance of DNA photolesions such as CPDs and preventing photoimmunosuppression, niacinamide actively disrupts the trajectory of field cancerization (42). Clinical evaluations in photo-damaged patients establish that the regular application of vitamin B3 reduces the development and progression of actinic keratoses, the most common precancerous skin lesions. Consequently, in the context of chronic sun exposure, topical niacinamide transcends cosmetic anti-aging; it acts as a robust chemopreventive pharmacological agent that actively preserves the genomic integrity of the epidermis (67).

4.1.8 Antimicrobial activity

Although niacinamide is widely recognized for its anti-aging, depigmenting, and barrier-repairing properties, its antimicrobial effect is considered a secondary benefit and has been the subject of comparatively fewer clinical studies. Rather than acting as a direct traditional biocide, low concentrations of topical niacinamide (1% to 3%) have been shown to stimulate the skin's innate immune system. As demonstrated by Mathapathi et al. (68), this active ingredient upregulates the production of endogenous antimicrobial peptides in keratinocytes, leading to a drastic reduction in the *in vivo* survival of transient pathogens such as *Staphylococcus (S.) aureus* and *Escherichia (E.) coli* on the skin surface within just 6 hours.

4.2 Summary of clinical evidence

To synthesize the extensive clinical data discussed in the previous sections, it is crucial to understand the dose-response relationship and the temporal dynamics of topical niacinamide. While marketing trends often push for higher active content, the clinical reality leads to a defined therapeutic window.

Table 5 provides a comprehensive overview of the *in vivo* efficacy of niacinamide, correlating the dermatological targets with the optimal concentrations, the timeframes required to achieve macroscopic results, and the pivotal clinical trials that support them.

Table 5: Summary of the *in vivo* clinical efficacy of topical niacinamide: Dermatological objective, effective niacinamide concentration studied, and timeframe for visible results.

Dermatological objective	Niacinamide concentration	Time to results	Key macroscopic outcomes	References
Anti-aging	4% – 6%	2 – 12 weeks	Reduction in periorbital wrinkles, fine lines, and textural unevenness.	(48, 47, 49, 50, 51, 52)
Sebum regulation	2%	2 – 6 weeks	Lowered sebum excretion rate, casual sebum levels, and oiliness.	(9, 53)
Barrier and hydration	2% – 4%	2 – 8 weeks	Reduced TEWL, increased SC hydration, and improved atopic/xerotic skin.	(5, 56, 57, 58, 59)
Hyperpigmentation	4% – 10%	4 – 8 weeks	Reduced facial/axillary hyperpigmentation, comparable efficacy to 4% hydroquinone.	(33, 60, 61, 62)
Inflammatory acne & rosacea	4% – 5%	8 weeks	Reduced papules, pustules, and facial erythema (rosacea), comparable to clindamycin.	(63, 54, 64, 65)
Antioxidant (sallowness & erythema)	5%	12 weeks / Pre-exposure	Significant reduction in skin yellowing and UV/pollution-induced erythema.	(48, 39)
Photoprotection & DNA repair	5%	Immediate (Post-UV)	Prevention of UV-induced immunosuppression.	(66)
Antimicrobial	1% – 3%	6 hours	Enhanced production of antimicrobial peptides and reduced survival of *E. coli* and *S. aureus*.	(68)

As illustrated in Table 5, the effective therapeutic niacinamide concentrations for almost all major dermatological concerns is reached between 2% and 5%. Lower concentrations (2%) are effective for sebum regulation and barrier repair, while higher concentrations within this window (4%–5%) and longer application periods (up to 12 weeks) are required to reverse complex structural damage, such as deep wrinkles and severe hyperpigmentation. The analysis of the current cosmetic market (Table 2) reveals a significant discrepancy between the clinical data presented above and commercial reality. While clinical

trials confirm robust efficacy at 2–5%, the market promotes serums with 10% and up to 20% niacinamide.

This increase doesn't seem to be based on any scientific data. The Cosmetic Ingredient Review (CIR) safety assessment proved no stinging up to 10% and no irritation up to 20% (20), but why use these high concentrations if not needed. At 20%, the risk of adverse effects increases due to the potential presence of nicotinic to acid impurities. As established by Barré et al. (21), niacinamide hydrolysis is pH and temperature-dependent. In high-concentration formulas, even a minor hydrolysis percentage results in a clinically significant amount of nicotinic acid, triggering vasodilation (flushing). Therefore, the 10–20% trend appears to be driven by marketing rather than pharmacodynamic necessity.

4.3 *In vitro* studies as a tool for the development of effective topical formulations

4.3.1 Defining quantitative tissue targets

A rational approach to topical formulation requires a defined therapeutic objective. When the target cutaneous concentration of niacinamide is known, the formula design can be precisely tailored to achieve this specific permeation goal. This targeted delivery is accomplished by carefully modulating the concentration of the active ingredient and strategically incorporating suitable penetration enhancers.

Effective concentrations from *in vitro* cell culture studies have been used to calculate the necessary μg of niacinamide per g of skin to exert each activity (Table 6). To do so, as skin density is 1.116 g/cm^3 (69), it was considered as 1.0 g/cm^3 to simplify the calculations. The concentration stated in the study, whether it was mM, μM, % or mg/mL, was multiplied by niacinamide's molecular weight (122.12 g/mol) and the necessary unit changes were applied. As the density is considered as 1.0 g/cm^3 or 1.0 kg/L, it can be assumed that 1 liter of skin volume is equivalent to 1 kilogram (1000 grams) of skin tissue mass. This direct equivalence allows volume-based concentrations to be seamlessly translated into mass-per-mass ratios, ultimately producing the target values expressed in μg of active ingredient per gram of skin.

Table 6: Niacinamide concentration needed per g of skin for each activity.

Activity	Niacinamide concentrations studied	Optimal niacinamide concentration	μg of niacinamide/g of skin	References
Inhibition of ROS generation	5, 25 and 50 μM	25 μM	3 μg/g	Camillo et al. (70)
	12.5, 25, 50, 100 and 200 μM	50 μM	6 μg/g	Zhen et al. (40)
Inhibition of melanogenesis and melanin transfer	200 μM	200 μM	24 μg/g	Li et al. (71)
Stimulation of fibroblasts and collagen synthesis for wound healing	2.5 mM	2.5 mM	305 μg/g	Wessels et al. (28)
Repair of DNA after UV radiation	3 and 10 mM	3 mM	366 μg/g	Riklis et al. (72)
Increasing expression of collagen and HSPs	0.8, 8.2 and 82 mM	8.2 mM	1000 μg/g	Philips et al. (44)
Protection against UV radiation	50 μM	50 μM	6 μg/g	Damian et al.(43)
	1 and 10 mM	10 mM	1221 μg/g	Izdebska et al. (73)
Bactericidal and fungicidal	123, 205, 246, 328 and 491 mM	491 mM	60000 μg/g	Ziklo et al. (45)

Using the quantitative data from Table 6, formulation optimization can be strategically directed towards specific therapeutic targets. Although some optimal concentrations may vary significantly for the same biological activity (often due to differences in the specific cellular pathways evaluated), these numbers provide a quantitative baseline. This theoretical framework serves as an initial guide for formulators, establishing target delivery profiles that can subsequently be verified and refined through empirical testing.

4.3.2 Formulation strategies and *in vitro* permeation testing

Once a prototype formulation is developed, its delivery performance is evaluated using Franz diffusion cells. By applying the formulation to skin membranes, researchers can accurately measure the precise amount of niacinamide retained within the tissue (74). The reliability of these laboratory models has been robustly confirmed by *in vitro-in vivo* correlation (IVIVC) studies, which demonstrate that Franz cell profiles accurately predict real-time skin penetration in living patients (75). If the retained dose falls short of the cellular targets, the formula must be adapted (76).

To scientifically validate these permeation assays, the European Medicines Agency (EMA) strictly requires calculating the mass balance (77). The total applied dose must equal the sum of the unabsorbed dose (recovered during surface washing), the tissue-retained dose, and the permeated dose. Achieving a recovery between 90% and 110% validates the integrity of the experiment and confirms the true topical bioavailability of the formulation.

According to Fick's first law, increasing the active ingredient concentration should theoretically enhance permeation. However, studies show that higher niacinamide concentrations do not translate to a proportional increase in cutaneous absorption (78). Consequently, simply increasing the active percentage is an inefficient strategy.

Instead, formulators must optimize the vehicle to maximize drug permeation and retention. The most common approach is the strategic use of cosolvents and penetration enhancers (76, 79, 80). Beyond traditional solvents, modern formulations employ different delivery systems to boost permeation while ensuring the final product is dermocosmetically acceptable. These include oil-in-water emulsions (81), microemulsions (82), lipid nanoparticles (83), and novel niacinamide-loaded elastic liposomes (84).

5 Conclusions

The integration of biopharmaceutical, pharmacokinetic, and clinical data allows for the following conclusions regarding the topical use of niacinamide:

1. **Biopharmaceutical challenge and vehicle dependency:** Despite its favorable low molecular weight (122.1 g/mol), the hydrophilic nature of niacinamide ($\log P = -0.37$) can compromise its partition into the lipophilic stratum corneum. Consequently, passive diffusion is highly vehicle-dependent. Relying solely on increasing the raw percentage of the active ingredient is an inefficient strategy; instead, formulations must utilize synergistic penetration enhancers to fluidize the intercellular lipid matrix and ensure adequate local bioavailability. These formulations must be optimized and validated through *in vitro* permeation testing using Franz diffusion cells, ensuring an accurate mass balance, to guarantee local bioavailability.

2. **Therapeutic concentration window:** The biopharmaceutical hypothesis that ”more is not always better” is confirmed. Clinical evidence demonstrates efficacy at concentrations ranging strictly from 2% (effective for sebum regulation) to 5% (optimal for antioxidant activity and photoprotection). There is no solid biopharmaceutical evidence justifying the current market trend of 10%–20% concentrations.

3. **Sustainability and rational design:** The cosmetic industry’s shift towards 10%–20% ”megadoses” represents a commercial marketing strategy rather than a rigorous scientific advancement. Formulating at these levels when the biopharmaceutical targets are saturated at much lower doses represents an unjustified waste of raw materials and unnecessarily increases the carbon footprint of the supply chain. Future dermatological research must pivot towards evidence-guided rational formulation design, prioritizing targeted skin retention, physiological tolerance, and sustainable ”green cosmetics” principles.

4. **Quantitative tissue targets:** The extrapolation of *in vitro* cellular effective concentrations to tissue concentrations (μg/g) demonstrates that the physiological targets for niacinamide are relatively low. Activities such as ROS inhibition or melanogenesis inhibition require below 50 μg/g, while to see bacteriostatic and fungicidal effects, the amount of niacinamide per g of skin must be of 60000 μg/g. This could be helpful when developing new formulations.

5. **Future perspectives and industry transparency:** Future clinical trials should focus on head-to-head *in vivo* comparisons of high-concentration niacinamide (10% to 20%) against the established 5% optimal dose, strictly utilizing the exact same vehicle without the inclusion of other active ingredients (such as keratolytics or retinoids). This would definitively isolate the concentration variable to determine whether these ”megadoses” actually provide any significant clinical advantage or merely heighten the risk of cutaneous irritation. Furthermore, as observed in the current market analysis, many commercial formulations do not disclose their specific niacinamide content. The cosmetic industry should move towards greater transparency by declaring the exact percentage of active ingredients on product packaging. This practice would empower dermatologists, pharmacists, and consumers to make informed, evidence-based therapeutic choices rather than relying on marketing claims.

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